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SC Court of Appeals

THE STATE OF SOUTH CAROLINA
In The Court of Appeals

APPEAL FROM RICHLAND COUNTY
Court of Common Pleas
Jean H. Toal, Circuit Court Judge

Appellate Case No. 2025-000065
Civil Action No. 2023-CP-40-04072

Michael L. Perry and Lonnie Long,..... Respondents,

v.

American International Industries et al.

Of whom Johnson & Johnson; LLT Management, LLC
f/k/a LTL Management, LLC; Kenvue, Inc.; and Johnson
& Johnson Holdco (NA), Inc. are the Appellants.

RECORD ON APPEAL - VOL. XV

RECORD ON APPEAL INDEX

VOLUME I

Orders:

Order Granting Default Against AII, October 3, 2023	1
Order Denying AII's Motion to Lift Default, November 2, 2023	4
Form 4 Order denying Janssen, Johnson & Johnson Holdco, Inc, and Kenvue's Motion to Dismiss, July 2, 2024	9
Form 4 Order granting Motion to Compel, July 2, 2024	11
Order Granting Joint Motion Requesting the Division of Plaintiff Michael L. Perry's Tissue, July 10, 2024	13
Order Regarding AII's Financial Discovery, August 8, 2024	17
Order on Plaintiffs' Motion to Compel and Motion for Sanctions against Defendants Kenvue, Inc and Johnson & Johnson Holdco (NA) Inc., August 9, 2024	20
Order on AII's Post-trial Motions, December 11, 2024	24
Order on Defendants Johnson & Johnson; LLT Management, LLC; Johnson & Johnson Holdco (NA) Inc., and Kenvue, Inc.'s Post Trial Motions, December 11, 2024	68
Amended Order on Defendants Johnson & Johnson; LLT Management, LLC; Johnson & Johnson Holdco (NA) Inc.; and Kenvue, Inc's Post Trial Motions, March 2, 2025	154
Order on Remand from the South Carolina Court of Appeals regarding Defendants Johnson & Johnson's Motion to Reconsider or to Alter and Amend this Court's December 11, 2024 Order, March 2, 2025	240

Verdict Form:

Verdict Form, August 19, 2024	259
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Pleadings:

Plaintiff's Summons and Complaint, August 4, 2023	263
Johnson & Johnson's Answer to Complaint, September 7, 2023	414
LTL Management's Answer to Complaint, September 7, 2023	448

VOLUME II

Plaintiff's First Amended Complaint, November 30, 2023	480
Johnson & Johnson's Answer to Amended Complaint, December 6, 2023	617
LTL Management's Answer to Amended Complaint, December 6, 2023	651
Plaintiff's Second Amended Complaint with Exhibits, February 1, 2024	683
Johnson & Johnson's Answer to Second Amended Complaint, February 16, 2024	815
LLT Management, LLC Answer to Second Amended Complaint, February 16, 2024.....	850
Johnson & Johnson's Holdco (NA) Answer to Second Amended Complaint, July 17, 2024.....	883
Kenvue Inc's Answer to 2 nd Amended Complaint, July 17, 2024.....	917

VOLUME III

Motions, Supporting Memoranda:

PreTrial Motions, Supporting Memorandums:

Kenvue, Janssen, and J&J Holdco's Motion to Dismiss & Exhibits, February 16, 2024	951
Ex A – 4/23/23 Kenvue S-1	1127
Ex B - <i>Ochoa v 3 M</i> – Order	1120
Ex C – <i>Henderson v Taylor-Seidenback</i> Order.....	960
Ex E – <i>LaSalle v. Am Int'l</i> – Order	1284
Ex F – <i>Yandell v J&J</i> – Order	961
Ex G – <i>Egli v J&J</i> – Order	1277
Johnson & Johnson Defendants Motion for Partial Summary Judgment, June 11, 2024.....	1292
Ex A – Michael Perry Vol 1 Deposition Excerpts.....	1302
Plaintiffs' Response in Opposition to Defendants Johnson & Johnson Holdco (NA) Inc. and Kenvue, Inc.'s Motion to Dismiss (and exhibits attached thereto), June 28, 2024.....	1306
Ex 1 – Special Verdict Form from <i>Lee v. Johnson & Johnson</i>	1323
Ex 2 – Verdict Form and Special Interrogatory, <i>Garcia v. Avon Products, Inc.</i> , ...	1327
Ex 3 – Order in <i>Garcia/Salcedo</i> in Cook County, Illinois, 2/26/2024	1333
Ex 4 – New Jersey (Middlesex Cty.) Hearing Transcript 5/24/2023	1335
Ex 5 – New Jersey Order 6/1/2023	1377
Ex 6 – Louisiana Hearing Transcript/Order 9/29/2023	1381
Ex 7 – Pennsylvania Order 10/20/2023	1388
Ex 8 – New Jersey (Atlantic Cty.) Order 9/27/2023	1390
Ex 9 – Order Denying J&J Defendants' Motion to Dismiss, 4/10/24.	1409
Ex 10 - Plaintiffs' Responses to Defendants' Standard Interrogatories, 9/13/23.....	1415

Ex 11 - List of Providers and Facilities.....	1426
Ex 12 - Kenvue (Mongon) depo. 8/14/2023	1428

VOLUME IV

Ex 13 - Kenvue (Ruh) depo. 8/16/2023.....	1473
Ex 14 – Transcript of JJCI (Goodridge) 2/14/2022	1511
Ex 15 – JJCI (Goodridge) depo. 12/20/2021	1557
Ex 16 - Donald McGraw Declaration 9/18/2023.....	1604
Ex 17 - Kenvue SEC S-4 8/3/2023	1629
Ex 18 - Kenvue, Inc. SEC Form S-1 1/4/2023	1637
Ex 19 – Old JJCI Annual Report (filed in NC) 4/5/2021	1660
Ex 20 – Johnson & Johnson Form 10k 2018	1662
Ex 21 – (a)-(e) , Certificates 10/12/2021	1673
Ex 22 - J&J/LTL (Kuffner) depo. 11/9/2023.....	1707
Ex 23 – New JJCI/Holdco Report (filed in NC) 4/5/2023.....	1729
Ex 24 – Janssen Pharmaceuticals Annual Report (filed in NC) 3/28/2023	1731
Ex 25 – LTL Management LLC Articles of Formation (NC) 10/12/2021	1734
Ex 26 – J&J Project Plato approval memo 10/11/2021	1738
Ex 27 - Draft of J&J’s Product List for the FDA, 12/5/11.....	1750
Ex 28 - Product List, undated (listing all baby powders under the same category: “baby powder”).....	1757

Plaintiffs’ Response in Opposition to Defendants Johnson & Johnson, Inc. and LTL Management, LLC’s Motion for Partial Summary Judgment (and exhibits attached thereto), July 8, 2024 — Pursuant to Plaintiff Counsel agreement only the below exhibits are to be included in the Record on Appeal	1784
Ex 01 – M. Perry Video Deposition, 10/10/2023	1801
Ex 21 - Dana, “A Text-book of Mineralogy”	1848
Ex 128 - Peretti, “Geology and Genesis of the Talc Deposits in the Pinerolese” 1966	1858
Ex 134 - Report of Dr. James Webber, 7/11/2022.....	1868
Ex 257- J&J Resp. to Requests for Admission, 7/26/2021	1889
Ex 258 - Old JJCI Responses to Requests for Admission, 7/26/2021	1906
Ex 259 - J&J Audit Testing of Windsor 66 for Asbestos 6/28/1977; J&J letter to R. Miller 2/23/1978; J&J Raw Material Spec. RM08006 1/7/1992; J&J Raw Material Spec. RM08006, 9/23/1997.....	1917
Ex 260 - Tran. of J&J (Dr. Hopkins), 7/22/2019	1938

VOLUME V

Ex 261 - International Agency for Research on Cancer (IARC) Monograph, “Asbestos,” 2012.....	1967
Ex 262- J&J Resp. to Interrog. (<i>Chapman</i>), 5/30/2018	1981
Ex 263 - J&J (Dr. Hopkins) depo., 4/11/2018	1992
Ex 264 - Gillson, “Origin of the Vermont Talc Deposits,” Econ. Geo., 1927	2080
Ex 265- J&J letter “Talc/Asbestos”, 9/5/1972	2103
Ex 266 - Affidavit of R. Mark Bailey, 10/30/2023	2113

Ex 267 - Report of Dr. Mark Rigler, 11/6/2023	2145
Ex 268 - J&J memo 1/3/1974 (TEM is “the only absolute proof”)	2197
Ex 269 - J&J internal memo, 5/16/1973	2199
Ex 270 - Decl. of Dr. Hopkins, 7/7/2016	2201
Ex 271 - Demonstrative Chart Summarizing Battelle Italian Results; Battelle Reports	2208
Ex 272 - J&J memo “Preliminary Evaluation”, 11/1/1967	2229
Ex 273 - J&J internal memo, 4/15/1969	2244
Ex 274 - Demonstrative of J&J’s Internal Documents 1957-2004; Transcript showing its admission	2247
Ex 275- Decades of Evidence” (1948-2020) Demonstrative Chart, 3/31/2021	2258
Ex 276 - Letter from Dr. Blount on her 1991 paper, 2/10/1992	2279
Ex 277 - J&J internal memorandum, 10/16/1997	2282
Ex 278 - NIOSH “Summary of Plant Observation Reports and Evaluation”, 3/1979	2288
Ex 279 - Depo. of Steven Mann (J&J), 2/15/2021	2306
Ex 280 - Dr. Reynolds report to J&J, 3/1974 (Dartmouth).	2377
Ex 281 - J&J “Proposed Specs For Analyzing Talc For Asbestos”, 5/22/1973	2412
Ex 282 - J&J letter, 2/18/1975	2422
Ex 283 - J&J memo, 11/24/1976	2424
Ex 284 - J&J memo “Talc Program”, 6/7/1971	2426
Ex 285 - J&J memo “Windsor Minerals and Talc”, 4/26/1973	2428
Ex 286 - J&J PowerPoint, 4/28/1997	2432
Ex 287 - J&J PowerPoint, 8/18/1997	2436
Ex 288 -, J&J memo on NIOSH study	2439
Ex 289 - J&J memo “Management Authorization for Additional Talc Safety Studies”, 3/3/1975	2449
Ex 290 - J&J memo “Talc/Powder Program and Strategy”, 3/17/1975	2452
Ex 291 - J&J “Antagonistic Personalities” memo, 11/29/1972	2455
Ex 292 - CTFA meeting minutes, 2/4/1975	2459
Ex 293 - J&J letter to FDA 9/6/1974; J&J letter to the CTFA 12/17/1974	2464

VOLUME VI

Ex 294 - Dr. Langer to J&J, 11/10/1971	2468
Ex 295 - Dr. Hutchinson report to McCrone/J&J	2473
Ex 296 - J&J letter to the CTFA (to be forwarded to the FDA), 3/15/1976	2517
Ex 297 - Depo. of J&J (Musco), 3/8/2019	2520
Ex 298 - J&J advertisement 1965	2533
Ex 299 - J&J guidebook for physicians and nurses, 6/10/1976	2535
Ex 300 - J&J purity claim support, 2/10/1974	2585
Ex 301- McCrone letter to Zeitz, 11/05/1975	2588

Motions in Limine, Memos, Replies and Trial Submissions:

Plaintiffs’ Motion in Limine No. 17 to Exclude the Testimony of Dr. Gregory Diette (and exhibits attached thereto), July 11, 2024	2593
Ex 01 – Diette Report, 6/27/24	2606

Ex 02 – Diette Supplemental Report, 7/2/24	2705
Ex 03 – Diette Deposition, 2/3/23.....	2744
Ex 04 – McDonald & McDonald, Mesothelioma: <i>Is there A Background?</i>	2779
Ex 05 – McDonald & McDonald, Mesothelioma: <i>The epidemiology of mesothelioma in historical context</i>	2791
Ex 06 – Hillerdal, <i>Mesothelioma: cases associated non-occupational and low does exposure</i>	2803
Ex 07 – Wiggins, <i>BTS Statement on malignant mesothelioma in UK.</i>	2813
Ex 08 – Moore, <i>Malignant mesothelioma</i>	2833
Ex 09 – Dail and Hammar’s Pulmonary Pathology.....	2845
Ex 10 – Teta, <i>US mesothelioma patterns.</i>	2849
Ex 11 – Tan, <i>Projection of mesothelioma mortality in Britain.</i>	2860
Ex 12 – Delgermaa, <i>global mesothelioma deaths reported to World Health.</i>	2868
Ex 13 – Report of Dr. David Madigan, 2/1/21	2882
Ex 14 – Moolgavkar, <i>Pleural and peritoneal mesotheliomas in SEER.</i>	2907
Ex 15 – Moolgavkar Reporting, <i>Hirshberg</i>	2918
Ex 16 – MUSC Medical Record	2921
Ex 17 – Dr. Diette Depo Transcript, 7/3/24.....	2923
Ex 18 – No exhibit reference	

VOLUME VII

Ex 19 – Playne/Plant MIL Hearing Transcript, 2/14/23	2951
Plaintiffs’ Motion in Limine No. 20 Regarding Admissibility of Documents Without Sponsoring Witness (and exhibits attached thereto), July 10, 2024	3031
Ex 01 – Stipulation regarding J&J Documents Produced.....	3036
Plaintiffs’ Motion in Limine No. 22 Motion for Evidentiary Sanctions Against Johnson & Johnson, LLT Management LLC, Johnson & Johnson Holdco (NA) Inc., and Kenvue, Inc. Based on Spoliation of Evidence (and exhibits thereto), July 10, 2024	3041
Ex 01 – Deposition of M. Perry, Vol 1	3081
Ex 02 – McBrayer Order, 11/5/21	3128
Ex 03 - Battelle Report 2/29/1956	3141
Ex 04 – Report of Dr. Webber, 6/10/21.....	3186
Ex 05 – Demonstrative summarizing reports of asbestos from 1957 to 2004.....	3225
Ex 06 – Demonstrative on findings of asbestos minerals 696 samples years 1967 to 1988	3233
Ex 07 – Memo from J&J ‘s Dr. Nash, 7/29/1971	3254
Ex 08 - Memorandum from J&J’s D.R. Petterson 4/26/1973	3257
Ex 09 - Memorandum from Dr. Nashed 10/23/1973	3261
Ex 10 - Ernest F. Fullam Inc. report to (codefendant) Whittaker, Clark & Daniels, Inc.	3264
Ex 11 - Luzenac report on Argonaut 5/23/2002	3270
Ex 12 - Blount, A.M., <i>Amphibole Content of Cosmetic and Pharmaceutical Talcs</i>	3273
Ex 13 - Steffen et. al. Serious ovarian cancer caused by exposure to asbestos.....	3282
Ex 14 - Report of Dr. Rigler 6/11/2021.....	3296
Ex 15 - Excerpt of Mark Bailey’s Report on Vermont talc 11/16/2020.....	3306

Ex 16 - Moline, J., et. al., <i>Mesothelioma associated with the use of cosmetic talc</i>	3328
Ex 17 - Emory, TS. <i>Malignant mesothelioma following repeated exposures to cosmetic talc</i>	3336
Ex 18 – Talc and Asbestos – J&J (Madigan)	3343
Ex 19 - J&J notebook 8/10/1972 (reporting tremolite “fibers”	3364

VOLUME VIII

Ex 20 - J&J memo 4/19/1973 (noting tremolite fibers in four JBP samples).....	3367
Ex 21 – J&J responses to Interrogatories, <i>Breakell v. 3M</i>	3369
Ex 22 - CSMRI report 4/14/1971.....	3505
Ex 23 - CSMRI report 7/7/1971.....	3501
Ex 24 - CSMRI report 2/26/1973.....	3515
Ex 25 - J&J memo 7/9/1971 at pg. 4	3522
Ex 26 - Dr. Langer to J&J 11/10/1971	3530
Ex 27 - J&J memo 9/9/1975	3535
Ex 28 - J&J memo 10/3/1975	3539
Ex 29 - Excerpt of report of Dr. Hutchins 1972	3543
Ex 30 - McCrone report 10/27/1972.....	3568
Ex 31 - McCrone report 2/11/1974	3572
Ex 32 - McCrone report 3/11/1974.....	3574
Ex 33 - McCrone report 7/8/1974.....	3578
Ex 34 - McCrone report 7/1/1975.....	3582
Ex 35 - McCrone report 11/5/1975	3588
Ex 36 - Windsor Mineral, 5/24/1976	3591
Ex 37 - Dr. Reynolds report 3/1974 at pg. 6	3593
Ex 38 - EMV Associates report 4/4/1977	3628
Ex 39 - RJ Lee report 3/14/1988.....	3631
Ex 40 - Dr. Blount to J&J attorney 4/23/1998	3635
Ex 41 - Excerpt of the J&J designee Dr. Hopkins 7/22/2019	3637
Ex 42 - J&J’s responses to discovery (excerpt) in Eggers.....	3644
Ex 43 - Expert report of Dr. Sanchez report 7/30/2021	3672
Ex 44 - Excerpts of) Mineralogy and Morphology of Amphiboles	3703
Ex 45 - <i>Misidentification of Asbestos in Talc</i> by J&J’s Mr. Ashton 1977.....	3718
Ex 46 - J&J’s TM7024 8/21/1995.....	3735
Ex 47 - McCrone to J&J (Windsor Mineral) 8/22/1985	3746
Ex 48 - J&J (Windsor Mineral) to McCrone 9/10/1985	3749
Ex 49 - McCrone to J&J (Windsor Mineral) 10/8/1985	3751
Ex 50 - McCrone to J&J 12/17/1990.....	3753
Ex 51 - McCrone to Cyprus Windsor Minerals 11/26/1990	3759
Ex 52 - ASTM D6620-19, Standard Practice for Asbestos Detection Limit Based on Counts (2019).....	3770
Ex 53 - EPA, Region III Fact Sheet, Quality Control Tools: Blanks (2009)	3782
Ex 54 - McCrone Standard Operating Procedure 3/24/1987	3785
Ex 55 - Email from Ruark Lanham, FDA Divisional Recall Coordinator, 10/17/2019	3791
Ex 56 - Decl. of Dr. Sanchez 3/29/2021	3793

Ex 57 - Letter from RJ Lee 10/28/2019	3797
Ex 58 - Excerpt of Dr. Van Orden 3/12/2020.....	3802
Ex 60 - McCrone to J&J 1/28/1987	3805
Ex 61 - McCrone 6/25/1995	3809
Ex 62 - Executive Summary of Preliminary Recommendations by the Interagency Working Group on asbestos in Consumer Products, 1/6/2020	3812
Ex 63 - CSMRI to J&J 5/18/1971.....	3819
Ex 64 - J&J “Assay of Talc in Baby Powder, 5/14/1971	3823
Ex 65 - J&J report 10/1980	3825
Ex 66 - RJ Lee to Mr. Ashton of J&J 3/9/2004.....	3831
Ex 67 - McCrone on JBP 8/19/1971	3833
Ex 68 - McCrone 1/7/1972	3842
Ex 69 - Dr. Pooley 2/3/1972	3845
Ex 70 - J&J internal document 12/20/1972	3852
Ex 71 - EMV Associates for J&J 6/3/1983.....	3854
Ex 72 - RJ Lee 5/23/1989	3859
Ex 73 - McCrone to Luzenac 1/24/1994.....	3861
Ex 74 - McCrone to Luzenac 6/25/1995.....	3863
Ex 75 - Mr. Ashton to Dr. Hildick-Smith 4/9/1969.....	3866

VOLUME IX

Ex 76 - Dr. Hildick-Smith regarding Dr. Cooper, 7/30/1971.....	3869
Ex 77 – J&J Alternate Domestic Talc Sources 04/15/1969	3872
Ex 78 - J&J’s privilege log (excerpt) from the deposition of Nancy Musco 2/15/2019	3875
Ex 79 - Deposition of Nancy Musco (excerpt) 2/15/2019.....	3902
Ex 80- J&J memorandum on the <i>Westfall</i> case 7/15/1981.....	3977
Ex 81 - J&J on <i>Jolly</i> case 12-3-1982	3980
Ex 82 - J&J list of inhalation complaints 6/17/1985.....	3982
Ex 83 - Schedule I to J&J-Cyprus contract 12/30/1988	3987
Ex 84 - Luzenac to J&J 10/17/1994.....	3990
Ex 85 - Ex. 21 to the deposition of James Mittenthal 10/18/2018.....	3993
Ex 86 - McCrone to Dr. Hutchinson, 10/5/1972	3995
Ex 87 - Report of Dr. Sanchez in Hirshberg (excerpt) 4/2/2021.....	3997
Ex 88 - CSMRI to J&J 8/13/1971	4026
Ex 89 - J&J’s Interrogatory Responses, <i>Eggers v. Colgate-Palmolive Co.</i> , ...	4029
Ex 90 - CSMRI to J&J 6/8/1973.....	4087
Ex 91 - McCrone report to J&J without percentages 10/27/1972	4094
Ex 92 - Dr. Hopkins deposition (excerpt) 8/16/2017	4098
Ex 93 - Deposition of James Mittenthal 10/18/2018	4102
Ex 94 - Deposition of J&J designee James Mittenthal (Vol. 3 of 3) dated 10/19/2018	4114
Ex 95 - <i>Coker</i> legal hold 10/6/1997	4132
Ex 96 - <i>Krushinski</i> legal hold 11/11/1999.....	4137
Ex 97 - J&J trip report 11/23/1993	4140
Ex 98 - George Lee files 7/1988	4145

Ex 99 - Talc Closet Cleanout 1/20/2000 and (d) J&J's file on all phone calls and correspondence it had with the FDA that no longer exists.	4150
Ex 100 - John O'Shaughnessy deposition (excerpt) 6/22/2021.....	4152
Ex 101 - J&J designee Dr. Hopkins deposition (excerpt) 8/15/2017.....	4220
Ex 102 - J&J marketing Power Point 4/28/1997	4230
Ex 103 - J&J marketing Power Point 8/18/1997	4234
Ex 104 - J&J on antagonistic personalities 11/29/1972	4237
Ex 105 - J&J's Vernon Zeitz 5/5/1975.....	4240
Ex 106 - J&J to FDA 9/6/1974	4255
Ex 107 - J&J to Dr. Estrin 12/17/1974	4258
Ex 108 - Testimony of Dr. Sanchez (excerpt) 5/22/2018.....	4260
Ex 109 - J&J re: Dutch Organization 9/20/1973	4263
Ex 110 - J&J's summary of submissions to the FDA 1971-1979.....	4271
Ex 111 - J&J letter to the CTFA (to be sent to the FDA) 3/15/1976	4285
Ex 112 - Dr. Hopkins deposition (excerpt) 8/17/2017	4287
Ex 113 - Dr. Hopkins deposition (excerpt) 4/11/2018	4297
Ex 114 - Dr. Langer to Mt. Sinai 3/17/1976.....	4305
Ex 115 - Pfizer memorandum on media coverage 3/25/1976.....	4310
Ex 116 - J&J regarding meeting with Don Ferry 10/2/1974.....	4312
Ex 117 - J&J on booklet 10/8/1974	4314
Ex 118 - J&J on trip to Italy 10/31/1974	4317
Ex 119 - J&J to UK confirming decision not to publish 11/26/1974.....	4320

VOLUME X

Ex 120 - Deposition of Nancy Musco	4322
Ex 121 - Roger Miller Affidavit (<i>Edley</i>) 7/3/1987.....	4378
Ex 122 - J&J interrogatory responses 5/23/2000 at #17	4384
Ex 123 - O'Shaughnessy Deposition, 6/30/21	4396
Ex 124 - J&J employee William Ashton's Affidavit 5/8/1989	4522
Ex 125 - J&J's Interrogatory Responses, <i>Eggers v. Colgate-Palmolive Co.</i> , ...	4531
Ex 126 - J & J revealed approximately 500 additional TEM evaluations were performed at #16	4536
Ex 127 - J&J Press Release, Oct. 29, 2019.....	4542
Ex 128 - Deposition of Walgreen's designee Rudy Kucera (excerpt) 2/26/21	4546
Ex 129 - Hopkins Testimony, <i>Herford</i> , 11/3/17	4554
Ex 130 - Hearing, <i>Hirshberg v. Johnson & Johnson</i>	4564
Ex 131 - J&J's Second Supplemental Responses to Certain of Plaintiff's First Set of Interrogatories, <i>Eggers v. Colgate Palmolive Co</i>	4573
Ex 132 - Webber Deposition, 5/31/2017.....	4580
Ex 133 - Deposition of J&J designee James Mittenthal (Vol. 1 of 3) dated 9/24/2018	4591
Ex 134 - Pl's McBrayer Motion.....	4648
Ex 135 - 10/28/2021 Transcript of Record.....	4688

VOLUME XI

Plaintiffs’ Motion in Limine No. 23 to Exclude Expert Hearsay Opinions (and exhibits attached thereto), July 10, 2024	4793
Ex 01 - Deposition Testimony of Dr. Matthew Sanchez, <i>Hirshberg v. Johnson & Johnson</i>	4800
Ex 02 - Expert Report of Matthew Sanchez PhD for Johnson & Johnson	4809
Ex 03 - Van Gosen, et al., <i>Using the geologic setting of talc deposits as an indicator of amphibole asbestos content</i> (2004)	4849
Ex 04 – Deposition Testimony of Dr. Matthew Sanchez (“Dr. Sanchez Depo.”), <i>Hirshberg v. Johnson & Johnson, et al.</i> , King County, Washington, dated April 5, 2021	4870
Ex 05 – Email from J&J’s Counsel stating Dr. Sanchez could not locate the e-mail he testified about, dated 4/15/10.....	4875
 J&J Defendants’ Motion in Limine to Partially Exclude Opinions of Dr. Steven Haber with exhibits, July 10, 2024	4877
Ex A - Plaintiffs’ Fact & Expert Witness Designation at 2-5, <i>Perry</i> , June 10, 2024	4886
Ex B – Haber Depo., <i>Garcia</i> , July 27, 2021.....	4901
Ex C – Haber Depo., <i>Chapman</i> , Sept. 6, 2022.....	4910
Ex D – Haber Depo., <i>Roy</i> , Jan. 13, 2022.....	4915
Ex E – Haber Depo., <i>Moore</i> , Nov. 24, 2021.....	4926
Ex F- Haber Depo., <i>Hirshberg</i> , Feb. 23, 2021	4930
Ex G - Haber Depo., <i>Perry</i> , June 24, 2024	4934
Ex H - Order in <i>Lynne Roy v. Colgate-Palmolive Co., et al.</i> , No. 2020-02718 (La. Dist. Ct. May. 4, 2023).....	4944
 J&J Defendants’ Motion in Limine No. 2 to Exclude Each and Every Exposure/Cumulative Dose Causation Opinions, July 10, 2024 – no exhibits	4969
 J&J Defendants’ Motion in Limine No. 5 to Exclude Plaintiffs’ Summary Evidence Charts, with exhibits, July 10, 2024.....	4989
Ex A - “Decades of Evidence” chart	4997
Ex B – <i>Perry</i> , June 24, 2024, Haber Dep.	5014
Ex C – Dr. Haber’s Reference List	5019
Ex D – five-page summary compilation entitled “J&J’s Internal Documentation	5096
 J&J Defendants’ Motion in Limine No. 8 to Exclude evidence, argument, regarding Certain Advertising Campaigns that Focused on Babies and the Mother-Infant Bond, with exhibits, July 10, 2024	5102
Ex A - Baby Camp PowerPoint	5107
Ex B – Vol. I, Michael L. Perry Dep., October 10, 2023	5110
Ex C – Vol. II, Michael L. Perry Dep., October 11, 2023, ...	5116
Ex D – Supplemental Answers to Master Interrogatories, June 10, 2024	5120
Ex E - Feb. 26, 2019 Trial Tr., <i>Rimondi, et al. v. BASF Catalysts LL, et al.</i> , Superior Court of New Jersey, Middlesex County, Law Division, Docket No. MID-2912-17AS.....	5139

Plaintiffs’ Motion in Limine No. 22 – Ex. 60 – McCrone Letter, July 11, 2024	5174
--	------

VOLUME XII

Plaintiffs’ Motion in Limine No. 19 to Exclude the 1986 Letter From H.W. Swanson to Phillippe Douillet (and exhibits attached thereto), July 15, 2024.....	5178
Ex 01 - Swanson Letter” and attachments parts IV to VII	5186

J&J Defendants’ Motion in Limine to Partially Exclude the Opinions of Dr. David Madigan with exhibits A to BB, July 23, 2024 –.....	5339
Ex A - July 15, 2024 <i>Perry Madigan</i> Dep excerpts	5353
Ex B - July 16, 2024 <i>Perry Longo</i> Dep excerpts.....	5369
Ex C - Madigan May 1, 2024, Report, <i>Talc, Asbestos, and Mesothelioma</i>	5377
Ex D – <i>Zimmerman</i> Madigan Dep. excerpts.....	5395
Ex E – <i>Lanzo</i> Madigan Dep. excerpts	5399
Ex F – <i>Citizen</i> Madigan Dep. excerpts.....	5411
Ex G - Compton 05/07/20 <i>Lopez</i> Dep. excerpts	5416
Ex H - Moline 06/11/20 <i>Lopez</i> Dep. excerpts.....	5427
Ex I - Gordon, et al., <i>Asbestos in Commercial Cosmetic Talcum Powder as a Cause of Mesothelioma in Women</i> , J. Occup. & Envir. Health (2014) (“Gordon 2014”)	5432
Ex J - Steffen et al., <i>Serous Ovarian Cancer Caused by Exposure to Asbestos and Fibrous Talc in Cosmetic Talc Powders—A Case Series</i> , J. Enviro. Occupational Medicine (2020)	5450
Ex K - MAS Chart of J&J Testing at 1 (M65205-001).....	5464
Ex L - Longo 9/21/19 <i>Weirick</i> Tr. Excerpt	5501
Ex M - <i>Davis</i> Madigan Dep. excerpts.....	5505
Ex N - Longo Expert Report	5513
Ex O - 10/30/23 <i>Lanzo</i> Longo Dep. excerpts	5526
Ex P - 4/25/2024 <i>Clark</i> Madigan Dep. excerpts.....	5530
Ex Q - Madigan General Report	5534
Ex R - <i>Alfaro v. Imerys Talc Am. Inc.</i> , 2017 WL 3668610, at *9 (Cal. Ct. App. Aug. 25, 2017).....	5560
Ex S - <i>Barlow v. ACandS, Inc.</i> , Consolidated No. 24X11000783, at 16–17 (Bal. Cir. Ct. Nov. 13, 2015)	
Ex T - <i>Greene v. ACandS, Inc.</i> , Consolidated No. 24X16000314, (Bal. Cir. Ct. May 16, 2017).....	5574
Ex U - <i>Nosse v. ArvinMeritor, Inc.</i> , LASC No. BC603354, Motion Hearing Tr. 41:16–24 (Cal. Super. Ct. Jun. 29, 2016).....	5578
Ex V - <i>Schoeniger v. Colgate-Palmolive Co.</i> , Dkt. No. MID-L-5869-16AS, Mot. Hr’g Tr. (N.J. Super. Ct. Oct. 19, 2017)	5598
Ex W - <i>Fishbain v. Colgate-Palmolive Co.</i> , Dkt. No. MID-L-5633-13 AS, Ruling at 7 (N.J. Super. Ct. Aug. 6, 2015)	5630
Ex X - <i>Ingham</i> Madigan Dep. Excerpts.....	5647
Ex Y - <i>Ingham</i> Madigan Tr. Excerpts	5653
Ex Z - Garcia, Madigan <i>Asbestos and Mesothelioma</i> Report	5658

VOLUME XIII

Ex AA - 2/7/2020 <i>Birch</i> Madigan Dep. excerpts	5678
Ex BB - <i>Hamilton</i> Madigan Dep. excerpts	5684
J&J Defendants' Motion in Limine to Exclude Evidence of or Reference to Tissue Testing with exhibits, July 23, 2024	
Ex A - Email Correspondences	5689
Ex B - Email Correspondences	5694
Ex C - Order Granting Joint Motion. On July 14, 2024.....	5710
Ex D – Longo Dep., <i>Perry</i> , July 16, 2024 excerpts	5715
Ex D – Longo Dep., <i>Perry</i> , July 16, 2024 excerpts	5720
Plaintiffs' Consolidated Response in Opposition to Defendants' Motions in Limine to Exclude or Limit Causation Testimony of Plaintiffs' Experts Witnesses (and exhibits attached thereto), July 24, 2024 –	
Ex 01 - Jolly v. General Electric Co., No. 2016-CP-42-1592 (S.C. Com. Pl. Dec. 15, 2017).....	5725
Ex 02 – Garvin v Agco Order 11/14/14.....	5758
Ex 03 - Brody Depo., Voelker v. Alfa Laval, Inc., 5/8/15.....	5798
Ex 04 - Brody Dep., Bodine v. 3M Company, 11/13/14.....	5839
Ex 05 - Larson v. Bondex Int'l, No. 09-69123	5868
Ex 06 - Dr. Haber curriculum vitae.....	5889
Ex 07- Dr. Haber report 6/11/2021	5895
Ex 08 - Dr. Haber (Exhibit D) Johnson & Johnson General Report 10/27/2023.....	5906
Ex 09 - Dr. Haber report 11/8/2023 – Exhibit C	5909
Ex 09 - Dr. Haber report 11/8/2023 – Exhibit C	5933

VOLUME XIV

Ex 10 - Haber Report, 3/30/23.....	6030
Ex 11 – Declaration of Dr. Longo, Prudencio v. Johnson & Johnson (5/13/21).....	6191
Ex 12 - Transcript of Proceedings, In Re Johnson & Johnson Powder Products Marketing, Sales Practices (“J&J Daubert Hearing”)-	6209
Ex 13 - Declaration of William Longo, Ph.D., Anderson v. Avon Products, Inc.....	6219
Ex 14 – Letter, Krishnamoorthi to Hahn (3/3/20).....	6259
Ex 15 - Steffen, Serous Ovarian Cancer Caused by Exposure to Asbestos and Fibrous Talc in Cosmetic Talc Powders – A Case Series (2020).	6264
Ex 16 - Order, Ingham v. Johnson & Johnson (6/4/18)	6278
Ex 17- Excerpt Transcript of Proceedings, Henry v. Brenntag (9/14/18).....	6286
Ex 18 - Notice of Ruling on Defendants' Motions in Limine, Blinkinsop v. Albertsons Companies, Inc. (2/26/19)	6298
Ex 19 - Transcript of Trial Proceedings, Zimmerman v. Whittaker Clark & Daniels (4/22/21)	6305
Ex 20 - Excerpt of Transcript of Proceedings, Chapman v. Avon Products, Inc. (12/12/22).....	6323
Ex 21 - Johnson & Johnson Baby Products Company correspondence from W. Ashton to J.P. Grange, Subject: Talc Asbestos, L. Paoletti (9/26/84)	6328
Ex 22 - Decades of Evidence summary chart	6346
Ex 23 - Bird, A Review of the Talc Industry's Influence on Federal Regulation and Scientific Standards for Asbestos in Talc.....	6363

Ex 24- Chart of Johnson & Johnson Positive Testing.....	6417
Ex 25 - Dr. Madigan report “Asbestos and Mesothelioma” 4/1/2023	6423
Ex 26- Dr. Madigan report “Talc, Asbestos and Mesothelioma” 9/1/2023	6444
Ex 27 - Dr. Madigan report “Talc and Asbestos – J&J” 9/21/2021	6459
Ex 28 - Kanarek, Asbestos in Talc and Mesothelioma: Review of the Causality Using Epidemiology, Med. Res. Archives, Vol. 8 (5): 2020	6485
Ex 29- IARC Monograph “Asbestos” 2012 at pgs. 219, 234, 280, 293, 294	6499
Ex 30- Magnani, “Italian Consensus Conference on Malignant Mesothelioma of the Pleura. Epidemiology, Public Health and Occupational Medicine Related Issues,” Med Lav 2015	6508
Ex 31 - Consensus Report: Asbestos, asbestosis, and cancer: the Helsinki criteria for diagnosis and attribution	6517
Ex 32- Consensus Report: Asbestos, asbestosis, and cancer: the Helsinki criteria for diagnosis and attribution 2014, Scand J Work Environ Health.....	6524

VOLUME XV

Ex 33 - Guide for Ship Scrappers: Tips for Regulatory Compliance, p. 2-6 (Summer 2000)	6536
Ex 34 - OSHA Website, Safety and Health Topics: Asbestos, https://www.osha.gov/SLTC/asbestos , ...	6547
Ex 35 - IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 14, Asbestos, § 5.2	6553
Ex 36 - National Cancer Institute Mesothelioma Fact Sheet.....	6556
Ex 37 - NIOSH Revised Recommended Asbestos Standard 1976	6568
Ex 38 - WHO Air Quality Guidelines, Chapter 6.2 Asbestos	6581
Ex 39 - CPSC Ban of Consumer Patching Compounds Containing Respirable Free- Form Asbestos, ...	6596
Ex 40 - Landrigan et al., The Hazards of Chrysotile Asbestos: A Critical Review, IND HEALTH 37:271-280, 275 (1999)	6610
Ex 41- Hillerdal, Mesothelioma: Cases Associated with Non-Occupational and Low Dose Exposures, OccUP ENVIRON MED 56:505-513, 510 (1999).	6621
Ex 42 - Welch, Asbestos Exposure Causes Mesothelioma, But Not This Asbestos Exposure: An Amicus Brief to the Michigan Supreme Court, INT J OccUP ENVIRON HEALTH 13:318-327 (2007).....	6631
Ex 43 - Joyce Rost v. Ford Motor Company, No. 56 EAP 2014 (Pa. April 7, 2015).....	6642
Ex 44 - Iwatsubo, et al, Pleural Mesothelioma: Dose-Response Relation at Low Levels of Asbestos Exposure in a French Population-based Case-Control Study, AM J EPID 148(2):122-142 (1998)	6685
Ex 45 - Rodelsperger et al., Asbestos and Man-Made Vitreous Fibers as Risk Factors for Diffuse Malignant Mesothelioma: Results From a German Hospital-Based Case-Control Study, AM J INDUS MED 39: 262-275, 262 (2001)	6696
Ex 46 - Rolland, Risk of pleural mesothelioma: A French population-based case- control study (1998-2002) (Oct. 20, 2006).	6711
Ex 47 - A. Lacourt et al., Occupational and non-occupational attributable risk of asbestos exposure for malignant pleural mesothelioma, Thorax, published online, at Table 4 (Feb. 7, 2014).....	6714

Ex 48 - Dr. Markowitz, Asbestos-Related Lung Cancer and Malignant Mesothelioma of the Pleura: Selected Current Issues, Semin Respir Crit Care Med 36:334-346, 336, Table 1 (2015)	6725
Ex 49 - Smith and Wright, Chrysotile Asbestos Is the Main Cause of Pleural Mesothelioma, AM J IND MED 30:252-266, 255 (1996).....	6739
Ex 50 - Kanarek, Mesothelioma from Chrysotile Asbestos: Update, ANN EPIDEMIOL 21:688-697, 695 (2011)	6756
Ex 51 - R.P. Everatt et al., Occupational Asbestos Exposure Among Respiratory Cancer Patients in Lithuania, Am. J. Indus. Med., Supplement 50:455-463 (2007).....	6767
Ex 52 - M.T. Madkour, Environmental exposure to asbestos and the exposure-response relationship with mesothelioma, E. Mediterranean Health J. 15(1):25-38 (2009)	6777
Ex 53 - Bianchi, Latency periods in asbestos-related mesothelioma of the pleura, EUR J CANCER PREV 6:162-166 (1997).	6792

VOLUME XVI

Plaintiffs' Response to Johnson & Johnson Defendants' Motion in Limine to Partially Exclude the Opinions of Dr. Steven Haber (and exhibits attached thereto), July 24, 2024	6798
Ex 01 - Trial Tr., 2/27/23, Plant v. Avon Prods, Inc., S.C. Court of Common Pleas, Richland Cty, at 682-769	6781

VOLUME XVII

Ex 02 – Haber Aff., 4/4/24, Newton, at 1-2	7178
Ex 03 - Haber, supra, Malignant Mesothelioma: A Clinical Study of 238 Cases	7366
Ex 04 - Trial Transcript, Chapman v. Avon Products, Inc., No. 22STCV05968 (Oct. 26, 2022), at 180:23-187:4.....	7374
Ex 05 - Trial Transcript, Chapman v. Avon Products, Inc. (October 27, 2022), at 45:3-11	7427
Ex 06 - Excerpts of Trial Transcript, Hirshberg v. Johnson & Johnson, No. 20-2-05603-1 SEA (May 10, 2021).....	7478
Ex 07 - Excerpts of Trial Transcript, Chatfield v. Avon Products, Inc., No. 21CV40522 (Feb. 26, 2023).	7529
Ex 08 - Judgment, Roy v. Colgate-Palmolive Co., No. 2020 – 02718 (May 4, 2023....	7545
Ex 09 - Reasons for Judgment, Roy v. Colgate-Palmolive Co., No. 2020 - 02718 (May 4, 2023).....	7551
Ex 10 - Excerpts of Trial Transcript, Salcedo v. Johnson & Johnson (March 25, 2024)	7572
Ex 11 – Haber Dep., 11/15/21, Moore, at 248:2-21.....	7596
Ex 12 - Ghio and Roggli, Letter to the Editor: Talc Should Not Be Used in Pleurodesis in Patients with Nonmalignant Pleural Effusions.....	7661

VOLUME XVIII

Ex 13 - Haber Dep., Vol. II, 11/24/21, Moore, at 463:25-464:5	7664
Ex 14 - Hinch to Luckewicz, 12/18/87 (acknowledging that TEM limit of detection is 0.003% compared to XRD at 0.5%).....	7729

Ex 15 - Report of CTFA Talc Subcommittee on Method to Detect Chrysotile and Tremolite in Talc, 12/10/73	7733
Ex 16 - Practical Aspects of Talc and Asbestos, at 409 (Nov. 1978)	7741
Ex 17 - Lemen, Asbestos in Brakes: Exposure and Risk of Disease, Am J Indus Med 45:229-237, 234 (2004)	7751
Ex 18 - Rohl, Consumer Talcums and Powders: Mineral and Chemical Characterization 261 (1976).	7761
Ex 19 - Rohl, Consumer Talcums and Powders: Mineral and Chemical Characterization 261 (1976).	7792
Ex 20 - Rohl Asbestos in Talc, Env Health Persp J, 9:129-132, 129 (Dec 1974)	7798
Ex 21 - Dana, A Textbook of Mineralogy, at 678	7803
Ex 22 - Pfizer Technical Report for Ceramic Materials, Jan. 1967	7813
Ex 23 - Moline, J., et. al., Mesothelioma associated with the use of cosmetic talc (2020);	7819
Ex 24 - Emory, TS, et al., Malignant mesothelioma following repeated exposures to cosmetic talc: A case series of 75 patients (June 2020)	7827
Ex 25 - Consensus Report: Asbestos, asbestosis, and cancer: the Helsinki criteria for diagnosis and attribution, Scand J Work Environ Health, 23:311-316, 311 (1997)	7834
Ex 26 - Hearing Transcript, Henderson, at 2:7-12 (denying the defendants' motion).	7842
Ex 27 - Hearing Transcript, Hirshberg v. Johnson & Johnson (April 29, 2021), at 132:16-23	7846
Ex 28 - Relevant excerpts of the Position Statement of the Societies of Epidemiology 6/4/2012	7851
Ex 29 - Relevant excerpts of the IARC Monograph on Asbestos 2012, at 219, 234, 238,280, 293, 294	7879
Ex 30 - Kanarek, Asbestos in Talc and Mesothelioma: Review of the Causality Using Epidemiology, Med. Res. Archives, Vol. 8 (5) (2020).	7891
Ex 31 - Magnani, "Italian Consensus Conference on Malignant Mesothelioma of the Pleura. Epidemiology, Public Health and Occupational Medicine Related Issues," Med Lav 5:106, 325-332, at 328 (2015).	7905
J&J Defendants' Opposition to Plaintiffs' Motion in Limine No. 15 to Exclude Any Speculative Testimony that Blames Laboratory Contamination for the Presence of Asbestos in a Talc Sample with exhibits, July 24, 2024.....	7914
Ex A – Dep. of R. Mark Bailey, P.G., <i>Garcia v. Colgate-Palmolive Co.</i> , May 23, 2018 ("Garcia Bailey Dep.") excerpts	7922
Ex B - Dep. of Matthew Sanchez, Ph.D., <i>Hirshberg v. Johnson & Johnson</i> , March 1, 2021 (" <i>Hirshberg</i> Bailey Dep.") excerpts	7926
Ex C - Curriculum Vitae for Matthew S. Sanchez, Ph.D.....	7932
J&J Defendants' Opposition to Plaintiffs' Motion in Limine No. 17 to Preclude the Testimony of Dr. Gregory Diette with exhibits, July 24, 2024	7939
Ex A - Diette <i>Perry</i> Rep. excerpts	7949
Ex B - February 28, 2023, <i>Payne/Plant</i> MIL Order	8048

Ex C - Diette's <i>Perry</i> Supp. Ex. Rep	8054
Ex D - Garcia, March 20, 2024, Brody Trial Tr. excerpts	8093
Ex E - February 22, 2021, Brody <i>Eggers</i> Dep. excerpts	8098
Ex F - Diette Dep., July 3, 2024 excerpts	8102

VOLUME XIX

J&J Defendants' Opposition to Plaintiffs' Motion in Limine No.19 to Exclude the 1986 Letter from H.W. Swanson to Phillippe Douillet with exhibits, July 24, 2024	8016
Ex A - FDA's certificate of authenticity and 1986 FDA Response.....	8114
Ex B - 2018.11.09 <i>Boyd-Bostic</i> Trial excerpts	8305
Ex C - 11/15/72 letter to Dr. Goudie (DX7052).....	8309
Ex D - 2024.05.23 <i>Lee</i> Trial excerpts	8311
Ex E - 2024.03.22 <i>Garcia</i> trial excerpts	8316

VOLUME XX

J&J Defendants' Opposition to Plaintiffs' Motion in Limine No. 22 Seeking Evidentiary Sanctions Based on Spoliation of Evidence with exhibits, July 24, 2024	8320
Ex 1 to 11- (Hood) Johnson & Johnson Defendants memorandum in opposition and supporting exhibits, October 25, 2021	8325
McBrayer Order	8917

VOLUME XXI

J&J Defendants' Reply in Support of Omnibus Motion in Limine No. 5 to Exclude Plaintiffs' Summary Evidence Charts with exhibits, July 29, 2024	8929
Ex A - January 6, 2024, Kuffner <i>Eggers</i> Dep. excerpts	8934
Ex B - Eggers- Def J&J March 21 Supplemental Response to Plainiff's First Set of Interrogatories and Request for Production.....	8941
Ex C - August 11, 2022, <i>Payne</i> Pfizer Dep. excerpts	9403

VOLUME XXII

J&J Defendants' Opposition to Plaintiffs' Motion in Limine No. 21 to Exclude Testimony of Dr. David Weill with exhibits, July 29, 2024.....	9412
Ex A - February 28, 2023, <i>Payne/Plant</i> MIL Order	9424
Ex B - July 11, 2024, Weill <i>Perry</i> Rep.	9434
Ex C - Weill Curriculum Vitae	9565
Ex D - July 18, 2024, David Weill Dep. excerpts	9581
Ex E - <i>Garcia</i> , March 20, 2024, Brody Trial Tr. excerpts.....	9587
Ex F - February 22, 2021, Brody <i>Hirshberg</i> Dep. excerpts	9591
Ex G - July 12, 2024, Weill <i>Perry</i> Supp. Report	9594
Ex H - June 24, 2024 <i>Perry</i> Longo Dep. excerpts.....	9597
J&J Defendants' Motion in Limine to Exclude Evidence of or Reference to Tissue Testing with exhibits, August 1, 2024	9601
Ex A -J&J Defs.' MTE	9605
Ex B - Geyer Affidavit.....	9611
Ex C - Longo Dep., <i>Perry</i> , July 16, 2024	9615

Ex D - 7/31/24 K. Bueno Email Correspondence.....	9620
J&J Defendants’ Mode of Trial Motion Regarding Successor Liability and Amalgamation, August 3, 2024	9622
J&J Defendants Objection to Plaintiffs’ Proposed Instructions on Parties in Default and Conditional Motion to Sever with exhibits, August 3, 2024	9626
Ex 1 – 8/2/24 email to Atty McVey.....	9630
J&J Defendants Objection to Plaintiffs’ Proposed Order regarding Plaintiffs’ Motion in Limine No. 22 Based on Spoliation of Evidence with exhibit, August 3, 2024.....	9637
Ex A – 8/3/24 email with attachment	9640
Ex B – Redline comparison of proposed order to Hood (McBrayer) order.....	9658
J&J Defendants’ Objection to Plaintiff Efforts to Submit to the Jury Evidence of Successor Liability or Amalgamation Issued for the Court but Unrelated to Plaintiffs’ Products Liability Claims with exhibit, August 6, 2024.....	9670
J&J Defendants’ Proffer of Evidence re: Mr. Perry’s Exposure to Asbestos in the Library while working at Embassy Suites with exhibits, August 6, 2024.....	9674
Ex A - Dep. of Michael Perry excerpts	9678
Ex B - July 11, 2023 Office Visit, DX12000.398.....	9692
Ex C - Dr. Haber Report.....	9697
Ex D - January 18, 2024 Testimony of William Longo.....	9707
J&J Defendants’ Memorandum related to Procedure and Evidence for Successor Liability with exhibits, August 6, 2024	9713
Ex A – Deposition Designations of Mongon.....	9722
Ex B - Deposition Designations of Ruh.....	9767
Ex C – Proposed Joint Stipulation	9789
Ex D - Dep. of M. Perry excerpts	9792
Ex E - Notice of Commencement of Chapter 11 Case and Meeting of Creditors	9798
Ex F - 8/5/2024 Trial Tr. Excerpts	9804
J&J Defendants’ Objection to Sanctions Order, August 8, 2024	9810
VOLUME XXIII	
J&J Defendants’ Motion for Mistrial with exhibits, August 10, 2024	9813
Ex A – <i>Hood-McBrayer</i> 11/02/2021 Spoliation Order	9828
Ex B - <i>Perry</i> 7/30/2024 Tr excerpts	9841
Ex C – 08/05/2024 Trial Tr excerpts	9868
Ex D - 08/10/2024 Trial Tr. excerpts	9875
Ex E - 2019 Health Hazard Evaluation of Johnson’s Baby Powder (“HHE”).....	9894
VOLUME XXIV	
Ex F - Sanchez Report on Longo Samples.....	9907

VOLUME XXV

Ex G - Longo Affidavit	10407
Ex G - Longo Affidavit (CONTINUED).....	10584
Ex H - PowerPoint Slides (Kuffner-1940s Talc).	10655
Ex I - 8/7/2024 Tr. Transcript (Longo)	10658

VOLUME XXVI

J&J Defendants’ Proposed Jury Charges and Verdict Form, Exhibit A, August 11, 2024	10663
Ex A – Perry v. American Int’l 8/7/2024 Transcript (Day 3).	10667

VOLUME XXVII

Ex A – Perry v. American Int’l 8/7/2024 Transcript (Day 3). (Continued)	10907
Plaintiffs’ Response to J&J’s Motion for Mistrial (and exhibits attached thereto), August 12, 2024.....	11019
Ex 1 – Email exchange 8/1/2024 -8/4/2024.....	11031
J&J Defendants’ Submission of Law Regarding Proper Causation Standard, August 12, 2024.....	11038
J&J Defendants’ Proffer of Evidence re: The 1986 FDA Citizen Petition Response with exhibits, August 12, 2024	11041
Ex A – 1986 FDA Response	11046
Ex B - 85 Fed. Reg. 51035, 51035 (August 19, 2020).....	11237
Ex C - 11/9/2018 <i>Boyd-Bostic</i> Trial Tr. excerpts	11239
Ex D - 5/23/2024 <i>Lee</i> Trial Tr excerpts	11243
Ex E - 3/22/2024 <i>Garcia</i> Trial Tr excerpts	11248
Ex F - 12/17/2019 <i>Forrest</i> Trial Tr. excerpts.....	11252
J&J Defendants’ Proffer of Evidence re: The “Health Hazard Evaluation of Johnson Baby Powder” with exhibits, August 12, 2024	11259
Ex A – 2019 Health Hazard Evaluation of Johnson’s Baby Powder (HHE).....	11262
Ex B - 3/14/2024 Dep. of Dr. Kuffner, Newton excerpts	11275
J&J Defendants’ Memorandum regarding Successor Liability with exhibits, August 12, 2024.....	11294
Ex A – Deposition Designations Thibaut Mongon, 8/14/2023	11307
Ex B – Deposition Designations of Paul Ruh, 8/16/2023.....	11333
J&J Defendants’ Objections to Plaintiffs’ Requested Jury Charges with Exhibits, August 12, 2024.....	11354
Ex A – Plaintiffs’ Requested Jury Charges.....	11359

J&J Defendants’ Objections to Plaintiffs’ Proposed Verdict Form with exhibits, August 12, 2024.....	11390
Ex A – Plaintiffs’ Proposed Verdict Form.....	11394

VOLUME XXVIII

J&J Defendants’ Proffer of Evidence regarding Dr. Kuffner’s Excluded Testimony on Winchite with exhibits, August 13, 2024.....	11399
Ex A - 8/9/2024 Tr. Transcript (Kuffner) excerpts	11403
Ex B - Sanchez Report on Longo Samples	11409

VOLUME XXIX

Ex B – Sanchez Report on Longo Samples (continued).....	11900
Ex C - Longo Affidavit	12086
Ex D - PowerPoint Slides (Kuffner-1940s Talc).....	12157
Ex E - 8/7/2024 Tr. Transcript (Longo)	12160
 J&J Defendants’ Motion and Memorandum in Support of Motion for Directed Verdict with exhibits, August 13, 2024	12164
 J&J Defendants’ Objections to the Court’s Final Jury Charges and Related Final Court Verdict Form, August 14, 2024	12199

J&J Defendants’ Motion for Mistrial with exhibits, August 15, 2024 -14 pgs	12203
Ex A - Perry Trial Transcript, 8/14/2024 excerpt	12207
Ex B - Perry Trial Transcript, 8/14/2024 excerpt	12213

Plaintiffs’ Trial Brief on Successor Liability of The Johnson & Johnson Defendants (and exhibits attached thereto), August 22, 2024.....	12217
Ex 01 - J&J & Old JJCI Resp. to Interrog. (<i>Leavitt</i>) 3/21/2018	12242
Ex 02 -J&J & Old JJCI Resp. to Interrog. (<i>Rimondi</i>) 7/5/2018	12259
Ex 03 - Old JJCI Resp. to RFAs (<i>Garcia</i>) 7/26/2021	12264
Ex 04 - Trans. of J&J (Hopkins) 7/22/2019 at 20:11-17	12275
Ex 05 - Trans. of Mr. Kim 10/22/2021 at 45, 85, 87-89, 90-91	12283
Ex 06 - J&J (Kuffner) depo. 11/9/2023 excerpts.....	12295
Ex 07-. J&J Project Plato approval memo 10/11/2021	12317
Ex 08 - J&J e-mail 10/5/2021	12329
Ex 09 - JJCI (Goodridge) depo. 12/20/2021 at 312:8-9	12331
Ex 10 - Kenvue (Mongon) depo. 8/14/2023 at 22:6-11	12357

VOLUME XXX

Ex 11 - Kenvue (Ruh) depo. 8/16/2023 excerpts.....	12402
Ex 12 -Transcript of New JJCI (Goodridge) 2/14/2022 excerpts	12425
Ex 13 - Mr. Kim Declaration 4/4/2023 at ¶ 24	12471
Ex 14 - Donald McGraw Declaration (with PowerPoint) 9/18/2023.	12482
Ex 15 – Bankruptcy Court Dismissal Order dated 8/11/2023	12507
Ex 16 - <u>16(a)-(e)</u> , Agreements and Certificates 10/12/2021.	12519

Ex 17- J&J “Project Plato Master Q&A” 10/10/2021 at 9 (instructing employees to state that the Texas Two Step “has no impact on our operations.”	12553
Ex 18 - Old JJCI Annual Report (NC) 4/5/2021 (listing Michelle Goodridge as president and director with Kevin Neat as Treasurer	12569
Ex 19 - New JJCI Annual Report (NC) 4/14/2022	12571
Ex 20 - Dr. Kuffner depo. 10/30/2021 at 32:5-7, 32:12-15	12573
Ex 21 - Continued Video-Recorded Deposition of Kenvue Inc. and Johnson & Johnson Holdco (NA) Inc. (through John Kim, Esq.), 8/10/24, at 60:22-25...	12597
Ex 22 - New Jersey Certificate of Amendment 12/16/2022	12705
Ex 23 - Donald McGraw depo. 9/28/2023. New JJCI 3.0 was initially incorporated in Nevada in June 2022 before converting to a Delaware corporation in January 2023	12707
Ex 24 - New JJCI 3 Certificate (NV);.....	12791
Ex 25 - New JJCI 3 Certificate of Conversion (DE).	12793
Ex 26 - Kenvue, Inc. SEC Form S-1 1/4/2023	12795
Ex 27 - Kenvue SEC Prospectus 9/18/2023	12818
Ex 28 - Kenvue LinkedIn profile compilation.....	12824
Ex 29 - Kenvue SEC S-4 8/3/2023..	12858
Ex 30- Kenvue SEC S-4 9/6/2023.....	12866
Ex 31 - Johnson & Johnson Form 10k for the year 2018	12872
Ex 32 - Order on Plaintiffs’ Motion to Compel and Motion for Sanctions Against Defendants Kenvue, Inc. and Johnson & Johnson Holdco (NA) Inc., 8/9/24	12883
Ex 33 - Oral and Videotaped Deposition of James Mittenthal as Defendant Kenvue Inc. 30(b)(6) Representative, Vol. I, 7/26/24, at 38:19-39:7	12888
Ex 34 - Video-Recorded Deposition of Kenvue Inc. (through James P. Mittenthal), Vol. II, 7/30/24, at 313:8-314:7.....	12897

VOLUME XXXI

Ex 35 - Mass. SOS filing 3/14/2022	12911
Ex 36 – Business Corp Annual Report for J&J Holdco, 12/31/2022.....	12914
Ex 37- Mittenthal Outline for Perry/ Kenvue Deposition—updated 7/25/2024, at pgs. 37-38.....	12916
Ex 38 - Draft of J&J’s Product List for the FDA, 12/5/11.....	12955
Ex 39 - Product List, undated (listing all baby powders under the same category: “baby powder”).	12962

Post Trial Motions & Memos:

Plaintiffs’ Trial Brief, Ex. 10 – Dep. of Thibaut Mongon, August 22, 2024.....	12989
Plaintiffs’ Trial Brief, Ex. 13 – Decl. of John Kim, August 22, 2024.....	13034
Plaintiffs’ Trial Brief, Ex. 15 – Decl. of Donald McGraw, August 22, 2024.....	13045
Plaintiffs’ Trial Brief, Ex. 21 – Dep. of John Kim, August 22, 2024.....	13057

Plaintiffs’ Trial Brief, Ex. 34 – Kenvue Depo. (Mittenthal), Vol. II, 7/30/24	13165
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J&J Defendants’ Motions for JNOV, New Trial Absolute Based on Errors of Law, New Trial Absolute based on the Thirteenth Juror Doctrine, and New Trial nisi Remittitur with exhibits, August 26, 2024	13179
Ex A - Trial Transcripts excerpts	13274
Ex B – Weill Kuffner (Valadez) Tr. excerpts	13390
Ex C – <i>Salcedo</i> Tr. excerpts	13398
Ex D – Arnoldy Brody (Hirshberg) 2/22/2021 excerpt.....	13402
Ex E – Longo Dep. (Yerkes/Hofmaister), 01/18/2024 excerpts	13407

VOLUME XXXII

Ex F – Perry Pre-Trial Transcript excerpts	13412
Motion to Substitute Pecos River Talc, LLC as a Party Defendant for LLT Management LLC f/k/a LTL Management, LLC, August 26, 2024	13438
J&J Defendants’ Motion for Setoff and Motion for Production of Settlement, August 26, 2024.....	13441
J&J Defendants’ Motion to Stay Execution on Judgment, August 26, 2024	13448
J&J Defendants’ Reply to Substitute Pecos River Talc, LLC as a Party Defendant for LLT Management, LLC f/k/a LTL Management, LLC, September 9, 2024.....	13453
Ex 1 – Declaration of John Kim	13456
Ex A – Amended and Restated Funding Agreement.....	13461
Plaintiffs’ Consolidated Response to Defendants’ Motion for Setoff and Production of Plaintiffs’ Settlement Agreements, September 13, 2024	13478
Plaintiffs’ Consolidated Response to Defendants’ Motions to Stay Execution of Judgment (and exhibits attached thereto), September 13, 2024.....	13483
Ex 01 – Perry v. American Int’l Trial Transcript (Day 6), 8/13/24.....	13488

VOLUME XXXIII

Plaintiffs’ Response in Opposition to Defendants Johnson & Johnson, LLT Management, LLC, Johnson & Johnson Holdco (NA) Inc., and Kenvue, Inc.’s Motions for JNOV, New Trial Absolute Based on Errors of Law, New Trial Absolute Based on the Thirteenth Juror Doctrine, and New Trial Nisi Remittitur (and exhibits attached thereto), September 13, 2024	13636
Ex 01 – TT 8/5/24 excerpts.....	13742

VOLUME XXXIV

Ex 02 – TT 8/6/24, excerpts	14046
Ex 03 - TT 8/7/24, excerpts	14391

VOLUME XXXV (beginning 14546)

Ex 04 – TT 8/9/24, excerpts	14743
-----------------------------------	-------

VOLUME XXXVI (beginning 15046)

Ex 05 – TT 8/12/24, excerpts	15117
Ex 06 – TT 8/13/24, excerpts	15448

VOLUME XXXVII

Ex 07 – TT 8/14/24 excerpts	15596
Ex 08 - TT 8/15/24 excerpts	15867

VOLUME XXXVIII

Ex 09 - Pre-Trial Hearing, 7/30/24 excerpts	16048
Ex 10 - Trial Ex. 611	16294
Ex 11 - Punitive Damages Verdict Form, 8/19/24.....	16301
Ex 12 - Plaintiffs’ Trial Exhibit No. 72-Chart-Decades of Evidence of Asbestos in Johnson & Johnson Products).....	16306
Ex 13 - Plaintiffs’ Trial Exhibit No. 3.....	16323
Ex 14 – Plaintiff Trial Exhibit No 62	16327
Ex 15 - Plaintiffs’ Trial Exhibit No. 106.....	16329
Ex 16 - Plaintiffs’ Trial Exhibit No. 49	16332
Ex 17 - Plaintiffs’ Trial Exhibit No. 7	16338
Ex 18 –Plaintiffs’ Trial Exhibit No. 136.....	16341
Ex 19 - Plaintiffs’ Trial Exhibit No. 193.....	16344
Ex 20 - Plaintiffs’ Trial Exhibit No. 194	16347
Ex 21 –Plaintiffs’ Trial Exhibit No. 196.....	16385
Ex 22 - Plaintiffs’ Trial Exhibit No. 111.....	16389
Ex 23 - Plaintiffs’ Trial Exhibit No. 113	16408
Ex 24 - Plaintiffs’ Trial Exhibit No. 191	16411
Ex 25 - Plaintiffs’ Trial Exhibits Nos. 92-94	16421
Ex 26 - Plaintiffs’ Trial Exhibits Nos. 117-118.....	16427
Ex 27 - Plaintiffs’ Trial Exhibit No. 181	16435
Ex 28 - Plaintiffs’ Trial Exhibit No. 203.....	16441
Ex 29 - Plaintiffs’ Trial Exhibit No. 10	16443
Ex 30 - Plaintiffs’ Trial Exhibit No. 90	16451
Ex 31 - Plaintiffs’ Trial Exhibit No. 55	16453
Ex 32 - Plaintiffs’ Trial Exhibit No. 61	16462
Ex 33 - Plaintiffs’ Trial Exhibit No. 5.....	16464
Ex 34 - Deposition of Gregory Diette, 2/3/23, at 80:13-2	16466
Ex 35 - <i>Jolly v. General Electric Co.</i> , Order denying Defs’ Post Trial Motions	16501

VOLUME XXXIX

Ex 36 - <i>Garvin v. Agco Corp.</i> , Order denying in part and granting in part Def Crane Co’s Motion for Post Trial Relief, 11/10/14.....	16541
--	-------

Ex 37 - <i>Tort Law—Expert Testimony in Asbestos Litigation—District of South Carolina Holds the Every Exposure Theory Insufficient to Demonstrate Specific Causation Even if Legal Conclusions Are Scientifically Sound</i> , 131 Har. L. Rev. 658 (Dec. 2017).....	16582
Ex 38 – Order granting Joint Motion requesting the Division of PL Perry Tissue, 7/10/24	16591
Ex 39 – Video Deposition of William E Longo 8/6/24.....	16596
Ex 40 - Johnson & Johnson Defendants’ Witness List	16630
Ex 41 - Letter from Donald Kennedy, Commissioner of Food and Drugs, dated 1/11/1979	16636
Ex 42 - Goudie, Examination of Johnson & Johnson’s Baby Powder (10/27/72)	16645
Ex 43 - Chart of Decades of Evidence of Asbestos Content in Johnson & Johnson Products at pp. 1 – 10.....	16649
Ex 44 - “Swanson Letter” and attachments (parts 44-2 to 44-7)	16666
Ex 45 - J&J Defendants’ Objections to the Court’s Final Jury Charges and Related Final Court Verdict Form, 8/14/24.....	16861
Ex 46 - Johnson & Johnson Defendants Proposed Verdict Form, ...	16866
Ex 47 - Notice of Joint Stipulation, 7/31/24	16876
Ex 48 - <i>Lee v. Johnson & Johnson, et al.</i> , No. 23CV40369, Circuit Court of Multnomah County, Oregon, Special Verdict Form, 6/3/24	16879
Ex 49 - <i>Salcedo v. Avon</i> , 4/19/24, Cook County, Illinois Circuit Court)	16883
Ex 50 - <i>Vanklive</i> , 12/9/21, Alameda County Superior Court.).....	16890
Ex 51 - <i>Chapman v. Avon Products</i> , 12/14/22, Los Angeles Superior Court).....	16898
Ex 52 - <i>Plant v. Whitake Clark & Daniels</i> , 3/3/23, South Carolina Court of Common Pleas	16922
Ex 53 – Hood-McBrayer Spoliation Order, 11/5/21	16926
Ex 54 - Email Exchange from Kim Bueno, Re: Perry Trial Schedule, 8/3/24	16939

VOLUME XL

J&J Defendants’ Renewed Motion for Directed Verdict and Nonsuite as a Matter of Law and J&J Defendants’ Memorandum in Support Thereof regarding Successor Liability and in Opposition to Plaintiffs’ Requests with exhibits, September 19, 2024 –	16957
Ex A – <i>LaSalle</i> - Order granting Defendants J&J Holdco and Kenvue Motion to Dismiss, 9/12/2023	16973
Ex B – <i>Egli</i> – 10/26/23 Order on Motion to Quash	16982
Ex C – Yandell – 8/15/2023 Order on Motion to Quash	16990
Ex D – Johnson & Johnson SEC Form 8-K, 05/17/2024	17000
Ex E - 08/23/2023 J&J Announces Final Result of Exchange Offer and Finalize Separation from Kenvue, Inc.	17004
Ex F – Johnson & Johnson SEC Schedule to Amendment No.4 – Tender Offer Statement.....	17008
Plaintiffs’ Response to J&J Defendants’ Renewed Motion for Directed Verdict and Nonsuit as a Matter of Law Regarding Successor Liability (and exhibits attached thereto), September 20, 2024 – (Exhibits referenced refer to Plaintiff’s Trial brief on Successor Liability	17013

J&J Defendants’ Objections to Plaintiffs’ Proposed Order, and Supplemental Memorandum Supporting Johnson & Johnson Defendants’ Post Trial Filings with exhibits, October 7, 2024	17027
Ex 1 – C. Brown letter to Honorable Jean Toal, 10/7/2024.....	17030
Ex 2 – Proposed Order 1 – does not rule on Successor Liability	17033
Ex 3 – Proposed Order 2 – rules on Successor Liability	17046
 J&J Defendants Objection to Proposed Order on Successor Liability and Further Memorandum in Support of J&J Defendants’ JNOV and Other Legal Positions with exhibits, November 8, 2024.....	17059
Ex A – Plaintiffs’ Proposed Order on Successor Liability	17077
 J&J Defendants’ Motion to Reconsider, December 23, 2024	17096
 Plaintiffs’ Response to J&J Defendants’ Motion to Reconsider (and exhibits attached thereto), February 21, 2025	17105
Ex 01 – JJ Defendants Mode of Trial Motion re. Successor Liability and Amalgamation, 8/3/24.....	17118
Ex 02 - TT 8/5/24, excerpts.....	17123
Ex 03 - Hearing on Post-Trial Motions, Vol. II, 9/25/24 excerpts.....	17132
Ex 04 – Verdict Form, 8/19/24	17138
Ex 05 – TT 8/13/24 excerpts	17143
Ex 06 - J&J Defendants’ Objections to the Court’s Final Jury Charges and Related Final Court Verdict Form	17153
Ex 07 - J&J Defendants’ Objections to Plaintiffs’ Proposed Verdict Form, 8/12/24.....	17158
Ex 08 - Order on Defendants Johnson & Johnson; LLT Management, LLC; Johnson & Johnson Holdco (NA) Inc.; and Kenvue, Inc.’s Post-Trial Motions, 12/11/24.....	17168
Ex 09 – TT 8/6/24 excerpts.....	17255
Ex 10 – TT 8/7/204 excerpts.....	17264
Ex 11 - Mongon Depo., 8/14/23, 55:3-12	17274

VOLUME XLI

Transcripts:

Pre-Trial Hearing Transcript, July 30, 2024	17280
 Trial Transcripts Vols I – VIII, August 5, 2024 to August 14, 2024.....	17525
Vol 1, August 5, 2024	17525

VOLUME XLII (beginning 17780)

Vol 2, August 6, 2024.....	17828
Vol 3, August 7, 2024.....	18172

VOLUME XLIII (beginning 18280)	
Vol 4, August 9, 2024.....	18523
VOLUME XLIV (beginning 18780)	
Vol 5, August 12, 2024.....	18896
Vol 6, August 13, 2024	19226
VOLUME XLV (beginning 19280)	
Vol 7, August 14, 2024.....	19281
Vol 8, August 15, 2024.....	19643
VOLUME XLVI	
Post Trial Hearing Transcripts Vols I & II	19823
Vol I, September 24, 2024	19823
Vol II, September 25, 2024.....	19981
Other:	
Johnson & Johnson Defendants’ Witness List, 7/20/2024	20022
J&J Defendants’ Proposed Jury Charges and Verdict Form, August 11, 2024.....	20027
J&J Defendants’ Notice of Appeal with exhibits, January 10, 2025	20190
VOLUME XLVII	
J&J Defendants’ Supplemental Notice of Appeal, March 3, 2025.....	20295
Supersedeas Bond, March 19, 2025.....	20405
Email Correspondence:	
Re: Perry Trial Schedule, July 29-August 2, 2024	20410
Re: Perry-Outstanding Issues, August 4, 2024	20422
Re: Perry Trial Schedule, August 6-10, 2024	20424
Depositions:	20429
Deposition of Dr. William Longo, 8/6/24.....	20429
Deposition of Michael Perry, Vol. I, 10/10/23	20438
Deposition of Michael Perry, Vol. IV, 10/13/23	20616
Deposition of Gregory B. Diette, M.D., 7/3/24	20738
VOLUME XLVIII	
Deposition of David Weill, M.D., 7/18/24	20765
Trial Exhibits:	
Plaintiffs’ Exhibit 10	20816
Plaintiffs’ Exhibit 40	20823
Plaintiffs’ Exhibit 49	20825
Plaintiffs’ Exhibit 72	20830

Plaintiffs’ Exhibit 117	20846
Plaintiffs’ Exhibit 289	20849
Plaintiffs’ Trial Ex. 4274	20855

I certify that this Designation does not contain any matters which are irrelevant to this appeal.

EXHIBIT 33

A GUIDE FOR SHIP SCRAPPERS: TIPS FOR REGULATORY COMPLIANCE

SUMMER 2000

Prepared for:

**U.S. Environmental Protection Agency
Office of Enforcement and Compliance Assurance
Federal Facilities Enforcement Office
Ariel Rios Building
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NOTICE

This document provides guidance to assist regulated entities to understand their obligations under environmental laws; however, for a complete understanding of all legal requirements, you must refer to applicable federal and state statutes and regulations. This guide is a compliance assistance tool only, and it neither changes nor replaces any applicable legal requirements, nor does it create any rights or benefits for anyone. This guide also describes in a summary fashion the roles and activities of federal agencies; however, the guidance does not limit their otherwise lawful prerogatives, and the agencies may act at variance with it, based on specific circumstances. This guidance may be revised without prior notice. Mention of trade names or commercial products in this document, or in associated references, does not constitute an endorsement or recommendation for use.

RECOMMENDATIONS FOR USING THE GUIDE

We recommend that users organize this guide in 3-ring binders. Each separate stand-alone section can then be removed from the binder, copied, and easily posted or handed out to workers undertaking specific ship scrapping operations. Each section can also be used in training workers about the best practices for specific ship scrapping operations. Additionally, Appendix C, which is a series of summaries of inspector highlights, can be used to review important regulatory requirements for each process. Users may want to laminate copies of the summaries for each worker or to post the summaries near the job site as reminders of regulations and best practices. It would be helpful to have someone translate the information if your workers are more familiar with a language other than English.

SURVEY REQUEST !!!!!!!!!!!!!!!

You are invited to share your opinions and thoughts about this document. Please complete the survey questionnaire—A Guide for Ship Scrappers Survey. It is located on the U.S. EPA Web Site at: <http://www.epa.gov/oeca/fedfac/fflex.html>.

PREFACE

This guide is intended to provide site supervisors at ship scrapping facilities with an overview of the most pertinent environmental and worker health and safety requirements to assist them in ensuring compliance at their facilities. The guide is structured by specific processes (e.g., asbestos removal, metal cutting, fuel and oil removal) that occur in ship scrapping operations. Taking a process-specific approach allows the guide to be a more manageable and useful reference tool for key ship scrapping facility personnel. Ship scrappers can review key environmental, safety, and health requirements for each process. References of where to find the requirements in the *Code of Federal Regulations* have been provided throughout the guide, and readers are encouraged to review these regulations in detail. Where possible, helpful shadow and check boxes have been provided to emphasize guidance or tips.

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TABLE OF CONTENTS

1. INTRODUCTION	1-1
1.1 The Guide	1-1
What it is; What it does	1-1
2. ASBESTOS REMOVAL AND DISPOSAL	2-1
2.1 Information About Asbestos	2-1
What is asbestos?	2-1
Why has asbestos been so widely used?	2-2
Where is asbestos found on a ship?	2-2
What are the four classes of asbestos work?	2-3
How can exposure to asbestos occur?	2-3
What are the effects of exposure to asbestos?	2-4
2.2 Who Regulates Asbestos Removal and Disposal?	2-5
2.3 Asbestos Removal Practices and Procedures	2-5
2.3.1 Worker Protection Practices	2-6
Are exposure assessments and monitoring conducted as required?	2-6
Are worker exposure limits met?	2-6
Medical surveillance requirements	2-6
Are workers and supervisors trained in asbestos removal?	2-7
Do workers wear personal protective equipment as required?	2-8
Do workers use hygiene facilities and follow hygiene practices during asbestos removal work?	2-8
2.3.2 Asbestos Removal Activities	2-8
Is a supervisor present for all removal activities?	2-8
Has a survey of asbestos-containing materials on the ship been conducted?	2-9
How can asbestos be identified?	2-10
Has a notification been submitted?	2-10
Will RACM be removed before scrapping activities begin?	2-11
Are wet methods being used during RACM removal and disposal?	2-12
To remove units or sections with RACM	2-13
Regulated areas must be established and clearly marked	2-14
Are other engineering controls and work practices used to control asbestos emissions during removal?	2-15
2.4 Disposal Procedures for Asbestos-Containing Waste Material	2-16
Is the ACWM properly contained?	2-16
Is the ACWM labeled?	2-17
Are there visible emissions during disposal activities?	2-17

2. ASBESTOS REMOVAL AND DISPOSAL

During ship scrapping activities, the removal and disposal of asbestos is a primary environmental concern, as well as a health and safety concern for your workers. The following sections present background information on asbestos, discuss the effects of asbestos exposure, and describe some of the regulatory requirements with which your facility must comply.

2.1 INFORMATION ABOUT ASBESTOS

This section provides background information on asbestos, including what it is, where it can be found on ships, how exposure can occur, and the dangers of exposure.

What is asbestos?

“Asbestos” refers to a group of minerals that occur naturally as masses of long silky fibers. There are three main types of asbestos fibers:

- Chrysotile fibers (white asbestos) are fine, silky flexible white fibers. They are pliable and cylindrical, and arranged in bundles. This was the most commonly used asbestos in the United States.
- Amosite fibers (brown asbestos) are straight, brittle fibers that are light grey to pale brown. This was the most commonly used asbestos in thermal system insulation.
- Crocidolite fibers (blue asbestos) are straight blue fibers that are like tiny needles.

There are three other types of asbestos fibers: anthophyllite, tremolite, and actinolite.

Unlike most minerals, which turn into dust particles when crushed,

asbestos
breaks
up into
fine
fibers
that are
too
small to
be seen
by the
human
eye.

Individual asbestos fibers are often mixed with a material that binds them together, forming what is commonly called asbestos-containing material (ACM). There are two kinds of ACM: friable and non-friable.

- **Friable ACM** is any material containing more than 1% asbestos that, when dry, may be crumbled, pulverized, or reduced to powder by hand pressure.
- **Non-friable ACM** is any material containing more than 1% asbestos that, when dry, cannot be crumbled, pulverized, or reduced to powder by hand pressure. Non-friable ACM is divided into two categories.

S **Category I** non-friable ACM includes asbestos-containing resilient floor coverings, packings, and gaskets.

S **Category II** non-friable ACM includes all other non-friable ACM that is not included in Category I.

What is presumed asbestos containing material (PACM)? Thermal system insulation and surfacing material found in buildings, vessels, and vessel sections constructed no later than 1980 may be considered PACM.

Why has asbestos been so widely used?

Asbestos was widely used in construction and industry due to its unique properties, and because there were few other available substances that combined the same qualities. Asbestos is resistant to abrasion and corrosion, inert to acid and alkaline solutions, and stable at high temperatures. It is strong yet flexible, non-combustible, conducts electricity poorly, and is an effective thermal insulator.

Where is asbestos found on a ship?

Asbestos is found on ships in many types of materials, including, but not limited to:

- Bulkhead and pipe thermal insulation
- Bulkhead fire shields/fireproofing
- Uptake space insulation
- Exhaust duct insulation
- Electrical cable materials
- Brake linings
- Floor tiles and deck underlay
- Steam, water, and vent flange gaskets
- Adhesives and adhesive-like glues (e.g., mastics) and fillers
- Sound damping
- Molded plastic products (e.g., switch handles, clutch facings)
- Sealing putty
- Packing in shafts and valves
- Packing in electrical bulkhead penetrations
- Asbestos arc chutes in circuit breakers
- Pipe hanger inserts
- Weld shop protectors and burn covers, blankets, and any fire fighting clothing or equipment
- Any other type of thermal insulating material

Caution!! ACM may be found underneath materials that do not contain asbestos.

Status of the Asbestos Ban

There is a rather common misunderstanding about the status of the EPA 1989 ban on asbestos-containing products or uses. Two years after EPA's ban, the U.S. Fifth Circuit Court of Appeals vacated much of EPA's rule in 1991 leaving only six asbestos-containing product categories (including corrugated paper, rollboard, commercial paper, specialty paper, flooring felt, and new uses of asbestos) still subject to the asbestos ban. In addition, several uses of ACM products remained banned, including the sprayed-on application of ACM (>1% asbestos) and the installation of certain types of asbestos-containing insulation. **Besides the products and uses listed above, EPA has no existing bans on other asbestos containing products or uses.** EPA does not track the manufacture, processing or distribution in commerce of asbestos-containing products. For further information, contact the TSCA Assistance Information Service at 202-554-1404, call your EPA Regional Asbestos Coordinator (see *Section 9. Resources*), or access <http://www.epa.gov/asbestos> and go to the "Helpful Information" button.

What are the four classes of asbestos work?

The Occupational Safety and Health Administration (OSHA) standard for asbestos specifies four classes of asbestos activities [29 CFR 1915.1001(b)]. These are:

- "Class I" asbestos work means activities involving the removal of thermal system insulation (TSI) and sprayed-on or troweled-on or otherwise applied surfacing ACM or PACM.
- "Class II" asbestos work means activities involving the removal of ACM which is neither TSI or surfacing ACM. This includes, but is not limited to, the removal of asbestos-containing wallboard, floor tile, and construction mastics.
- "Class III" asbestos work means repair and maintenance operations where ACM (including TSI and surfacing ACM and PACM) is likely to be disturbed.
- "Class IV" asbestos work means maintenance and custodial activities during which employees contact, but so as not disturb ACM or PACM, and activities to clean up dust, waste, and debris resulting from Class I, II, and III activities.

How can exposure to asbestos occur?

As a site supervisor, you should be aware that you and your workers can be exposed to asbestos in several ways. When ACM is deteriorated, crushed, or otherwise disturbed,

asbestos fibers break up into very fine fibers and are released to the environment by either dispersing in the air, floating on water or accumulating on the ground. Exposure to asbestos can occur by:

- **Occupational exposure:** Workers may be exposed to asbestos if working at facilities, including ships, which contain asbestos. Because asbestos fibers are small and light, they can be suspended in the air for long periods and possibly inhaled by those working in these areas. Airborne asbestos fibers are small, odorless, and tasteless. They range in size from 0.1 to 10 microns in length (a human hair is about 50 microns in diameter). The amount of asbestos a worker is exposed to will vary according to: (1) the concentration of fibers in the air; (2) duration of exposure; (3) the worker's breathing rate (workers doing manual labor breathe faster); (4) weather conditions; and (5) the protective devices the worker wears. It is estimated that between 1940 and 1980, 27 million Americans had significant occupational exposure to asbestos. People may also ingest asbestos if they eat in areas where there are asbestos fibers in the air.

During ship scrapping, the most significant asbestos concerns for workers arise when removing asbestos-bearing thermal insulation; handling of circuit breakers, cable, cable penetrations; and removing floor tiles (from asbestos in the mastic and in the tile). Additional concerns can arise from handling and removing gaskets with piping and electrical systems, as well as molded plastic parts.

- **Paraoccupational exposure:** Workers' families may inhale asbestos fibers released by their clothes that have been in contact with ACM.
- **Neighborhood exposure:** People who live or work near asbestos-related operations may inhale asbestos fibers that have been released into the air by these operations.

What are the effects of exposure to asbestos?

While scientists have not been able to determine a "safe" or threshold level for exposure to airborne asbestos, EPA, OSHA, and the National Institute for Occupational Safety and Health (NIOSH) believe there is no known safe level of asbestos exposure.

Preventing exposure. Using controls to prevent asbestos exposure is vital to protecting the health of workers.

In short, some people exposed to asbestos develop asbestos-related health problems; some do not. Some known diseases caused from asbestos exposure include: (1) asbestosis (scarring of

the lungs resulting in loss of lung function that often progresses to disability and to death), and (2) cancer, such as mesothelioma (cancer affecting the membranes lining the lungs and abdomen), lung cancer, or cancers of the esophagus, stomach, colon, and rectum.

If inhaled, asbestos fibers can easily penetrate body tissues, and may be deposited and retained in the airways and lung tissue. Because asbestos fibers remain in the body, each exposure increases the likelihood of developing an asbestos-related disease. Asbestos-related diseases may not appear until years after exposure. Ingesting asbestos may be harmful, but the consequences of this type of exposure have not been clearly documented. Note: The risks of asbestos exposure are multiplied 10-fold or more if a worker smokes.

2.2 WHO REGULATES ASBESTOS REMOVAL AND DISPOSAL?

Asbestos regulations are important to the ship scrapping industry because many ships being scrapped contain significant amounts of ACM. During ship scrapping activities, ACM must be properly removed and disposed of. Therefore, being aware of and complying with all applicable regulations for asbestos removal and disposal is important for your ship scrapping operation. The process of removing and disposing of ACM is subject to various federal, state, and local environmental and safety and health requirements.

- **EPA.** EPA is responsible for developing and enforcing regulations necessary to protect human health and the environment. Asbestos is regulated by EPA under two laws: (1) the Clean Air Act (CAA), under the Asbestos National Emissions Standards for Hazardous Air Pollutants (NESHAP), and (2) the Toxic Substances Control Act (TSCA). Some of the requirements for asbestos removal and disposal under these laws include inspections; notifications; supervisor training; and the proper removal, transport and disposal of asbestos.

Specifically, the Asbestos NESHAP [40 CFR 61 Subpart M] is intended to minimize the release of asbestos fibers during demolition and renovation activities (including ship scrapping) through work practices. EPA has delegated authority to inspect and enforce the asbestos NESHAP regulations to most states. Where the program has been delegated, the state agency may have requirements that are more stringent than the federal requirements. The asbestos NESHAP requirements will be discussed in more detail in the following sections.

- **OSHA.** OSHA is responsible for the health and safety of workers who may be exposed to asbestos in the work place. OSHA regulations covering asbestos exposure set a maximum exposure limit and include provisions for engineering controls and

EXHIBIT 34

Asbestos

Asbestos Menu
Workers' Rights

Overview

What is asbestos?

Asbestos is the name given to a group of naturally occurring minerals that are resistant to heat and corrosion. Asbestos has been used in products, such as insulation for pipes (steam lines for example), floor tiles, building materials, and in vehicle brakes and clutches. Asbestos includes the mineral fibers chrysotile, amosite, crocidolite, tremolite, anthophyllite, actinolite and any of these materials that have been chemically treated or altered. Heavy exposures tend to occur in the construction industry and in ship repair, particularly during the removal of asbestos materials due to renovation, repairs, or demolition. Workers are also likely to be exposed during the manufacture of asbestos products (such as textiles, friction products, insulation, and other building materials) and during automotive brake and clutch repair work.

What are the hazards of asbestos?

Asbestos is well recognized as a health hazard and its use is now highly regulated by both OSHA and EPA. Asbestos fibers associated with these health risks are too small to be seen with the naked eye. Breathing asbestos fibers can cause a buildup of scar-like tissue in the lungs called asbestosis and result in loss of lung function that often progresses to disability and death. Asbestos also causes cancer of the lung and other diseases such as mesothelioma of the pleura which is a fatal malignant tumor of the membrane lining the cavity of the lung or stomach. Epidemiologic evidence has increasingly shown that all asbestos fiber types, including the most commonly used form of asbestos, chrysotile, causes mesothelioma in humans.^{1,2,3}

What can be done to reduce the hazards of asbestos?

Worker exposure to asbestos hazards are addressed in specific OSHA standards for the construction industry, general industry and shipyard employment sectors. These standards reduce the risk to workers by requiring that employers provide personal exposure monitoring to assess the risk and hazard awareness training for operations where there is any potential exposure to asbestos. Airborne levels of asbestos are never to exceed legal worker exposure limits. There is no "safe" level of asbestos exposure for any type of asbestos fiber.^{4, 5} Asbestos exposures as short in duration as a few days have caused mesothelioma in humans.^{4, 5, 6, 7} Every occupational exposure to asbestos can cause injury of disease; every occupational exposure to asbestos contributes to the risk of getting an asbestos related disease.⁸ Where there is exposure, employers are required to further protect workers by establishing regulated areas, controlling certain work practices and instituting engineering controls to reduce the airborne levels. The employer is required to ensure exposure is reduced by using administrative controls and provide for the wearing of personal protective equipment. Medical monitoring of workers is also required when legal limits and exposure times are exceeded.

Hazards

Provides references that describe health hazards of asbestos and how to recognize them.

[More »](#)

Evaluating and Controlling Exposure

Provides assistance for evaluating and controlling asbestos exposures.

[More »](#)

Construction

Provides information specific to asbestos in construction.

[More »](#)

Standards

Asbestos is addressed in specific OSHA standards for general industry, maritime, and construction.

[More »](#)

Additional Resources

Provides links and references to additional resources related to asbestos.

[More »](#)

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Highlights

- Asbestos. OSHA Fact Sheet (Publication 3507), (2014). Also available in Spanish.
-  Self-Inspection Checklist. OSHA. Use this checklist to determine compliance to the asbestos standard.

Other Related Topics

- Carcinogens
- Chemical Hazards and Toxic Substances
- Hazardous Waste

¹ "Asbestos (Chrysotile, Amosite, Crocidolite, Tremolite, Actinolite, and Anthophyllite)." World Health Organization (WHO), International Agency for Research on Cancer (IARC) Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 100C, 2012.

² Pira et. al. "Mortality from cancer and other causes in the Balangero cohort of chrysotile asbestos miners." *Occup Environ Med* 2009;66:12 805-809.

³ Wang X, Lin S, et. al. "Cause-specific mortality in a Chinese chrysotile textile worker cohort." JC School of Public Health and Primary Care, The Chinese University of Hong Kong, Hong Kong, China.

⁴ Skammeritz, E. et al. "Asbestos Exposure and Survival in Malignant Mesothelioma: A Description of 122 Consecutive Cases at an Occupational Clinic." *The International Journal of Occupational and Environmental Medicine (IJOEM)*, Vol 2, No 4 October 2011.

⁵ Greenberg M., Davies L, T. A. Mesothelioma Register 1967-68. *British Journal of Industrial Medicine*, 31, 91-104, 1974.

⁶ Asbestos (Actinolite, amosite, anthophyllite, chrysotile, crocidolite, tremolite). World Health Organization (WHO), International Agency for Research on Cancer (IARC) Monographs on the Evaluation of Carcinogenic Risks to Humans, Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42, Supplement 7, 1998.

⁷ Hodgson JT, Darton A. "The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure." Epidemiology and Medical Statistics Unit, Health and Safety Executive, Magdalen House, Stanley Precinct, L20 3QZ, Bootle, UK, 2000.

⁸ Hammar SP, Henderson DW, Klebe S, Dodson RF. "Chapter 43: Neoplasms of the pleura." In: Tomashefski JF Jr., ed. Dail and Hammar's *Pulmonary Pathology*, 3rd Edition. New York: Springer, 2008.

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EXHIBIT 35



WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

Volume 14 Asbestos

Summary of Data Reported and Evaluation

Asbestos

Last updated: 26 March 1998

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ASBESTOS

VOL.: 14 (1977)

5. Summary of Data Reported and Evaluation

5.1 Animal data

All commercial forms of asbestos tested are carcinogenic in mice, rats, hamsters and rabbits. In mice, mesotheliomas were induced following intraperitoneal injection of asbestos fibres. In rats, various types of asbestos produced lung carcinomas and mesotheliomas following their inhalation and mesotheliomas and sarcomas following their intrapleural or intraperitoneal injection. The oral administration of asbestos filter material to rats also resulted in an increased incidence of tumours. Mesotheliomas were produced in hamsters and rabbits after intrapleural injection of a number of types of asbestos fibre.

The size and shape of the fibres influence the incidence of tumours; fibres less than 0.5 µm in diameter are more active in producing tumours. Glass fibres and nemalite of a similar size can also produce mesotheliomas following their intrapleural or intraperitoneal injection in rats.

5.2 Human data

In humans, occupational exposure to chrysotile, amosite, anthophyllite and mixed fibres containing crocidolite has resulted in a high incidence of lung cancer; a predominantly tremolitic material mixed with anthophyllite and small amounts of chrysotile has also caused an increased incidence of lung cancer. Many pleural and peritoneal mesotheliomas have been observed after occupational exposure to crocidolite, amosite and chrysotile. An excess risk of gastrointestinal tract cancers has been demonstrated in groups exposed occupationally to amosite, chrysotile or mixed fibres containing crocidolite. An excess of cancers of the larynx was also observed in exposed workers. Mesotheliomas also occur in individuals living in the neighbourhood of asbestos factories and crocidolite mines and in household contacts of asbestos workers.

Occupational exposure to asbestos may occur during the mining of fibrous minerals, as well as of minerals embodied in rocks, which may contain asbestiform fibres as a contaminant.

Both cigarette smoking and occupational exposure to asbestos fibres independently increase lung cancer incidence, but when they are present together they act in a multiplicative fashion.

The general population may also be exposed to asbestos fibres in air, beverages, drinking-water, food and pharmaceutical and dental preparations and by consumer use of asbestos-containing products. The presence of asbestos and asbestiform minerals from natural sources in the environment, other than mines or quarries, has only recently shown itself to be a further potential problem.

At present, it is not possible to assess whether there is a level of exposure in humans below which an increased risk of cancer would not occur.

Previous evaluation: Vol. 2 (1973)

Subsequent evaluation: Suppl. 7 (1987)

Last updated: 26 March 1998

EXHIBIT 36



Asbestos Exposure and Cancer Risk

What is asbestos?

Asbestos is the name given to six minerals that occur naturally in the environment as bundles of fibers that can be separated into thin, durable threads for use in commercial and industrial applications. These fibers are resistant to heat, fire, and chemicals and do not conduct electricity. For these reasons, asbestos has been used widely in many industries. Additional asbestos-like minerals are found in the natural environment, including erionite.

Chemically, asbestos minerals are silicate compounds, meaning they contain atoms of silicon and oxygen in their molecular structure.

Asbestos minerals are divided into two major groups: Serpentine asbestos and amphibole asbestos. Serpentine asbestos includes the mineral chrysotile, which has long, curly fibers that can be woven. Chrysotile asbestos is the form that has been used most widely in commercial applications. Amphibole asbestos includes the minerals actinolite, tremolite, anthophyllite, crocidolite, and amosite. Amphibole asbestos has straight, needle-like fibers that are more brittle than those of serpentine asbestos and are more limited in their ability to be fabricated ([1](#), [2](#)).

How is asbestos used?

Asbestos has been mined and used commercially in North America since the late 1800s. Its use increased greatly during World War II ([3](#), [4](#)). Since then, asbestos has been used in many industries. For example, the building and construction industries have used it for strengthening cement and plastics as well as for insulation, roofing, fireproofing, and sound absorption. The shipbuilding industry has used asbestos to insulate boilers, steam pipes, and hot water pipes. The automotive industry uses asbestos in vehicle brake shoes and clutch pads. Asbestos has also been used in ceiling and floor tiles; paints, coatings, and adhesives; and plastics. In addition, asbestos has been found in vermiculite-containing garden products and some talc-containing crayons.

In the late 1970s, the U.S. Consumer Product Safety Commission (CPSC) banned the use of asbestos in wallboard patching compounds and gas fireplaces because the asbestos fibers in these products could be released into the environment during use. In addition, manufacturers of electric hairdryers voluntarily stopped using asbestos in their products in 1979. In 1989, the U.S. Environmental Protection Agency (EPA) banned all new uses of asbestos; however, uses developed before 1989 are still allowed. The EPA also established regulations that require school systems to inspect buildings for the presence of damaged asbestos and to eliminate or reduce asbestos exposure to occupants by removing the asbestos or encasing it (2).

In June 2000, the CPSC concluded that the risk of children's exposure to asbestos fibers in crayons was extremely low. U.S. manufacturers of these crayons agreed to eliminate talc from their products.

In August 2000, the EPA conducted a series of tests to evaluate the risk for consumers of adverse health effects associated with exposure to asbestos-contaminated vermiculite. The EPA concluded that exposure to asbestos from some vermiculite products poses only a minimal health risk. The EPA recommended that consumers reduce the low risk associated with the occasional use of vermiculite during gardening activities by limiting the amount of dust produced during vermiculite use. Specifically, the EPA suggested that consumers use vermiculite outdoors or in a well-ventilated area; keep vermiculite damp while using it; avoid bringing dust from vermiculite into the home on clothing; and use premixed potting soil, which is less likely to generate dust (2).

The regulations described above and other actions, coupled with widespread public concern about the health hazards of asbestos, have resulted in a significant annual decline in the U.S. use of asbestos. Domestic consumption of asbestos amounted to about 803,000 metric tons in 1973, but it had dropped to about 360 metric tons by 2015 (3, 5).

What are the health hazards of exposure to asbestos?

People may be exposed to asbestos in their workplace, their communities, or their homes. If products containing asbestos are disturbed, tiny asbestos fibers are released into the air. When asbestos fibers are breathed in, they may get trapped in the lungs and remain there for a long time. Over time, these fibers can accumulate and cause scarring and inflammation, which can affect breathing and lead to serious health problems (6).

Asbestos has been classified as a known human carcinogen (a substance that causes cancer) by the U.S. Department of Health and Human Services (HHS), the U.S. Environmental

Protection Agency (EPA), and the International Agency for Research on Cancer (IARC) (2, 3, 7, 8). According to IARC, there is sufficient evidence that asbestos causes mesothelioma (a relatively rare cancer of the thin membranes that line the chest and abdomen), and cancers of the lung, larynx, and ovary (8). In fact, it is thought that most mesotheliomas are due to asbestos exposure (9). There is limited evidence that asbestos exposure is linked to increased risks of cancers of the stomach, pharynx, and colorectum (8).

Asbestos exposure may also increase the risk of asbestosis (an inflammatory condition affecting the lungs that can cause shortness of breath, coughing, and permanent lung damage) and other nonmalignant lung and pleural disorders, including pleural plaques (changes in the membranes surrounding the lung), pleural thickening, and benign pleural effusions (abnormal collections of fluid between the thin layers of tissue lining the lungs and the wall of the chest cavity). Although pleural plaques are not precursors to lung cancer, evidence suggests that people with pleural disease caused by exposure to asbestos may be at increased risk for lung cancer (2, 10).

Erionite has also been classified as a known human carcinogen by IARC (8) and by HHS (3). It is [not currently regulated](#) by the EPA.

Who is at risk for an asbestos-related disease?

Everyone is exposed to asbestos at some time during their life. Low levels of asbestos are present in the air, water, and soil. However, most people do not become ill from their exposure. People who become ill from asbestos are usually those who are exposed to it on a regular basis, most often in a job where they work directly with the material or through substantial environmental contact.

Since the early 1940s, millions of American workers have been exposed to asbestos. Health hazards from asbestos fibers have been recognized in workers exposed in the shipbuilding trades, asbestos mining and milling, manufacturing of asbestos textiles and other asbestos products, insulation work in the construction and building trades, and a variety of other trades. Demolition workers, drywall removers, asbestos removal workers, firefighters, and automobile workers also may be exposed to asbestos fibers. Studies evaluating the cancer risk experienced by automobile mechanics exposed to asbestos through brake repair are limited, but the overall evidence suggests there is no safe level of asbestos exposure (3, 8). As a result of government regulations and improved work practices, today's workers (those without previous exposure) are likely to face smaller risks than did those exposed in the past.

Individuals involved in the rescue, recovery, and cleanup at the site of the September 11, 2001, attacks on the World Trade Center (WTC) in New York City are another group at risk of developing an asbestos-related disease. Because asbestos was used in the construction of the North Tower of the WTC, when the building was attacked, hundreds of tons of asbestos were released into the atmosphere. Those at greatest risk include firefighters, police officers, paramedics, construction workers, and volunteers who worked in the rubble at Ground Zero. Others at risk include residents in close proximity to the WTC towers and those who attended schools nearby. These individuals will need to be followed to determine the long-term health consequences of their exposure (11). However, it is important to note that any symptoms these individuals experience may be related to exposure to debris components other than asbestos.

Although it is clear that the health risks from asbestos exposure increase with heavier exposure and longer exposure time, investigators have found asbestos-related diseases in individuals with only brief exposures. Generally, those who develop asbestos-related diseases show no signs of illness for a long time after exposure. It can take from 10 to 40 years or more for symptoms of an asbestos-related condition to appear (2).

There is some evidence that family members of workers heavily exposed to asbestos face an increased risk of developing mesothelioma (12). This risk is thought to result from exposure to asbestos fibers brought into the home on the shoes, clothing, skin, and hair of workers. To decrease these exposures, Federal law regulates workplace practices to limit the possibility of asbestos being brought home in this way. Some employees may be required to shower and change their clothes before they leave work, store their street clothes in a separate area of the workplace, or wash their work clothes at home separately from other clothes (2).

Cases of mesothelioma have also been seen in individuals without occupational asbestos exposure who live close to asbestos mines (12).

What factors affect the risk of developing an asbestos-related disease?

Several factors can help to determine how asbestos exposure affects an individual, including:

- Dose (how much asbestos an individual was exposed to)
- Duration (how long an individual was exposed)

- Size, shape, and chemical makeup of the asbestos fibers
- Source of the exposure
- Individual risk factors, such as smoking and pre-existing lung disease
- Genetic factors, such as having a germline mutation in *BAP1* (13)

Although all forms of asbestos are considered hazardous, different types of asbestos fibers may be associated with different health risks. For example, the results of several studies suggest that amphibole forms of asbestos may be more harmful than chrysotile, particularly for mesothelioma risk, because they tend to stay in the lungs for a longer period of time (1, 2).

How does smoking affect risk?

Many studies have shown that the combination of smoking and asbestos exposure is particularly hazardous. Smokers who are also exposed to asbestos have a risk of developing lung cancer that is greater than the individual risks from asbestos and smoking added together (3, 6). There is evidence that quitting smoking will reduce the risk of lung cancer among asbestos-exposed workers (4). Smoking combined with asbestos exposure does not appear to increase the risk of mesothelioma (10). However, people who were exposed to asbestos on the job at any time during their life or who suspect they may have been exposed should not smoke.

How are asbestos-related diseases detected?

Individuals who have been exposed (or suspect they have been exposed) to asbestos fibers on the job, through the environment, or at home via a family contact should inform their doctor about their exposure history and whether or not they experience any symptoms. The symptoms of asbestos-related diseases may not become apparent for many decades after the exposure. It is particularly important to check with a doctor if any of the following symptoms develop:

- Shortness of breath, wheezing, or hoarseness
- A persistent cough that gets worse over time
- Blood in the sputum (fluid) coughed up from the lungs
- Pain or tightening in the chest
- Difficulty swallowing

- Swelling of the neck or face
- Loss of appetite
- Weight loss
- Fatigue or anemia

A thorough physical examination, including a chest x-ray and lung function tests, may be recommended. The chest x-ray is currently the most common tool used to detect asbestos-related diseases. Although chest x-rays cannot detect asbestos fibers in the lungs, they can help identify any early signs of lung disease resulting from asbestos exposure (2).

A lung biopsy, which detects microscopic asbestos fibers in pieces of lung tissue removed by surgery, is the most reliable test to confirm exposure to asbestos (2). A bronchoscopy is a less invasive test than a biopsy and detects asbestos fibers in material that is rinsed out of the lungs (2). It is important to note that these procedures cannot determine how much asbestos an individual may have been exposed to or whether disease will develop. Asbestos fibers can also be detected in urine, mucus, and feces, but these tests are not reliable for determining how much asbestos may be in an individual's lungs (2).

How can workers protect themselves from asbestos exposure?

The **Occupational Safety and Health Administration (OSHA)** is a component of the U.S. Department of Labor (DOL) and is the Federal agency responsible for health and safety regulations in maritime, construction, manufacturing, and service workplaces. OSHA established regulations dealing with asbestos exposure on the job, specifically in construction work, shipyards, and general industry, that employers are required to follow. In addition, the **Mine Safety and Health Administration (MSHA)**, another component of DOL, enforces regulations related to mine safety. Workers should use all protective equipment provided by their employers and follow recommended workplace practices and safety procedures. For example, National Institute for Occupational Safety and Health (NIOSH)-approved respirators that fit properly should be worn by workers when required.

Workers who are concerned about asbestos exposure in the workplace should discuss the situation with other employees, their employee health and safety representative, and their employers. If necessary, OSHA can provide more information or make an inspection. Information about regional offices can also be found on OSHA's website at <https://www.osha.gov/html/RAmap.html>.

More information about asbestos is available on OSHA's [Asbestos](#) page, which has links to information about asbestos in the workplace, including what OSHA standards apply, the hazards of asbestos, evaluating asbestos exposure, and controls used to protect workers. OSHA's national office can be contacted at:

Office of Public Affairs
Occupational Safety and Health Administration
U.S. Department of Labor

202-693-1999

1-800-321-6742 (1-800-321-OSHA)

1-877-889-5627 (TTY)

<https://www.osha.gov/workers> (workers' page)

Mine workers can contact MSHA at:

Office of Public Affairs
Mine Safety and Health Administration
U.S. Department of Labor

202-693-9400

<https://www.msha.gov>

<https://www.msha.gov/support-resources/forms-online-filing/2015/10/15/hazardous-condition-complaint> (Hazardous Condition Complaint)

The National Institute for Occupational Safety and Health (NIOSH), which is part of the Centers for Disease Control and Prevention (CDC), is another Federal agency that is concerned with asbestos exposure in the workplace. NIOSH conducts asbestos-related research, evaluates work sites for possible health hazards, and makes exposure control recommendations. In addition, NIOSH distributes publications on the health effects of asbestos exposure and can suggest additional sources of information. NIOSH can be contacted at:

Education and Information Division
Information Resources Branch
National Institute for Occupational Safety and Health

1-800-CDC-INFO (1-800-232-4636)

<https://www.cdc.gov/niosh>

What programs are available to help individuals with

asbestos-related diseases?

Some people with asbestos-related illness may be eligible for **Medicare** coverage. Information about benefits is available from Medicare's [Regional Offices](#), located in 10 major cities across the United States and serving specific geographic areas. The Regional Offices serve as the agency's initial point of contact for beneficiaries, health care providers, state and local governments, and the general public. General information about Medicare is available by calling toll-free 1-800-633-4227 (1-800-MEDICARE) or by visiting the Medicare [website](#).

People with occupational asbestos-related diseases also may qualify for financial help, including medical payments, under state workers' compensation laws. Because eligibility requirements vary from state to state, workers employed by private companies or by state and local government agencies should contact their state workers' compensation board. Contact information for state workers' compensation officials may be found at the U.S. Department of Labor (DOL) [website](#).

If exposure occurred during employment with a Federal agency, medical expenses and other compensation may be covered by the **Federal Employees' Compensation Program**, which is administered by the DOL **Employment Standards Administration's Office of Workers' Compensation Programs**. This program provides workers' compensation benefits to Federal (civilian) employees for employment-related injuries and diseases. Benefits include wage replacement, payment for medical care, and, where necessary, medical and vocational rehabilitation assistance in returning to work. Benefits may also be provided to dependents if the injury or disease causes the employee's death.

In addition, the **Longshore and Harbor Workers' Compensation Program** provides benefits to longshoremen, harbor workers, other maritime workers, and other classes of private industry workers who are injured during the course of employment or suffer from diseases caused or worsened by conditions of employment. Information about eligibility and how to file a claim for benefits under either of these programs is available from:

Office of Workers' Compensation Programs
Employment Standards Administration
U.S. Department of Labor

1-866-692-7487 (1-866-OWCP-IVR)

202-693-0040 (**Federal Employees' Compensation Program**)

202-693-0038 (**Longshore and Harbor Workers' Compensation Program**)

<https://www.dol.gov/owcp>

Eligible veterans may receive health care at a **Department of Veterans Affairs (VA)** Medical Center for an asbestos-related disease. Veterans can receive treatment for service-connected and nonservice-connected medical conditions. Information about eligibility and benefits is available from the VA Health Benefits Service Center at 1-877-222-8387 (1-877-222-VETS) or on the VA [website](#).

What other organizations offer information related to asbestos exposure?

The organizations listed below can provide more information about asbestos exposure.

The **Agency for Toxic Substances and Disease Registry (ATSDR)** is the principal Federal agency responsible for evaluating the human health effects of exposure to hazardous substances. This agency works in close collaboration with local, state, and other Federal agencies, with tribal governments, and with communities and local health care providers to help prevent or reduce harmful human health effects from exposure to hazardous substances. The ATSDR provides information about asbestos and where to find occupational and environmental health clinics. The ATSDR can be contacted at:

Agency for Toxic Substances and Disease Registry

1-800-232-4636 (1-800-CDC-INFO)

1-888-232-6348 (TTY)

<https://www.atsdr.cdc.gov/>

The **U.S. Environmental Protection Agency (EPA)** regulates the general public's exposure to asbestos in buildings, drinking water, and the environment. The EPA offers a Toxic Substances Control Act (TSCA) Hotline and an Asbestos Ombudsman. The TSCA Hotline provides technical assistance and information about asbestos programs implemented under the TSCA, which include the Asbestos School Hazard Abatement Act and the Asbestos Hazard Emergency Response Act. The Asbestos Ombudsman focuses on asbestos in schools and handles questions and complaints. Both the TSCA Hotline and the Asbestos Ombudsman can provide publications on a number of topics, particularly on controlling asbestos exposure in schools and other buildings. The Ombudsman operates a toll-free hotline for small businesses, trade associations, and others seeking free, confidential help.

The EPA website includes a list of EPA [state asbestos contacts](#). In addition, EPA's [Asbestos](#) page provides links to information about asbestos and its health effects, including suggestions for homeowners who suspect asbestos in their homes, and laws and regulations applicable to asbestos. Questions may be directed to:

U.S. Environmental Protection Agency

202-554-1404 (TSCA Hotline)

1-800-368-5888 (Asbestos Ombudsman)

<https://www.epa.gov/asbestos>

Another EPA resource that may be of interest is the brochure titled *Current Best Practices for Preventing Asbestos Exposure Among Brake and Clutch Repair Workers*. Released in April 2007, this brochure includes work practices for both automotive professionals and home mechanics that may be used to avoid asbestos exposure. It also summarizes existing OSHA regulatory requirements for professional auto mechanics.

The **U.S. Consumer Product Safety Commission (CPSC)** is responsible for protecting the public from unreasonable risks of serious injury or death from more than 15,000 types of consumer products, including asbestos, under the agency's jurisdiction. The CPSC maintains a toll-free 24-hour hotline where callers can obtain product safety and other agency information and report unsafe products. In addition, CPSC publications provide guidelines for repairing and removing asbestos, and general information about asbestos in the home. CPSC can be contacted at:

Office of Information and Public Affairs

U.S. Consumer Product Safety Commission

(301) 504-7923 (M-F 8 am - 4:30 pm ET)

1-800-638-2772 (Hotline)

301-595-7054 (TTY)

<https://www.cpsc.gov/>

Individuals can also contact their local or state health department with questions or concerns about asbestos.

Selected References

1. Agency for Toxic Substances and Disease Registry. *Public Health Statement for Asbestos*. September 2001. Retrieved April 18, 2017.
2. Agency for Toxic Substances and Disease Registry. *Toxicological Profile for Asbestos*. September 2001. Retrieved April 18, 2017.
3. National Toxicology Program. *Asbestos*. In: *Report on Carcinogens. Fourteenth Edition*. U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program, 2016.
4. Ullrich RL. Etiology of cancer: Physical factors. In: DeVita VT Jr., Hellman S, Rosenberg SA, editors. *Cancer: Principles and Practice of Oncology*. Vol. 1 and 2. 7th ed. Philadelphia:

Lippincott Williams and Wilkins, 2004.

5. U.S. Geological Survey. [Mineral Commodity Summaries, January 2016: Asbestos](#). Retrieved April 18, 2017.
6. Agency for Toxic Substances and Disease Registry. [Health Effects of Asbestos](#). Retrieved April 18, 2017.
7. U.S. Environmental Protection Agency. [Health Effects Assessment for Asbestos](#). September 1984. EPA/540/1-86/049 (NTIS PB86134608). Retrieved April 18, 2017.
8. IARC Working Group on the Evaluation of Carcinogenic Risk to Humans. [Arsenic, Metals, Fibres and Dusts](#). Lyon (FR): International Agency for Research on Cancer; 2012. (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, No. 100C.)
9. Robinson BM. Malignant pleural mesothelioma: An epidemiological perspective. *Annals of Cardiothoracic Surgery* 2012; 1(4):491–496. [\[PubMed Abstract\]](#)
10. O'Reilly KMA, McLaughlin AM, Beckett WS, et al. Asbestos-related lung disease. *American Family Physician* 2007; 75(5):683–688. [\[PubMed Abstract\]](#)
11. Landrigan PJ, Liroy PJ, Thurston G, et al. Health and environmental consequences of the World Trade Center disaster. *Environmental Health Perspectives* 2004; 112(6):731–739. [\[PubMed Abstract\]](#)
12. Goldberg M, Luce D. The health impact of nonoccupational exposure to asbestos: What do we know? *European Journal of Cancer Prevention* 2009; 18(6):489–503. [\[PubMed Abstract\]](#)
13. Testa JR, Cheung M, Pei J, et al. Germline BAP1 mutations predispose to malignant mesothelioma. *Nature Genetics* 2011; 43(10):1022–1025. [\[PubMed Abstract\]](#)

Related Resources

[Lung Cancer—Patient Version](#)

[Malignant Mesothelioma—Patient Version](#)

Updated: November 29, 2021

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EXHIBIT 37

NIOSH

REVISED RECOMMENDED ASBESTOS STANDARD



U. S. DEPARTMENT OF HEALTH, EDUCATION, AND
WELFARE
Public Health Service
Center for Disease Control
National Institute for Occupational Safety and Health

REVISED RECOMMENDED ASBESTOS STANDARD



**U. S. DEPARTMENT OF HEALTH, EDUCATION, AND
WELFARE
Public Health Service
Center for Disease Control
National Institute for Occupational Safety and Health**

DECEMBER 1976

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V. BASIS FOR THE RECOMMENDED STANDARD

The first modern approach to the setting of an asbestos standard was proposed by the British Occupational Hygiene Society (BOHS 1968) in terms of fiber concentration. In 1968, a subcommittee of the Society evaluated data on 290 men at work in an asbestos factory. These data were provided by company sources. All the men had been employed after January 1933, following implementation of dust control measures mandated by the Factory Inspectorate in 1931. Estimates of the fiber exposure of these workmen were also provided by the company. Of the 290 individuals, 8 were stated to have x-ray evidence of asbestos disease and 16 had rales. Noteworthy in the 1968 data was the preponderance of individuals who had been employed less than 20 years. Only 118 of the 290 persons had worked for longer than 20 years and a scant 13 has been employed for 30 or more years.

After a review of these data, the BOHS proposed a standard which was adopted with minor modifications by the British government in 1969, and implemented in May 1970. All fibers between 5 and 100 microns in length were counted by light microscopy. The standard required no action to be taken below .2 fibers/cc. Between 2 fibers/cc and 12 fibers/cc, control measures commensurate with the exposure circumstances (time and frequency of worker exposure) were prescribed; above 12 fibers/cc, full application of control measures, including respiratory protection, was mandatory. The BOHS predicted that the risk of being affected, to the extent of having the earliest clinical signs of asbestos exposure (rales), would be less than 1% for an accumulated exposure of 100 fiber-years/cc (2 fibers/cc for 50

years, 4 fibers/cc for 25, etc). Data (Lewinsohn, 1972) from the same factory which formed the basis for the BOHS standard demonstrate that a greater prevalence of abnormalities now exist (Table V-1). These data, in addition to demonstrating a dose-response relationship for radiographically detected abnormalities consistent with asbestosis, further showed a 17% prevalence of abnormal radiographic findings (6% consistent with asbestosis) in individuals employed since 1950.

Weill et al (1975), when considering lung function and irregular small opacities, reported that there was little evidence of a dose-response relationship below 100 mppcf-years. They further concluded that a concentration of 5 fibers/cc could be cautiously considered as "safe". Ayer and Berg (1976), however, reported data which suggest that the BOHS standard, of an average cumulative exposure of 100 fiber-years/cc, for chrysotile asbestos may prevent significant decreases in pulmonary function only when combined with periodic spirometry and further reduction of exposure for affected workers. Holmes (1973) has since stated that the data upon which the BOHS standard was based were inadequate to set a standard to prevent asbestosis. The BOHS-recommended standard of 2 fibers/cc was based on data related only to asbestosis and the Society clearly cautioned that, since a quantitative relationship between asbestos exposure and cancer risk was not known, it was not possible at that time to specify an air concentration which was known to be free of increased cancer risk. (BOHS 1968)

Howard et al (1976), in a follow-up examination of the textile workers previously studied by Doll (1955) and Knox et al (1965, 1968) for cancer, and by Lewinsohn (1972) for asbestosis, reported a statistically

significant increase in the risk of developing lung cancer (1.8 times the expected) among those first entering scheduled areas from 1933 to 1950. In the same study, they also reported an excess of deaths due to lung cancer (1.9 times the expected) after 15 or more years from initial exposure among those who started work subsequent to 1950, a period of improved industrial engineering control technology and regulation.

In a study of miners exposed to amphibole fibers (amosite) in the cummingtonite-grunerite ore series, with airborne concentrations of less than 2.0 fibers/cc (average concentration, 0.25 fibers/cc) and 94% of the fibers shorter than 5 μ m in length, Gillam et al (1976) have demonstrated threefold increases in the risks of mortality from both malignant and nonmalignant respiratory diseases.

Newhouse (1969, 1973) and Newhouse et al (1972) have shown that the cancer risk to factory workers following mixed exposure to chrysotile, amosite, and crocidolite is dose-related. The women reported to have heavier exposures (as judged by their occupations) showed a sixfold excess of cancer following only 15 years' latency, whereas those with moderate or low exposures required 25 years' latency to demonstrate an excess. The rate of mesothelioma increased with both the severity and the length of exposure. However, even with as little as two years of asbestos exposure, six mesotheliomas occurred among female employees.

McDonald (1973) stated that the risk of developing lung cancer was essentially confined to persons with a dust index above 200 mppcf-years, and Enterline et al (1973) showed no direct dose-response for respiratory cancer below 125 mppcf-years. In a review of these two papers, Schneiderman (1974) concluded that, instead of being consistent with a

threshold level at which no cancer risk exists, these data did not provide evidence for a threshold or for a "safe" level of exposure. He pointed out that in the paper by Enterline et al (1973) there is no dose group for which the Standardized Mortality Ratio (SMR) is below 100 (100 = normal), but that the 95% confidence limits on the SMR's included 100 for two of the three dose groups below 125 mppcf-years. One of the dose groups (25-62.4) had a statistically significant excess mortality from lung cancer, whereas for the other two this mortality rate was insignificantly elevated above the expected values. Regarding McDonald's paper, Schneiderman stated that it is hard to determine what is excess since no expected numbers for each group were given upon which to base this comparison.

Among amosite workers with employment of 3 months or less, Selikoff (1976) reported excess cancer risks of 3.87, 1.68, and 1.65 times those expected for cancer of the lung, colon and rectum, and all sites, respectively.

Anderson et al (1976) have reported a significant excess of radiographic abnormalities of the chest characteristic of asbestos exposure (pleural and/or parenchymal) 25 - 30 years after the onset of household contamination. These abnormalities were observed in 35% of 326 otherwise healthy workers who had household contacts with amosite asbestos. In addition, four pleural mesotheliomas were found in this group.

VI. THE RECOMMENDED STANDARD

Available studies provide conclusive evidence that exposure to asbestos fibers causes cancer and asbestosis in man. Lung cancers and asbestosis have occurred following exposure to chrysotile, crocidolite, amosite, and anthophyllite. Mesotheliomas, lung and gastrointestinal cancers have been shown to be excessive in occupationally exposed persons, while mesotheliomas have developed also in individuals living in the neighborhood of asbestos factories and near crocidolite deposits, and in persons living with asbestos workers. Asbestosis has been identified among persons living near anthophyllite deposits.

Likewise, all commercial forms of asbestos are carcinogenic in rats, producing lung carcinomas and mesotheliomas following their inhalation, and mesotheliomas after intrapleural or ip injection. Mesotheliomas and lung cancers were induced following even 1 day's exposure by inhalation.

The size and shape of the fibers are important factors; fibers less than 0.5 μm in diameter are most active in producing tumors. Other fibers of a similar size, including glass fibers, can also produce mesotheliomas following intrapleural or ip injection.

There are data that show that the lower the exposure, the lower the risk of developing cancer. Excessive cancer risks have been demonstrated at all fiber concentrations studied to date. Evaluation of all available human data provides no evidence for a threshold or for a "safe" level of asbestos exposure.

In view of the above, the standard should be set at the lowest level detectable by available analytical techniques, an approach consistent with NIOSH's most recent recommendations for other carcinogens (ie, arsenic and vinyl chloride). Such a standard should also prevent the development of asbestosis.

Since phase contrast microscopy is the only generally available and practical analytical technique at the present time, this level is defined as 100,000 fibers $>5 \mu\text{m}$ in length/ m^3 (0.1 fibers/cc), on an 8-hour-TWA basis with peak concentrations not exceeding 500,000 fibers $>5 \mu\text{m}$ in length/ m^3 (0.5 fibers/cc) based on a 15-minute sample period. Sampling and analytical techniques should be performed as specified by NIOSH publication USPHS/NIOSH Membrane Filter Method for Evaluating Airborne Asbestos Fibers - T.R. 84 (1976).

This recommended standard of 100,000 fibers $>5 \mu\text{m}$ in length/ m^3 is intended to (1) protect against the noncarcinogenic effects of asbestos, (2) materially reduce the risk of asbestos-induced cancer (only a ban can assure protection against carcinogenic effects of asbestos) and (3) be measured by techniques that are valid, reproducible, and available to industry and official agencies.

However, some difficulties arise in that specific work practices and innovative engineering control or process changes are needed. But because of the well-documented human carcinogenicity from all forms of asbestos, these difficulties should not be cited as cause for permitting continued exposure to asbestos at concentrations above 100,000 fibers $>5 \mu\text{m}$ in length/ m^3 .

This standard was not designed for the population-at-large, and any extrapolation beyond general occupational exposures is not warranted. The standard was designed only for the processing, manufacturing, and use of asbestos and asbestos-containing products as applicable under the Occupational Safety and Health Act of 1970.

REFERENCES FOR CHAPTERS V AND VI

1. 1969 Standard for asbestos dust concentration for use with the asbestos regulations. Department of Employment and Productivity, Her Majesty's Factory Inspectorate. Technical Note 13, 1970
2. Lewinsohn HC (1972): The medical surveillance of asbestos workers. Soc Health 92:69
3. Weill H, Ziskind MM, Waggenspack C, Possiter CE (1975): Lung function consequences of dust exposure in asbestos cement manufacturing plants. Arch Environ Health 30:248-52
4. Ayer H, Berg J (1976): Cumulative asbestos exposure and forced vital capacity. Submitted for publication to Arch Environ Health
5. Holmes S (1973): Environmental data in industry, in Bogovski P, Timbrell V, Gilson JC, Wagner JC (eds): Proceedings of the Conference on Biological Effects of Asbestos. Lyon, pp 135
6. Newhouse ML (1969): A study of the mortality of workers in an asbestos factory. Br J Ind Med 26:294
7. Newhouse ML (1973): Cancer among workers in the asbestos textile industry, in Bogovski P, Gilson JC, Timbrell V, Wagner JC (eds): Proceedings of the Conference on Biological Effects of Asbestos. Lyon, pp 203
8. Newhouse ML, Berry G, Wagner JC, Turok ME (1972): A study of the mortality of female asbestos workers. Br J Ind Med 29:134
9. Howard S, Kimben LJ, Lewinsohn HC, Peto J, Doll R (1976); A Mortality Study among Workers in an English Asbestos Factory. Oxford University, (in press)
10. Doll R (1955): Mortality from lung cancer in asbestos workers. Br J Ind Med 12:81-86
11. Knox JF, Doll RS, Hill ID (1965): Cohort analysis of changes in incidence of bronchial carcinoma in a textile asbestos factory. Am NY Acad Sci 132:526-35
12. Knox JF, Holms S, Doll R, Hill ID (1968): Mortality from lung cancer and other causes among workers in an asbestos textile factory. Br J Ind Med 25:293-303
13. Gillam JD, Dement JM, Lemen RA, Wagoner JK, Archer VE, Beljer HP (1976): Mortality patterns among hard rock gold miners exposed to an asbestiform mineral. Ann NY Acad Sci 271:336-44

TABLE VI-1

B.O.H.S. ASBESTOS STANDARD
 X-RAY FINDINGS IN AN ASBESTOS TEXTILE FACTORY
 DECEMBER 1970 (MALES)

Years of Exposure	No.	X-ray Findings			
		Normal	Pleural Fibrosis*	Pulmonary Fibrosis	Total Abnormal**
0 - 9	613	548	10	0	65(11%)
10 - 19	189	122	18	20	67(36%)
20 - 29	114	51	30	21	63(55%)
30 - 39	42	9	17	17	33(78%)
40 - 49	12	2	6	3	10(83%)

* Consistent with asbestos exposure

**Including changes not considered due to asbestos exposure

Adapted from reference 2

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HEALTH, EDUCATION, AND WELFARE
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EXHIBIT 38

WHO

Chapter 6.2

Asbestos

General Description

The term “asbestos” designates a group of naturally occurring fibrous serpentine or amphibole minerals that have extraordinary tensile strength, conduct heat poorly and are relatively resistant to chemical attack. The principal varieties of asbestos are chrysotile, a serpentine mineral, and crocidolite, amosite, anthophyllite, tremolite and actinolite, all of which are amphiboles.^a

Chrysotile fibres consist of aggregates of long, thin, flexible fibrils that resemble scrolls or cylinders of uniform chemical composition. Although chrysotile is a reasonably well defined mineral, the five amphibole asbestiform fibres have such variable chemical compositions and physical properties that positive identification is sometimes troublesome.

The macroscopic asbestos fibres are actually bundles of thinner fibres made up of fibrils which, in the case of chrysotile, have a diameter of 20-25 nm. Each macroscopic fibre is highly anisotropic and tends to decompose into its thinner constituents under industrial handling or from weathering, giving rise to a fibrous, partially respirable aerosol.

Sources

Natural sources are important, because asbestos minerals are widely spread throughout the earth's crust and are not restricted to the few mineable deposits. In particular, chrysotile is present in most serpentine rock formations. Emissions are due to natural weathering and can be enhanced by man's activities, such as quarrying or street building. Very little, however, is known about the amounts emitted from natural sources.

Man-made emissions originate from activities in the following categories:

- (a) mining and milling
- (b) manufacture of products
- (c) construction activities
- (d) transport and use of asbestos-containing products
- (e) disposal.

There has been a steep rise in the production and use of asbestos in the last 100 years. Asbestos consumption has levelled off in recent years (1) to about 4 million tonnes (1983) and, because of the relative decline in crocidolite and amosite usage (1) the figure represents essentially chrysotile production (in 1982 only about 5% of the total asbestos produced was in the form of amphibole asbestos (crocidolite and amosite) (2)).

In many industrialized countries most of the asbestos used was in the building sector (70-90% in several western European countries) (2), and the demand for asbestos in these

^a Man-made mineral fibres and other natural mineral fibres such as fibrous zeolites, wollastonite, attapulgite and sepiolite will not be discussed here.

countries had already reached a constant level before the health effects of asbestos were widely debated. Because of its specific technical properties, asbestos has found an extremely large variety of applications (in about 3000 different products). In the future, legislative restrictions and the success in finding substitutes for asbestos in fibre-cement, brake-linings, insulation and many other applications will most probably lead to declining asbestos consumption in the above-mentioned countries.

Asbestos emissions occur during processing. When air filtration is used, the dust emissions from processing can be kept below 100 g per tonne (3).

Rain acidity (from carbon dioxide and air pollutants) is known to corrode asbestos-cement sheets, constituting a further source of emission (4). Brake-linings in cars are another source in the urban environment. Only a few measurements have been made of the contribution made by these sources to fibre emissions in urban air (5,6).

Indoor asbestos fibre concentrations can be considerably higher than outdoor concentrations (7). Indoor asbestos dust originates from insulation material sprayed on steelwork or ceilings (such material may become highly friable after some years), asbestos plasters, low-weight insulation plates, etc. (8,9). Sometimes such materials have been used in direct or close contact with air-conditioning equipment. Even though some of these materials, such as spray asbestos, are no longer used, they are still found in many public buildings. Until the mid-1970s electric storage-heaters and some other electrical household equipment contained asbestos. One of the main forms of use of asbestos is as asbestos-cement; in this case the release of fibres to the general environment is minimized, since the fibres are essentially "locked" in the cement matrix. Asbestos cement products, therefore, do not usually pose problems for indoor air quality.

Factors such as renovation and repair, maintenance, external vibrations and vandalism can considerably increase the emission of asbestos dust from existing indoor sources (10,11). Increased emission is also possible as a result of changes in temperature and reduction of humidity.

Unlike levels of asbestos fibres in ambient air, fibre concentrations in the air of indoor environments can always be related to their source, thus offering the possibility of modifying or removing the source of emission. Because people in temperate climates live indoors most of the time, the most relevant source of inhalation exposure will often be asbestos fibre concentrations in buildings.

Occurrence in air

Asbestos fibres of respirable size form part of a range of fibrous aerosols in the lower atmosphere. Other fibres include man-made mineral fibres, fibrous silica and aluminium oxide, fibrous gypsum and, in some geographical areas, fibrous zeolite, attapulgite, sepiolite and wollastonite (1).

Once emitted into the atmosphere, asbestos fibres may travel considerable distances owing to their aerodynamic properties. Because no chemical breakdown of the fibres occurs, washout by rain or snow is the only cleaning mechanism.

Asbestos fibres normally constitute only a relatively small fraction of the total fibrous aerosol in ambient air (6,12). The biologically more important so-called "critical" fibres are those equal to or longer than 5 µm and having diameters up to 3 µm (1,10,12) with an aspect ratio equal to or greater than 3 : 1.

Although asbestos fibres can be readily detected and monitored in occupational situations by using phase-contrast optical microscopy, their assessment in the environment calls for an integrated method capable of microchemical analysis of single fibres, measurement of fibre length and diameter, and counts of fibre numbers in given air samples. Electron microscopy is the only method which can detect and identify asbestos fibres among the very wide range

of other fibrous and nonfibrous particles, of greatly varying toxic potency, in the ambient air. Used in conjunction with each other, these methods allow the identification of samples. In order positively to identify asbestos fibres in environmental ambient air it is necessary to use selected-area electron diffraction and/or energy-dispersive X-ray diffraction analysers attached to an electron microscope. Such instrumentation is costly and highly-trained personnel are required in order to obtain reliable results. Although integrated electron microscopy methods have been developed during the last 15 years (13), they are still not in widespread use. Therefore, all data measured by these methods are, strictly speaking, representative only for the location tested and the time interval chosen. However, if one compares various sets of such data and restricts quantification to orders of magnitude, the following concentration pattern emerges:^b

Rural areas (remote from asbestos emission sources):

- below 100 F/m³ (6,10)

Urban areas:

- general levels may vary from below 100 to 1000 F/m³ (6,12)

Near various emission sources the following figures have been measured as yearly averages (6,12,14):

- downwind from an asbestos-cement plant at 300 m: 2200 F/m³; at 700m: 800 F/m³; at 1000 m: 600 F/m³ (6);
- at a street crossing with heavy traffic, 900 F/m³ (14);
- on an express-way, up to 3300 F/m³ (9)

Indoor air:

- in buildings without specific asbestos sources, concentrations are generally below 1000 F/m³ (12);
- in buildings with friable asbestos, concentrations vary irregularly; usually less than 1000 F*/m³ are found, but in some cases exposure reaches 10 000 F*/m³ (9), where F* = fibres counted with an optical microscope.

Occupational levels are orders of magnitude higher than those found in the environment, with values from 10⁵ F*/m³ to more than 10⁸ F*/m³ (12,15), but are now being reduced to below 2 × 10⁶ F*/m³ in most countries and to (0.2-0.5) × 10⁶ F*/m³ in some.

^b Note. If not otherwise stated, concentrations in the following text are given as numbers of critical asbestos fibres per m³, i.e. all fibres of length L > 5 µm, diameter D < 3 µm and aspect ratio L : D > 3 : 1 measured by electron microscopy methods. All concentrations are expressed as fibres per m³ air, although concentrations in terms of fibres per litre and fibres per ml are often reported. Some studies have been carried out where results have been expressed as ng or µg per m³ air. Because only results such as fibre number concentrations are considered to be directly relevant to an index of exposure with regard to possible health implications (1,12) and factors in attempts to convert mass to number concentrations are so variable (12), mass concentrations are not considered here.

Routes of Exposure

Air

Various subgroups of the population are exposed to different fibre concentrations for varying lengths of time. It is usually assumed that the risks of any two persons are roughly comparable - other factors being equal - if their accumulated fibre burdens are the same. The fibre burden is the accumulated number of critical fibres (F) = fibre concentration (F/m^3) $\times$ number of years of exposure $\times$ air volume inhaled each year at place of exposure ($m^3/year$). In this context it is important to note that not all fibres inhaled are deposited and available for retention in the body. However, it is assumed that the fraction of fibres exhaled is more or less the same during all inhalation exposures. Assuming a breathing rate of $10 m^3$ for an 8-hour working day and 200 working days per year, a worker inhales $2000 m^3$ per year during working hours, while total inhalation for the general population is $7300 m^3$ per year (10).

Table 1 gives orders of magnitude of lifetime fibre burdens in various population subgroups, thus indicating the relative importance of different types of inhalation exposure (10,16). Values for indoor air exposure have not been included because only a few are available and details are insufficient. Only for the USA has a calculation of indoor concentration been made in terms of average fibre concentration. The median values range from $400 F/m^3$ (10) to $500 F/m^3$ (12). If these estimates were correct, they would result in a lifetime fibre burden of up to $2 \times 10^8 F$. In this case outdoor exposure would be of minor importance to most of the US population.

There can also be more irregular exposure of the general public, with peak concentrations at specific sites. Table 1 shows that such exposure for 1% of a lifetime (0.24 hours per day) could contribute significantly to the total accumulated burden of fibres. Peak exposures in people passing building sites have been reported by several authors. These exposures occurred when asbestos-cement sheets were being cut (16) or spray insulation was being carried out (17); in these cases no dust suppression measures were applied. Peak exposures may also occur in para-occupational situations (e.g. household activities (18)).

Table 1. Lifetime fibre burdens typical for industrial countries

Population ^a (%)	Subgroup	Fibre concentration (F/m^3) ^b	Exposure time (years)	Inhaled volume ($m^3/year$)	Accumulated critical fibres ($F > 5 \mu m$)
70	Urban population (moderate exposure)	30	70	7300	$\sim 1.5 \times 10^7$
25	Rural population	10	70	7300	$10^5 - 10^6$
5	Urban population (high exposure)	200	70	7300	$\sim 10^8$
1-2	General construction workers	$10^3 - 10^5$ ^c	50	2000	$10^8 - 10^{10}$ ^c
0.1	Asbestos workers	$10^5 - 10^6$ ^c	50	2000	$10^{10} - 10^{11}$ ^c
	Irregular exposure (example)	10^4	0.7	7300	5×10^7

^a These percentages reflect an assumed population distribution.

^b $F > 5 \mu m$.

^c Fibre count with optical microscope.

Drinking-water and food

Drinking-water and food may contain asbestos fibres from natural sources (e.g. rock) and man-made sources (e.g. asbestos-cement pipes). The total fibre content (fibres of all lengths) in drinking-water can vary from $10^4 F/litre$ to more than $10^8 F/litre$ (3,4,19,20).

Relative significance of different routes of exposure

Inhalation is by far the most important route of exposure of humans to critical fibres, the amount of uptake by ingestion being questionable and, at the least, significantly lower.

Kinetics

Health effects due to asbestos exposure in the occupational environment have been clearly associated with inhalation. The relevance of the oral intake of asbestos fibres for human health is unclear; in any case, ingestion is far less important than inhalation. For this reason, only the deposition, retention and clearance of fibres from the human lungs are described here.

Deposition

Fibres with a diameter greater than 3 µm are not respirable (10). Symmetrical fibres have a lower probability of deposition in the upper airways than nonsymmetrical fibres such as the “curly” chrysotile. A considerable number of fibres are deposited in the upper ciliated airways, where fibres can be removed by cleaning mechanisms (10). Chrysotile fibres can split into fibrils and undergo partial dissolution within the lungs. The amphiboles do not subdivide into fibrils of smaller diameter or break up by length. They are much less soluble in lung fluids, and they have long residence times in the lungs (10).

Clearance

Several mechanisms are involved in the clearing of fibres from their site of deposition, i.e. mucociliary clearance, translocation of alveolar macrophages containing small fibres, and uptake by epithelial cells lining the airways (17). Overall, the clearing mechanisms are very effective (95-98%), although in the alveolar regions some fibres can remain. It should be noted, however, that one of the most effective clearance mechanisms (mucociliary clearance) is impaired by smoking (1). Deposited fibres less than 5-10 µm long may often be engulfed by a single macrophage and thereafter be translocated; fibres longer than this are more difficult to clear. Long fibres may, however, become chemically dissolved or even mechanically broken down in the lung tissue. Durability seems to be greatest for amphiboles, less for chrysotiles (9,12,21,22); chrysotile can, in fact, split readily into fibrils and undergo partial dissolution in lung fluids (1).

The number of fibres retained in the lungs has been investigated very intensively in post-mortem lung material. All sorts of fibres known to exist in the atmospheric aerosol, including asbestos, have been found. The number of asbestos fibres per cm³ of lung sample is related to past exposure, the ratio of lung burdens for asbestos workers and controls being roughly the same as that of their respective exposures (10,12).

Health Effects

There is an intensive and well documented series of case studies and epidemiological observations which link past occupational exposure to asbestos with asbestosis, lung cancer and mesothelioma (1,3,9,10,12,23). Another series of studies has mainly examined subgroups of the population in particular exposure situations, mostly indoor exposure or para-occupational exposure (see above).

Asbestosis is a slowly developing fibrosis of the lung caused by the inhalation of high concentrations of asbestos dust and/or long exposure (24). Its severity depends both on the

length of time since onset of exposure and on the intensity of the latter (23). Although nonmalignant in itself, advanced asbestosis is often associated with lung cancer, especially among smokers. Hypoxia with cor pulmonale does occur in severe cases, while mild forms may not necessarily be associated with marked disablement (10).

Lung cancer (bronchial carcinoma) is the most frequent kind of cancer in the male population (accounting for about 10% of all male deaths in many industrialized countries) and is clearly related to external factors such as smoking, ionizing radiation (e.g. radon) and occupational exposures to certain substances, including asbestos inhalation, in the latter case even without co-existing asbestosis (9). Many studies have shown that smokers have a higher risk of developing lung cancer than nonsmokers when exposed to asbestos (23).

Mesothelioma is a malignant tumour of the pleura or peritoneum (9,23). It is a rare type of cancer (less than 0.04% of all deaths in the general population of the USA) (10). A higher incidence of mesothelioma has nearly always been related to the inhalation of mineral fibres, and in the majority of cases to occupational asbestos exposure (9). Causing few symptoms initially, mesothelioma is incurable when diagnosed (10).

Effects on experimental animals and *in vitro* test systems

Experimental toxicology has developed models to establish the relative carcinogenic potency of different types and sizes of fibres and to examine possible interactive effects with other airborne pollutants (3). This approach has proved helpful in the interpretation of epidemiological studies. Besides inhalation studies, ingestion and implantation studies have also been carried out; these have additionally been used to explore the association between asbestos and other forms of cancer in man, e.g. cancers of the gastrointestinal tract, which are epidemiologically less well established (9,23).

Species vary in their response to asbestos. Effects in rats seem to resemble those in man more closely than those in other animals (9); if not otherwise stated, the results reported refer to this species.

Inhalation

Lung cancer, mesothelioma and asbestosis have been observed in several studies regarding various asbestos and other fibres (10). In three inhalation experiments with 10 mg chrysotile per m³ over a period of 1 year, at least 20% of exposed rats developed lung tumours (25-27).

Intrapleural and intraperitoneal injection

The direct injection of a specific amount of dust with a given particle-size distribution into the pleura or the peritoneum makes it possible to study carcinogenic potency as a function of fibre type and shape without interference from variable factors such as deposition, clearance and disintegration, which are difficult to control in inhalation experiments.

The injection of asbestos produced mesotheliomas, the resulting incidence being highly fibre-specific and sensitive (3,9). Intraperitoneal injection of 1 mg chrysotile (UICC Canada) or 0.3 mg Actinolite resulted in a tumour rate of about 90% and 80%, respectively (28). Experiments show that fibre length and diameter are the most important factors in causing mesothelioma. As shown by Pott in his graph of the carcinogenicity factor (29), fibres shorter than 5 µm and thicker than 2 µm elicit little response, while those longer than 10 µm and thinner than 0.5 µm yield the highest response. Nonasbestos fibres of the same critical dimensions also caused mesothelioma in animals, while experiments with fibres of noncritical dimensions are negative, irrespective of fibre category (29). This finding is important considering the presence of many other fibre types in ambient air.

Ingestion

In several studies, rats and other laboratory animals were exposed to asbestos in diet or drinking-water. Only a single - usually very high - dose was applied in each investigation. The results are inconclusive, if not negative (1,20).

Effects on humans*Asbestosis*

While early stages of asbestosis are still observed at asbestos-cement plants under modern regulations (24), asbestosis has never been observed in relation to nonoccupational asbestos exposure. It is therefore concluded that environmental concentrations of asbestos are not sufficient to induce asbestosis (1,9).

Mesothelioma

Without doubt, exposure to all kinds of asbestos is closely linked to mesothelioma. Several epidemiological studies indicate that amphibole asbestos is more potent in inducing mesothelioma than chrysotile (1), which seems to contradict the findings from intraperitoneal injection experiments (9). The contradiction is, however, to a great extent resolved by the observation that technical processes involving amphiboles produce dust with a higher proportion of long, thin - i.e. more dangerous - fibres (9). Furthermore, amphibole fibres are more resistant in the body and have a lower lung clearance than chrysotile (9).

The time elapsing between first exposure to asbestos and the clinical manifestation of tumours ranges from 20 to 50 years for mesothelioma in the populations of workers studied (23). Dose-response relationships are derived from retrospective epidemiological studies of exposure data relating to situations several decades ago. Clearly these exposure data can only be approximations (9,15). Increased incidence rates seen in nonoccupationally exposed people living in the same household as asbestos workers or in the vicinity of strong asbestos emission sources have been attributed to this exposure (30).

Lung cancer

Clarifying the relationship between asbestos exposure and lung cancer is a much more complicated task. Both the synergism of smoking and asbestos inhalation and the high level of lung cancer in the general population (background exposure) must be taken into account. The synergistic effect can be described by a multiplicative model (31) which is used below in connection with the extrapolation of lung cancer risk. The risk of lung cancer seems to rise consistently from mining and milling operations, through branches such as asbestos-cement production, to asbestos textile and insulation work, according to the increasing portion of more dangerously shaped fibres in these processes (see Table 2).

Other cancers

Recent evaluations (9,10,20,23) of epidemiological occupational studies provide little evidence for the induction of other cancers, including gastrointestinal cancers, although recently it has been suggested that laryngeal cancer may be related to heavy occupational exposure to asbestos (23). Clearly the risk, if any, for the general population from "other" cancers is very small (9,20,45).

Table 2. Increase in the relative risk of lung cancer, as shown by different studies

K _L per 100 F*year/ml	Type of activity	Reference
0.04	mining and milling	(33)
0.045	mining and milling	(34)
0.06	friction material	(35)
0.1	factory processes	(36,37)
(M) 0.4-1.1	factory processes	(38) ^b
(F) 2.7 ^a	factory processes	
0.2	asbestos-cement	(39)
0.07	textiles (before 1951)	(40)
0.8 ^a	textiles (after 1950)	
6(M) 1.6 ^a	textiles	(41)
1.6	textiles	(42) ^c
1.1	insulation products	(43) ^b
1.5	insulation	(44) ^b

^a Fewer than 10 cases of lung cancer expected (i.e. small cohort).

^b Inadequate knowledge of actual fibre concentrations.

^c Same factory as in (41), but larger cohort.

Source: based on a table by Liddell (32).

Evaluation of Human Health Risks

Exposure

Actual indoor and outdoor concentrations in air range from below one hundred to several thousand fibres per m³.

Health risk evaluation

On the basis of the evidence from both experimental and epidemiological studies, it is clear that asbestos inhalation can cause asbestosis, lung cancer and mesothelioma. The evidence that ingested asbestos causes gastrointestinal or other cancers is insufficient. Furthermore, the carcinogenic properties of asbestos are most probably due to its fibre geometry and remarkable integrity; other fibres with the same characteristics may also be carcinogenic.

Current environmental concentrations of asbestos are not considered a hazard with respect to asbestosis. However, a risk of mesothelioma and lung cancer from the current concentrations cannot be excluded.

A WHO Task Group recently expressed reservations about the reliability of risk assessment models applied to asbestos risk. Its members suggested that such models can only be used to obtain a broad approximation of the lung cancer risk of environmental exposures to asbestos and “that any number generated will carry a variation over many orders of magnitude”. The same was found to be true for estimates of the risk of mesothelioma. The same document stated: “In the general population the risks of mesothelioma and lung cancer attributable to asbestos cannot be quantified reliably and probably are undetectably low.” (1).

The following estimates of risk are based on the relatively large amount of evidence from epidemiological studies concerning occupational exposure. Data from these studies have been

conservatively extrapolated to the much lower concentrations found in the general environment. Although there is evidence that chrysotile is less potent than amphiboles, as a precaution chrysotile has been attributed the same risk in these estimates.

Mesothelioma

A formula by which the excess incidence of mesothelioma can be approximated has been derived by Peto (46). Fibre concentration, duration of exposure and time since first exposure are parameters incorporated in this model, which assumes a linear dose-response relationship. Peto verified this model from data on an urban population exposed for its whole life and on workers exposed for many decades. In both cases, duration of exposure is assumed to be equal or close to time since first exposure. The data show that the incidence of mesothelioma is proportional to the fibre concentration to which the workers were exposed and to time^{3,5} since first exposure for both workers and the general population. Starting from this relationship, one may calculate the risk of lifetime exposure to environmental concentrations from the incidence of mesothelioma in occupational populations exposed to much higher concentrations, but for a shorter time.

Apart from incomplete knowledge about the true workplace exposure, a further complication arises from the fact that workplace concentrations were measured by means of an optical microscope, counting only fibres longer than 5 µm and thicker than, say, 0.5 µm.^c

Several studies have been performed to calculate the risk of mesothelioma resulting from nonoccupational exposure to asbestos. Lifetime exposure to 100 F*/m³ has been estimated by various authors to carry differing degrees of mesothelioma risk (see Table 3).

Table 3. Estimates of mesothelioma risk resulting from lifetime exposure to asbestos

Risk of mesothelioma from 100 F*/m ³	Values in original publication (risk for fibre concentration indicated)	Reference
1.0×10^{-5}	1.0×10^{-4} for 1000 F*/m ³	(45)
$\sim 2.0 \times 10^{-5}$	1.0×10^{-4} for (130-800) F*/m ³	(47)
$\sim 3.9 \times 10^{-5}$	1.56×10^{-4} for 400 F*/m ³	(10,48)
$\sim 2.4 \times 10^{-5}$	2.75×10^{-3} (females)	(17)
	1.92×10^{-3} (males)	

The risk estimates in Table 3 differ by a factor of 4. A "best" estimate may be 2×10^{-5} for 100 F*/m³.

An independent check of this risk estimate can be made by calculating the incidence of mesothelioma in the general population, based on a hypothetical average asbestos exposure 30-40 years ago (49). If the latter had been 200-500 F*/m³ (corresponding to about 400-1000 F/m³ as measured today), the resulting lifetime risk of mesothelioma would be $(4-10) \times 10^{-5}$. With the average United States death rate of 9000×10^{-6} per year, this would give 0.4-0.9 mesothelioma cases each year per million persons from past environmental asbestos exposure. The reported mesothelioma incidence in the USA ranges from 1.4×10^{-6} per year

^c In this chapter all fibre concentrations based on optical microscopy are marked F*/m³ and risk estimates will be based on F*/m³. If concentrations measured by optical microscope are to be compared with environmental fibre concentrations measured by a scanning electron microscope, a conversion factor has to be used: $2 \text{ F/m}^3 = 1 \text{ F*/m}^3$.

to 2.5×10^{-6} per year according to various authors (10, 49). Thus, the calculated risk figures would account for only part of the observed incidence. However, other factors which may account for this discrepancy must be considered.

- Uncertainties in the risk extrapolations result from the lack of reliable exposure data in the cohort studies, errors in the medical reports, and necessary simplifications in the extrapolation model itself (17). Furthermore, the amount of past ambient exposure can only be an educated guess.
- The incidence of nonoccupational mesotheliomas is calculated from the difference between the total of observed cases and the number of those probably related to occupational exposure. Neither of these two figures is exactly known. Moreover, the influence of other environmental factors in the generation of mesothelioma is unknown.

In the light of these uncertainties, the result obtained by using the risk estimate can be considered to be in relatively good agreement with the annual mesothelioma death rate based on national statistical data.

Lung cancer

Unlike mesothelioma, lung cancer is one of the most common forms of cancer. As several exogenous noxious agents can be etiologically responsible for bronchial carcinoma, the extrapolation of risk and comparison between different studies is considerably complicated. In many epidemiological studies, in particular, the crucial effect of smoking has not been properly taken into account. Differentiation of the observed risks according to smoking habits has been carried out, however, in the cohort of North American insulation workers studied by Hammond et al. (31).

This study suggests that the relative risk at a given time is approximately proportional to the cumulative amount of fine asbestos dust received up to this point, for both smokers and nonsmokers. The risks for non-asbestos-exposed nonsmokers and smokers must therefore be multiplied by a factor which increases in proportion to the cumulative exposure.

The dose-response relationship in the case of asbestos-induced lung cancer can be described by the following equation (17).

$$I_L(\text{age, smoking, fibre dose}) = I_L^0(\text{age, smoking}) [1 + K_L \times C_f \times d]$$

This equation could also be written as:

$$K_L = [(I_L/I_L^0) - 1]/C_f \times d = (\text{relative risk} - 1)/(\text{cumulative exposure})$$

where:

K_L = a proportionality constant, which is a measure of the carcinogenic potency of asbestos

C_f = fibre concentration

d = duration of exposure, in years

I_L = lung cancer incidence, observed or projected, in a population exposed to asbestos concentration C_f during time d

I_L° = lung cancer incidence expected in a group without asbestos exposure but with the same age and smoking habits (this factor includes age dependence).

There are several studies which allow the calculation of K_L . Liddell (32, 50) has done this in an interesting and consistent manner. The results are given in Table 2.

Taking the data in Table 2 as a basis, a reasonable estimate for K_L is 1.0 per 100 F*years/ml. For a given asbestos exposure, the risk for smokers is about 10 times that for nonsmokers (31). In extrapolating from workers to the general public, a factor of 4 for correction of exposure time has to be applied to K_L .

The incidence of lung cancer in the general population exposed to 100 F*/m³ is calculated as follows:

$$I_L = I_L^\circ (1 + 4 \times 0.01 \times 10^{-4} \text{ F*/ml} \times 50 \text{ years})$$

or

$$I_L = I_L^\circ (1 + 2 \times 10^{-4} \text{ F*/ml})$$

The extra risk is $I_L - I_L^\circ$. Values for I_L° are about 0.1 for male workers and 0.01 for male nonsmokers (10).

Lifetime exposure to 100 F*/m³ (lifetime assumed to be 50 years since, in a lifetime of 70 years, the first 20 years without smoking probably do not make a large contribution) is therefore estimated as follows.

Status	Risk of lung cancer per 100 000	Range (using the highest and lowest values of K_L from Table 2)
Smokers	2.0	0.08-3.2
Nonsmokers	0.2	0.008-0.32

This risk estimate can be compared, when adjusted to 100 F*/m³, with estimates for male smokers made by other authors or groups:

Breslow (National Research Council) (48): 7.3×10^{-5} ;

Schneiderman et al. (47): $(14-1.4) \times 10^{-5}$;

US Environmental Protection Agency (17): 2.3×10^{-5} .

A fibre concentration of 100 F*/m³ (about 200 F*/m³ as seen by scanning electron microscope) thus gives a total risk of $(2 + 2) \times 10^{-5}$ for smokers or 2.2×10^{-5} for nonsmokers.

Guidelines

Asbestos is a proven human carcinogen (IARC Group 1). No safe level can be proposed for asbestos because a threshold is not known to exist. Exposure therefore should be kept as low as possible.

Several authors and working groups have produced estimates indicating that, with a lifetime exposure to 1000 F/m^3 (0.0005 F*ml or 500 F*ml^3 , optically measured) in a population of whom 30% are smokers, the excess risk due to lung cancer would be in the order of 10^{-6} - 10^{-5} . For the same lifetime exposure, the mesothelioma risk for the general population would be in the range of 10^{-5} - 10^{-4} . These ranges are proposed with a view to providing adequate health protection, but their validity is difficult to judge. An attempt to calculate a "best" estimate for the lung cancer and mesothelioma risk is described above.

References

1. *Asbestos and other natural mineral fibres*. Geneva, World Health Organization, 1986 (Environmental Health Criteria, No. 53).
2. *Asbestos*. Paris, OECD, 1984, p. 21 (Env/Air 81.18; 2nd Rev.).
3. **Umweltbundesamt** [Federal Office for the Environment]. *Umweltbelastung durch Asbest und andere faserige Feinstäube* [Environmental pollution by asbestos and other fibrous fine dusts]. Berlin (West), Erich Schmidt Verlag, 1980 (Berichte 7/80).
4. **Meyer, E.** Vorkommen von Asbestfasern im Trinkwasser [Occurrence of asbestos fibres in drinking-water]. In: Fischer, M. & Meyer, E., ed. *Zur Beurteilung der Krebsgefahr durch Asbest* [Assessment of the cancer risk of asbestos]. Munich, Medizin Verlag, 1984, pp. 62-78.
5. **Fischer, M. & Meyer, E.** The assessment of the health risk from asbestos fibres by the Federal Health Office of the Federal Republic of Germany. *VDI-Berichte*, 475: 325-330 (1983).
6. **Marfels, H. et al.** Immissionsmessungen von faserigen Stäuben in der Bundesrepublik Deutschland - I. Messungen in der Nähe einer Industriequelle [Measurements of fibrous dusts in ambient air of the Federal Republic of Germany. I. Measurements in the vicinity of an industrial source]. *Staub, Reinhaltung der Luft*, 44: 259-263 (1984).
7. **Lohrer, W.** Asbestbelastete Innenräume - Analyse und Bewertung des Gefahrenpotentials [Asbestos exposed interiors - analysis and evaluation of risk potentials]. *Staub, Reinhaltung der Luft*, 43: 434-438 (1983).
8. **Nicholson, W.J., et al.** *Asbestos contamination of the air in public buildings*. Research Triangle Park, NC, US Environmental Protection Agency, 1975 (Final report, contract 68-02-1346).
9. *Report of the Royal Commission on Matters of Health and Safety Arising from the Use of Asbestos in Ontario*. Toronto, Ontario Ministry of the Attorney General, 1984, Vol.1-3.
10. **National Research Council.** *Asbestiform fibers: nonoccupational health risks*. Washington, DC, National Academy Press, 1984.
11. **Sawyer, R.N.** Indoor air pollution: application of hazard criteria. *Annals of the New York Academy of Sciences*, 330: 579-586 (1979).
12. **Commings, B.T.** *The significance of asbestos and other mineral fibres in environmental ambient air*. Maidenhead, Commings Ass., 1985.
13. **Chatfield, E.J.** Measurement and interpretation of asbestos fibre concentrations in ambient air. In: *Proceedings of the 5th Colloquium on Dust Measuring Technique and Strategy, October 1984*. Johannesburg, South African Asbestos Producers Advisory Committee, 1985, pp. 269-296.
14. **Marfels, H. et al.** Immissionsmessungen von faserigen Stäuben in der Bundesrepublik Deutschland - II. Messungen an der Kreuzung einer Großstadt [Measurements of fibrous dusts in ambient air of the Federal Republic of Germany. II. Measurements on a busy crossing of a large town]. *Staub, Reinhaltung der Luft*, 44: 410-414 (1984).
15. **Nicholson, W.J.** Asbestos and inorganic fibres. *Arbete och hälsa*, 17 (1981).

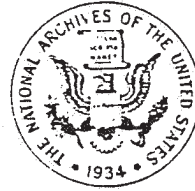
16. **Woitowitz, K.J. & Rodelsperger, K.** Asbestemissionen im Grenzbereich von Arbeitsplatz und Umwelt [Asbestos emissions in the borderline area of workplace and environment]. In: Fischer, M. & Meyer, E., ed. *Zur Beurteilung der Krebsgefahr durch Asbest* [Assessment of the cancer risk of asbestos]. Munich, Medizin Verlag, 1984.
17. **Airborne asbestos health assessment update.** Research Triangle Park, NC, US Environmental Protection Agency, 1985 (EPA-600/8-84-003F).
18. **Lilis, R. & Selikoff, I.J.** Asbestos disease in occupationally exposed workers and household contacts. In: Fischer, M. & Meyer, E., ed. *Zur Beurteilung der Krebsgefahr durch Asbest* [Assessment of the cancer risk of asbestos]. Munich, Medizin Verlag, 1984.
19. **Commins, B.T.** *Asbestos fibres in drinking water.* Maidenhead, Commins Ass., 1983.
20. **Toft, P. et al.** Asbestos in drinking water. *Critical reviews in environmental control*, 14(2): 151-197 (1984).
21. **Friedberg, K.D. & Ulmer, S.** Deposition und Elimination von Staub aus faserförmigem Material in der Lunge von Versuchstieren [Deposition and elimination of fibrous material dust in the lungs of experimental animals]. *VDI Berichte*, 475: 269-274 (1983).
22. **Lippmann, M.** Peer review: inhalation and elimination of MMMF - aids to the understanding of the effects of MMMF. In: *Biological effects of man-made mineral fibres.* Copenhagen, WHO Regional Office for Europe, 1984, Vol. 2, pp. 355-366.
23. **Doll, R. & Peto, J.** *Asbestos: effects on health of exposure to asbestos.* London, H.M. Stationery Office, 1985.
24. **Weicksel, P. & Ulrich, E.** Asbeststaubgefährdung in der modernen asbestverarbeitenden Industrie [The hazard of asbestos dust in the modern asbestos-processing industry]. In: Fischer, M. & Meyer, E., ed. *Zur Beurteilung der Krebsgefahr durch asbest* [Assessment of the cancer risk of asbestos]. Munich, Medizin Verlag, 1984.
25. **Davis, J.M.G. et al.** Mass and number of fibres in the pathogenesis of asbestos-related lung disease in rats. *British journal of cancer*, 37: 673-688 (1978).
26. **Wagner, J.C. et al.** Animal experiments with MMM(V)F fibres - effects of inhalation and intrapleural inoculation in rats. In: *Biological effects of man-made mineral fibres.* Copenhagen, WHO Regional Office for Europe, 1984, Vol. 2, pp. 209-233.
27. **McCohnell, E.E. et al.** A comparable study of the fibrogenic and carcinogenic effects of UICC Canadian chrysotile B asbestos and microfibres (JM 100). In: *Biological effects of man-made mineral fibres.* Copenhagen, WHO Regional Office for Europe, 1984, Vol. 2, pp. 234-250.
28. **Pott, F. et al.** Carcinogenicity studies on fibres, metal compounds, and some other dusts in rats. *Experimental pathology*, 32: 129-152 (1987).
29. **Pott, F.** Some aspects on the dosimetry of the carcinogen potency of asbestos and other fibrous dusts. *Staub, Reinhaltung der Luft*, 38: 486- 490 (1978).
30. **Ham, E.** Untersuchungen über gesundheitliche Asbestschäden in Hamburg (1969-1979) [Studies of health damage caused by asbestos in Hamburg (1969-1979)]. In: Fischer, M. & Meyer, E., ed. *Zur Beurteilung der Krebsgefahr durch Asbest* [Assessment of the cancer risk of asbestos]. Munich, Medizin Verlag, 1984.
31. **Hammond, E.C. et al.** Asbestos exposure, cigarette smoking and death rates. *Annals of the New York Academy of Sciences*, 330: 473-490 (1979).
32. **Liddell, F.D.K.** Some new and revised risk extrapolations from epidemiological studies on asbestos workers. In: Fischer, M. & Meyer, E., ed. *Zur Beurteilung der Krebsgefahr durch Asbest* [Assessment of the cancer risk of asbestos]. Munich, Medizin Verlag, 1984.
33. **McDonald, J.C. et al.** Dust exposure and mortality in chrysotile mining, 1910-1975. *British journal of industrial medicine*, 37: 11-24 (1980).
34. **Nicholson, W.J. et al.** Long-term mortality experience of chrysotile miners and millers in Thetford Mines, Quebec. *Annals of the New York Academy of Sciences*, 330: 11-21

- (1979).
35. **Berry, G. & Newhouse, M.L.** Mortality of workers manufacturing friction materials using asbestos. *British journal of industrial medicine*, 40: 1-7 (1983).
 36. **Henderson, V.L. & Enterline, P.E.** Asbestos exposure: factors associated with excess cancer and respiratory disease mortality. *Annals of the New York Academy of Sciences*, 330: 117-126 (1979).
 37. **Enterline, P. et al.** Mortality in relation to occupational exposure in the asbestos industry. *Journal of occupational medicine*, 14: 897-903 (1972).
 38. **Newhouse, M.L. & Berry, G.** Patterns of mortality in asbestos factory workers in London. *Annals of the New York Academy of Sciences*, 330: 53-60 (1979).
 39. **Weill, H. et al.** Influence of dose and fiber type on respiratory malignancy risk in asbestos cement manufacturing. *American review of respiratory diseases*, 120: 345-354 (1979).
 40. **Peto, J.** Lung cancer mortality in relation to measured dust levels in an asbestos textile factory. In: Wagner, J.C., ed. *Biological effects of mineral fibres*. Lyon, International Agency for Research on Cancer, 1980 (IARC Scientific Publications, No. 30).
 41. **Dement, J.M. et al.** Estimates of dose—response for respiratory cancer among chrysotile asbestos textile workers. *Annals of occupational hygiene*, 26: 869-887 (1982).
 42. **Fry, J.S. et al.** Respiratory cancer in chrysotile production and textile manufacture. *Scandinavian journal of work, environment & health*, 9: 68-70 (1983).
 43. **Seidman, H. et al.** Short-term asbestos work exposure and long-term observation. *Annals of the New York Academy of Sciences*, 330: 61-67 (1979).
 44. **Selikoff, J.J. et al.** Mortality experience of insulation workers in the United States and Canada, 1943-1976. *Annals of the New York Academy of Sciences*, 330: 91-116 (1979).
 45. **Aurand, K. & Kierski, W.-S., ed.** *Gesundheitliche Risiken von Asbest*. Eine Stellungnahme des Bundesgesundheitsamtes Berlin [Health risks of asbestos. A position paper of the Federal Health Office, Berlin]. Berlin (West), Dietrich Reimer Verlag, 1981 (BgA-Berichte, No. 4/81).
 46. **Peto, J.** Dose and time relationships for lung cancer and mesothelioma in relation to smoking and asbestos exposure. In: Fischer, M. & Meyer, E., ed. *Zur Beurteilung der Krebsgefahr durch Asbest* [Assessment of the cancer risk of asbestos]. Munich, Medizin Verlag, 1984.
 47. **Schneiderman, M.S. et al.** *Assessment of risks posed by exposure to low levels of asbestos in the general environment*. Berlin (West), Dietrich Reimer Verlag, 1981 (BgA-Bericht, No. 4/81).
 48. **Breslow, L. et al.** Letter. *Science*, 234: 923 (1986).
 49. **Enterline, P.E.** Cancer produced by nonoccupational asbestos exposure in the United States. *Journal of the Air Pollution Control Association*, 33: 318-322 (1983).
 50. **Liddell, F.D.K. & Hanley, J.A.** Relations between asbestos exposure and lung cancer SMRs in occupational cohort studies. *British journal of industrial medicine*, 42: 389-396 (1985).

EXHIBIT 39

THURSDAY, DECEMBER 15, 1977

PART III



CONSUMER PRODUCT SAFETY COMMISSION

CONSUMER PATCHING
COMPOUNDS AND
ARTIFICIAL EMBERIZING
MATERIALS (EMBERS
AND ASH) CONTAINING
RESPIRABLE FREE-FORM
ASBESTOS

Banned Hazardous Products

KMX 01187

Original Product

FILED - 2019 May 03 2:09 PM - HAMPTON - COMMON PLEAS - CASE#2016CP2500440
FILED - 2024 Jul 24 1:43 PM - RICHLAND - COMMON PLEAS - CASE#2023CP4004072

[6355-01]

Title 16—Commercial Practices
**CHAPTER II—CONSUMER PRODUCT
 SAFETY COMMISSION**

**SUBCHAPTER B—CONSUMER PRODUCT
 SAFETY ACT REGULATIONS**

**PART 1145—REGULATION OF PRODUCTS
 SUBJECT TO OTHER ACTS UNDER THE
 CONSUMER PRODUCT SAFETY ACT**

Consumer Patching Compounds and Artificial Emberizing Materials (Embers and Ash) Containing Respirable Free-Form Asbestos

AGENCY: Consumer Product Safety Commission.

ACTION: Final rules.

SUMMARY: The Commission issues final rules determining that it is in the public interest to regulate consumer patching compounds and artificial emberizing materials (embers and ash) containing respirable, free-form asbestos, for the purpose of addressing the risk of cancer associated with inhalation of asbestos fibers, under the Consumer Product Safety Act (CPSA) rather than under the Federal Hazardous Substance Act (FHSA). According to the CPSA, a risk of injury that could be eliminated or reduced to a sufficient extent under the FHSA may not be regulated under the CPSA, unless the Commission finds by rule that it is in the public interest to do so.

EFFECTIVE DATES: For consumer patching compounds containing respirable, free-form asbestos, this rule becomes effective on January 16, 1978. For artificial emberizing materials (embers and ash) containing respirable free-form asbestos, this rule becomes effective December 15, 1977.

FOR FURTHER INFORMATION CONTACT:

Charles M. Jacobson, Compliance and Enforcement Regulatory Management Division, Consumer Product Safety Commission, Washington, D.C. 20207, 301-492-6100.

SUPPLEMENTARY INFORMATION:

BACKGROUND

On July 29, 1977, by publication of a notice in the Federal Register (42 FR 38782), the Commission proposed a rule under section 30(d) of the Consumer Product Safety Act (CPSA) (15 U.S.C. 2079(d)) as amended, that it is in the public interest to regulate consumer patching compounds and artificial emberizing materials (embers and ash) containing respirable free-form asbestos under the CPSA rather than under the Federal Hazardous Substances Act (FHSA), (15 U.S.C. 1261-1274). Section 30(d) reads:

A risk of injury which is associated with a consumer product and which could be eliminated or reduced to a sufficient extent under the Federal Hazardous Substances Act . . . may be regulated under the CPSA only if the Commission by rule finds that it is in the public interest to regulate such risk of injury under [the CPSA].

Also on July 29, 1977, the Commission proposed in the Federal Register (42 FR 38783) a regulation under the CPSA that would declare as banned hazardous products, consumer patching compounds and artificial emberizing materials (embers and ash) containing respirable free-form asbestos.

The Commission's reasons in the proposed section 30(d) rule for proceeding under the CPSA rather than the FHSA are:

1. The rulemaking proceedings for regulation of these products under the FHSA are likely to be lengthy and resource-consuming.

2. Rulemaking proceedings under the CPSA are governed by provisions of the Administrative Procedure Act (5 U.S.C. 553), and are informal and nonadversarial in nature and thus it would be more likely that participation of the public, including consumers, would be forthcoming in rulemaking proceedings under the CPSA.

3. The Commission believes that civil penalty provisions available under the CPSA against persons who knowingly violate the CPSA may provide additional incentive for compliance under the CPSA. The FHSA does not provide the remedy of civil penalties.

COMMENTS

No comments were received by the Commission which deal directly with the proposed section 30(d) rule. In comments on the proposed ban, however, several persons in the marketing chain commented approvingly on the decision to regulate under the CPSA because CPSA does not require repurchase of banned hazardous products by manufacturers, distributors, and retailers. On the other hand, several groups of consumer-oriented interests noted that they would have preferred regulation under FHSA because FHSA provides for such repurchase.

As noted in the proposed section 30(d) rule, the Commission is aware that regulation under CPSA would preclude mandated repurchase of banned hazardous products. However, the CPSA does not preclude voluntary arrangements for repurchase back up the distribution chain. Moreover, the advantages enumerated above, particularly, the advantage of having a final banning regulation in force without having to first provide for lengthy adjudicatory proceedings, appears to the Commission to be more beneficial to consumer health and safety than the refunds consumers would have under FHSA. In the matter of artificial emberizing materials, repurchase under the FHSA would have meant that many persons in the chain of distribution would have handled these materials rather than disposing of them quickly in order to avoid additional exposure.

Accordingly, the Commission finds that for the health and safety of consumers, it is in the public interest to regulate consumer patching compounds and artificial emberizing materials containing respirable free-form asbestos under the CPSA rather than the FHSA. Therefore, pursuant to section 30(d) of

the CPSA, Pub. L. 92-573, 86 Stat. 1231 as amended, 90 Stat. 510, 15 U.S.C. 2079(d), the Commission amends Title 16, Chapter II, Subchapter B, by adding new §§ 1145.4 and 1145.5.

§ 1145.4 Consumer patching compounds containing respirable free-form asbestos; risk of cancer associated with inhalation of asbestos fibers.

(a) The Commission finds that it is in the public interest to regulate the risk of cancer associated with inhalation of asbestos fibers from consumer patching compounds containing respirable free-form asbestos under the Consumer Product Safety Act (CPSA) rather than under the Federal Hazardous Substances Act (FHSA) because of the desirability of avoiding possibly lengthy resource-consuming, inefficient rulemaking proceedings under the FHSA and because of the availability of civil penalties under the CPSA for knowing noncompliance.

(b) Therefore, consumer patching compounds containing respirable free-form asbestos are regulated under CPSA.

§ 1145.5 Emberizing materials (embers and ash) containing respirable free-form asbestos; risk of cancer associated with inhalation of asbestos fibers.

(a) The Commission finds that it is in the public interest to regulate the risk of cancer associated with inhalation of asbestos fibers from artificial emberizing materials (embers and ash) containing respirable free-form asbestos under the Consumer Product Safety Act (CPSA) rather than under the Federal Hazardous Substances Act (FHSA) because of the desirability of avoiding possibly lengthy resource-consuming, inefficient rulemaking proceedings under the FHSA, and because of the availability of civil penalties under the CPSA for knowing noncompliance.

(b) Therefore, artificial emberizing materials (embers and ash) containing respirable free-form asbestos are regulated under the CPSA.

Effective dates: Section 1145.4 becomes effective January 16, 1978. Section 1145.5 becomes effective December 15, 1977.

(Sec. 30(d), Pub. L. 92-573, 86 Stat. 1231 as amended, 90 Stat. 510 (15 U.S.C. 2079(d)).)

Dated: December 12, 1977.

SHELDON D. BUTTS,
 Assistant Secretary, Consumer
 Product Safety Commission.

[FR Doc. 77-35744 Filed 12-12-77; 11:32 am]

[6355-01]

**CONSUMER PATCHING COMPOUNDS AND
 ARTIFICIAL EMBERIZING MATERIALS
 (EMBERS AND ASH) CONTAINING
 RESPIRABLE FREE-FORM ASBESTOS**

**Establishment As Banned Hazardous
 Products**

AGENCY: Consumer Product Safety Commission.

ACTION: Final rules.

SUMMARY: In this document the Commission declares that the following products containing respirable free-form asbestos are banned hazardous products under the Consumer Product Safety Act: (1) Consumer patching compounds used to join or repair interior walls and ceilings (mixing of the product before it is applied, sanding of the product after it is dried, and cleanup after completion of the process, release asbestos fibers that can be inhaled); and (2) artificial emberizing materials (embers and ash) used in fireplaces to simulate live embers and ash (ordinary air currents in the household move asbestos fibers that can be inhaled). The Commission issues this ban in order to reduce or eliminate the unreasonable risk of injury from certain types of cancer that may result from inhaling asbestos fibers released during the use of these products.

EFFECTIVE DATES: (1) For consumer patching compounds containing respirable free-form asbestos, the regulation issued below at section 1304, applies to products manufactured or initially introduced into commerce on January 16, 1978, or after that date. For all other consumer patching compounds containing respirable free-form asbestos, no matter when manufactured or initially introduced into commerce, the regulation at section 1304 applies on June 12, 1978, and after that date. (2) For artificial emberizing materials containing respirable free-form asbestos, the regulation issued below at section 1305 applies to products in commerce on December 15, 1977, or after that date.

FOR FURTHER INFORMATION CONTACT:

Charles M. Jacobson, Consumer Product Safety Commission, Compliance and Enforcement Regulatory Management Division, Washington, D.C. 20207, 301-492-6400.

SUPPLEMENTARY INFORMATION:

BACKGROUND

On July 29, 1977, by publication of a notice in the *FEDERAL REGISTER* (42 FR 38783), the Commission proposed rules to declare that consumer patching compounds and artificial emberizing materials (embers and ash) containing respirable free-form asbestos, are banned hazardous products under the Consumer Product Safety Act (CPSA). These rules were proposed because the Commission preliminarily determined that an unreasonable risk of injury of certain types of cancer, such as mesothelioma and lung cancer, is associated with inhalable asbestos found in these products. The information on which the Commission's preliminary determination was based is set forth in the proposal. The data in the proposal are incorporated herein by reference. The bibliography of 50 references cited in the proposal are repeated in this preamble for convenience. Numbers 51 and over refer to additional information considered in issuing this rule.

On July 29, 1977, by publication of a notice in the *FEDERAL REGISTER* (42 FR 38782), the Commission also proposed a rule finding that it is in the public interest to regulate consumer patching compounds and artificial emberizing materials containing respirable free-form asbestos under the Consumer Product Safety Act (CPSA) rather than under the Federal Hazardous Substances Act (FHSA). Section 30(d) of the CPSA (15 U.S.C. 2079(d)) requires the Commission to make such a finding by rule, before regulating under the CPSA, a risk of injury which could be reduced or eliminated to a sufficient extent under the FHSA. The Commission issues this rule elsewhere in the *FEDERAL REGISTER*. The data in these proposals are incorporated herein, by reference.

Section 9(a) (2) of the CPSA requires that, in addition to providing an opportunity for making written submissions, the Commission shall provide interested persons with an opportunity to make oral presentations of data, views or arguments relating to proposals to ban. Oral presentations on the bans were heard by the Commission on August 15, 1977. Views on the bans are discussed below under Comments on Proposal.

In order to have sufficient time to review all the responses to the banning proposal, including late responses, on October 4, 1977 (42 FR 53970), the Commission extended until November 28, 1977, the time in which it must either publish a consumer product safety rule or withdraw the proposals to ban. This date was further extended until December 12, 1977, by notice published in the *FEDERAL REGISTER* on November 29, 1977 (42 FR 60752).

COMMENTS ON PROPOSAL

Oral views on the proposal were presented by 7 persons on August 15, 1977 with 3 representing consumer groups and 4 representing manufacturers. In addition, the Commission received 30 written comments which represented 17 manufacturers and 2 distributors; 4 federal agencies; 3 public interest groups; 2 concerned citizens; a supplier of raw materials; and a chemical research and development firm. Among the 10 commenters who expressed support for the ban were 5 manufacturers of patching compounds, 3 federal agencies and 2 public interest groups.

The significant issues raised by the oral and written comments are set forth below.

A. Scope and definition. The proposal states that consumer patching compounds are those that are customarily produced or distributed for sale to or for the personal use, consumption or enjoyment of consumers in or around a household or residence, a school, in recreation or otherwise. The Commission considered in the proposal that patching compounds for application in these consumer environments are either distributed for sale to consumers or are for the personal use or enjoyment of consumers. Moreover,

information available to the Commission indicated that most patching compounds for commercial/industrial use are distributed in such ways that consumers have access to these products (51) either by purchase or for their use and enjoyment. Therefore, the Commission concluded that these are consumer products subject to the Commission's jurisdiction unless such patching compounds are labeled as, marketed, and sold solely for industrial use.

1. Patching compounds as consumer products. (a) Several commenters requested a clearer definition of consumer patching compound and a manufacturer questioned the boundaries of the term "consumer product." The manufacturer states that the definition of consumer patching compounds in the ban has been improperly broadened to include jurisdiction over building materials. He believes that the CPSA permits regulation only of articles used within the home, not the structure of the home itself or the integral parts of the structure. He states that since consumers have access to patching compounds containing respirable free-form asbestos through most marketing channels, these products can be considered consumer products under the CPSA. Thus, he believes that it was inappropriate to cite a recent case, ("U.S.A. v. Anaconda Co., et al.,", Misc. No. 77-0024, (D.D.C.) June 15, 1977) which indicates that the presence of a product in a consumer environment can help decide whether that product is a consumer product under the CPSA. Therefore, the commenter urges the Commission in its final regulation to delete the paragraph on "Anaconda" case in order to "avoid the creation of an unnecessary conflict . . . within the regulation itself."

In response to this comment, the Commission notes that the paragraph which cites the case in question is not in the proposed regulation but in that part of the preamble which explains the regulation. In the preamble, the Commission cited "Anaconda" not in reliance on the case as a basis for regulation but to show how the case interprets the definition of consumer product at section 3(a) (1) of the CPSA which reads,

The term "consumer product" means any article, or component part thereof, produced or distributed (i) for sale to a consumer for use in or around a permanent or temporary household or residence, a school, in recreation, or otherwise, or (ii) for the personal use, consumption or enjoyment of a consumer in or around a permanent, or temporary household or residence, a school, in recreation, or otherwise;

Although courts have not yet reached a definitive decision on the coverage of the term "consumer product," the Commission believes that the statute and legislative history, by themselves, afford sufficient authority for Commission jurisdiction over the defined product and its use in consumer environments. It appears to the Commission that the definition of consumer patching compound in the proposal falls within section 3(a) (1)

of the CPSA and that the "Anaconda" case underscores the definition.

In order to minimize any confusion, a new subsection (c) has been added to § 1304.1 Scope and Application, to show the coverage permitted by the CPSA. That subsection reads:

(c) Only consumer products are subject to this regulation. Patching compounds which are consumer products are those which a consumer can purchase. Merely labeling a patching compound for industrial use would not exclude such articles from the ban. If the sale or use of the product by consumers is facilitated, it is subject to the ban. Patching compounds which are labeled as, marketed, and sold solely for industrial use in non-consumer environments are not subject to the ban. In addition to those products which can be sold directly to consumers, the ban applies to patching compounds containing respirable free-form asbestos which are used in residences, schools, hospitals, public buildings or other areas where consumers have customary access.

It is clear from this language that use of patching compounds in consumer environments determines their status as consumer products, whether the patching compounds are applied professionally or by consumers. And, although the hazard may be greater for professional users of patching compounds because of their repeated exposure, residual dust from sanding during construction or renovation is also a hazard to consumers who may not apply the patching compounds themselves (23).

(b) A manufacturer who supports the ban states that he would have no way of policing the sale of different size containers. Therefore, although he packages a 1-gallon size of patching compound for sale to consumers and a 5-gallon size for commercial-industrial use, he believes the ban should apply to all sizes.

Given the availability of patching compounds to consumers through most marketing channels, the Commission agrees that it would be burdensome for manufacturers and distributors to assure that large sizes of patching compounds, which they claim to be industrial products, are not sold to consumers. Moreover, as noted in the preceding response, merely labeling a patching compound for non-consumer use would not exclude such articles from the ban. Where a manufacturer, distributor or retailer fosters or facilitates the product's sale to or use by consumers, the product is considered a consumer product and is within the scope of this ban. This comment indicates that it may be exceedingly difficult to differentiate a patching compound that is a consumer product from one that might be termed a product for industrial use only. Nevertheless, as stated in section 1304.1(c) Scope and Application, "patching compounds which are labeled as, marketed, and sold solely for industrial use in non-consumer environments are not subject to the ban."

2. Regulation of patching compounds by OSHA. A manufacturer of dry-wall joint compounds states that the commercial and professional market for such compounds is already regulated by the

Occupational Safety and Health Administration of the Department of Labor (OSHA) and, since the consumer part of his business is small, the ban should not apply to compounds for commercial and industrial use.

As is indicated herein, any patching compound containing respirable free-form asbestos that consumers have access to in consumer environments or may purchase would be subject to the ban. Therefore, such products, although they may be for industrial/commercial use, are also considered to be consumer products.

On the subject of regulation of these products by OSHA, the Commission notes that section 31 of the CPSA provides that the Commission shall have no authority to regulate any risk of injury associated with a consumer product if such risk could be eliminated or reduced to a sufficient extent by actions taken under the Occupational Safety and Health Act of 1970. Under that Act, OSHA has issued regulations which specify the airborne concentrations of asbestos fibers to which any employee may be exposed (29 CFR 1910.93a). However, OSHA regulations apply only to workplaces and not to places where consumers would use the products themselves. Therefore, the Commission considers that actions to regulate this product which can be taken under the Occupational Safety and Health Act of 1970, cannot reduce or eliminate to a sufficient extent the unreasonable risk of injury to consumers that is associated with the product. Accordingly, the Commission regulates this product under the CPSA.

3. Type of patching compound covered by the ban. A manufacturer of caulking, sealing, glazing, adhesive and coating products believes the reputation of his product could be adversely affected by the ban. Although the Commission has stated that the banned product presents a hazard because it is mixed, sanded and moved about during cleanup operations, the commenter believes that the definition of the banned product should specifically exclude the above-listed products because they are designed to remain flexible and are, therefore, not generally sanded. Therefore, the commenter requests that the definition be amended to cover only those compounds, "which after drying are required to be or are normally sanded to a smooth finish."

In response to this comment, the Commission notes that the patching compounds subject to the ban are those that contain asbestos which can be inhaled as a result of mixing, sanding and cleanup operations. Therefore, patching materials such as those listed by the commenter which are not sanded after application because they are intended to remain flexible, would be exempt if they are not available in dry, ready-to-mix form. The Commission believes it is clear that only consumer patching compounds containing asbestos which can be inhaled when the product is in dry form or being sanded are subject to the ban and therefore declines in this case

to amend the definition of patching compound at § 1304.3(d).

4. Asbestos terminology for both products. (a) In discussing the proposed definition of "asbestos," a writer from a chemical research and development center states that "silica" is a chemical compound and as a compound is not a component of asbestos. He suggests that the word "silicon" be used to denote that it is a single element which is present in asbestos.

The Commission concurs that the term "silica" should not be used, but rather it should be "silicates," since asbestos is a generic term used to describe a number of naturally-occurring hydrated mineral silicates. Therefore, the word "silica" is deleted from the definition of asbestos in §§ 1304.3(b) and 1305.3(b) below and the term "hydrated silicates" is substituted therefor.

(b) A public interest group takes issue with the definition of asbestos used in the proposal and urges the Commission to adopt a definition of asbestos proposed by OSHA in 1975. The definition of asbestos used in the Commission proposal is based on the definition used by the Bureau of Mines (56). The commenter believes that the OSHA proposed definition could help resolve disputes over the presence or absence of asbestos in consumer products.

As the commenter pointed out, several federal agencies with responsibilities for regulating asbestos (EPA, FDA, OSHA, CPSC) are working toward a uniform definition of asbestos. At a recent workshop, July 18-20, 1977, at the National Bureau of Standards on asbestos definition and identification problems, it was agreed that there should be a uniform definition of asbestos which would be mineralogically correct as well as reflect health concerns. However, there was clearly a lack of agreement on a definition and an interagency agreement on a definition has not yet been reached.

The definition which the commenter urges the Commission to adopt was proposed by OSHA on October 19, 1975; has not yet been finalized and is subject to change. The OSHA proposed definition reflects OSHA's concern for the health aspects of asbestos and is based on experimental findings associated with fiber morphology (size and shape). The Bureau of Mines also seeks to encourage uniform definition. Their definition which was used by the Commission is based on mineralogical composition. This has been adopted in final form by that agency.

The Commission has reviewed much of the available data on the characteristics of asbestiform mineral fibers and their nonasbestos counterparts. From these data, it would appear that use of the proposed OSHA definition could also include nonfibrous cleavage fragments and other particulate substances, as well as other mineral fibers within the proposed dimension range that are not asbestos fibers. While the Commission is interested in arriving at an unambiguous uniform definition of asbestos, there is not

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yet enough evidence to base a definition of "asbestos" on fiber morphology. Therefore, the Commission believes the proposed definition should not be changed in the final rule. As circumstances warrant, the definition could be amended at a later date.

5. *Asbestos contamination in patching compounds.* Several manufacturers expressed concern that all patching compounds would be subject to the ban rather than only those compounds to which asbestos has been intentionally added. They point out that asbestos is ubiquitous in the environment and that traces of asbestos may be present as a contaminant in other minerals that are mined in areas of serpentine rock. One commenter suggests that the Commission consider permitting patching compounds which contain such naturally occurring contaminants. Other commenters suggest that a percentage of asbestos contamination by weight be permitted. The lowest percentage suggested by one commenter is 1 percent because the Environmental Protection Agency (EPA) permits the presence of 1 percent asbestos by weight in spray-on asbestos insulation and fire proofing.

As noted in the proposal, the Commission is aware that asbestos is present in the environment. Further, the Commission does not wish to ban all consumer patching compounds in which traces of asbestos are present as a contaminant rather than as an intentionally added substance.

The suggestion that the Commission permit contamination of 1 percent by weight, however, appears to be inappropriate for consumer patching compounds because consumers would not be sufficiently protected. One percent by weight could mean a substantial number of small lightweight asbestos fibers, thus presenting a significant exposure to consumers of respirable free-form asbestos. Therefore, the Commission declines at this time to adopt a percentage by weight to define permissible contamination.

Industry experts do not agree as to the amount of asbestos that might be present in products without deliberately added asbestos. Nor is there agreement on the reliability of the techniques used to measure low levels (below 1 percent) of asbestos by weight. The Commission believes, however, that the use of appropriate quality control measures and careful selection of raw materials can serve to minimize contamination from unintentionally added asbestos (see the Commission's economic impact statement on file at the Office of the Secretary). In order to emphasize that only patching compounds with clearly unavoidable traces of asbestos contamination will be permitted, the Commission defines "intentionally-added asbestos" at § 1304.3(f) of the rule below to mean asbestos which is

- (1) added deliberately as an ingredient intended to impart specific characteristics; or
- (2) contained in the final product as a result of knowingly using a raw material contain-

ing asbestos. Whenever a manufacturer finds out that the finished product contains asbestos, the manufacturer will be considered as knowingly using a raw material containing asbestos unless the manufacturer takes steps to reduce the asbestos to the maximum extent feasible.

Therefore, the ban applies only to consumer patching compounds containing intentionally-added respirable free-form asbestos and will not apply to products having unavoidable trace amounts.

6. *Artificial emberizing materials—exemption from ban.* A manufacturer of electric artificial logs and electric fireplaces states that although the Commission proposed to ban only artificial emberizing materials containing respirable, free-form asbestos, references in the media to artificial logs and artificial fireplaces reflect adversely on his business. He asks, therefore, that his products, which use an artificial ash bed of vermiculite, be exempted from the ban.

As the commenter noted, the Commission ban applies only to emberizing materials containing respirable free-form asbestos and not to any artificial logs or artificial fireplaces with which they may be used. Since the banned product is used with artificial logs, it is understandable that questions are raised as to different kinds of artificial logs. The Commission does not believe it would be appropriate to exempt from the ban all electric logs coated with unidentified substances, or all artificial ash used in electric fireplaces, since some of these articles could include the banned product. However, in order to clarify the matter for consumers as well as producers, the Commission adds a statement to § 1305.3(d), the definition of emberizing materials, which reads, "electric artificial logs and artificial ash beds used in electric fireplaces which do not contain respirable free-form asbestos are not included in this definition."

B. *Effective date.* Six commenters discussed the proposed effective date of the ban of consumer patching compounds which was 30 days after publication of the final rule. Five manufacturers suggested a date later than 30 days after publication. A public interest group suggested that the effective date be the date of publication of the final rule.

(1) One commenter suggested that the Commission consider a series of effective dates for the ban on consumer patching compounds: 30 days for manufacturers, 90 for distributors and 180 days for retailers in order to clear inventories. Several commenters believe that a 30-day effective date might prove burdensome to small manufacturers because of the inventory problem.

The matter of inventories was considered in the July 29, 1977 proposal to ban and further discussed at the public meeting of August 15, 1977. The concern of those involved to clear their existing inventories of consumer patching compounds containing respirable free-form asbestos was considered. Information available to the Commission indicates that manufacturers are now maintain-

ing a relatively small inventory. Distributors report that they maintain a small inventory compared to their sales. Retailers have a much slower-moving inventory (51).

The Commission considered the possible adverse economic impact of a 30 day effective date on inventories of manufacturers, distributors and retailers. The Commission also considered the possible adverse effects of exposing consumers to inhalable asbestos by permitting the manufacture, distribution and sale to consumers of patching compounds until 180 days after publication of a ban. It appears to the Commission that early discontinuance of the manufacture of this product would be necessary in order to stop its continuing proliferation in the market. On the other hand, substantial adverse economic impacts could result from the freezing of distributors' and retailers' inventories at an early effective date. The Commission concludes therefore that the ban should become effective at two different points in time. For manufacturers, the effective date should be close to publication of the rule in order to stop the continuing manufacture of the product. For distributors and retailers, the effective date should be delayed to help ameliorate adverse economic impacts.

Therefore, the Commission declares below at § 1304.4 that consumer patching compounds containing respirable free-form asbestos which have been manufactured or initially introduced into commerce 30 or more days after publication of this rule are banned hazardous products. This means that a banned hazardous product, having been manufactured or initially introduced into commerce, retains its status as a banned hazardous product; thus, its subsequent sale, offering for sale, or distribution in commerce, is prohibited by any person in the chain of distribution. In addition, the Commission declares that all other consumer patching compounds containing respirable free-form asbestos, no matter when manufactured or initially introduced into commerce, are banned hazardous products 180 or more days after publication of this rule. (As stated below in § 1304.4(g) of the rule, initial introduction into commerce of this product occurs when the product is physically shipped from a manufacturer's facility to a distributor, retailer, consumer or to another person for application in a consumer environment.)

In summary, 30 days after publication of this rule, manufacturers will be prohibited from manufacturing or shipping the product to distributors, retailers, consumers, or to others for application in consumer environments. Further, 180 days after publication of this rule, distributors and retailers will be prohibited from selling, offering for sale, or distributing any of the described products, no matter when manufactured or initially introduced into commerce, to distributors, retailers, consumers or to others for application in consumer environments.

(2) The public interest group recommends that the effective date of the ban

on consumer patching compounds containing respirable free-form asbestos be the date of publication of the final rule, as it is for artificial emberizing materials.

The Commission proposed that the effective date of the ban on artificial emberizing materials be the date of publication although the Administrative Procedure Act (5 U.S.C. 553) which governs publication of consumer product safety rules, provides that a rule should be published 30 days before its effective date unless the Commission finds good cause to provide otherwise. Unlike patching compounds, where exposure to asbestos fibers is most prevalent during mixing, sanding and cleanup operations, although the fibers may remain suspended for a considerable duration of time, asbestos fibers in emberizing materials can be resired as long as such materials are in the home because they are always in dry form and ready to be moved about by ordinary household air currents. It appeared to the Commission, therefore, that these emberizing materials should be removed from commerce as quickly as possible and that there is good cause to have the ban effective on the date of publication. To assist persons who already had such materials in their homes, the Commission, on July 21, 1977, issued a press release on the impending ban which included a Consumer Alert advising consumers of the dangers associated with these emberizing materials and issuing instructions for their safe removal.

Economic advice to the Commission indicates, in addition, that no significant adverse economic impacts are anticipated as a result of the immediate effective date for emberizing materials (51). As is indicated in the foregoing discussion, the economic impact of a 30-day and even a 180-day effective date for patching compounds would be significant and therefore it appears that the economic impact of an immediate effective date would be more significant. Since no new information has been presented to show that an earlier effective date should be promulgated, the Commission declines the suggestion of the public interest group. Therefore, the effective date of the regulation on consumer patching compounds containing respirable free-form asbestos is 30 days after publication of this rule as to manufacture and initial introduction into commerce and 180 days after publication as to all other units of the defined product no matter when manufactured or initially introduced in commerce.

C. Product risks and risk assessment. Several commenters discussed the Commission's risk assessment for patching compounds and questioned other aspects of the hazard.

(1) A manufacturer suggests that use by the general public or by asbestos workers is not hazardous and that the greatest hazard is to a worker during sanding operations if he also smokes.

The Commission notes that while data from an epidemiological study of asbestos insulation workers indicated there was an increased risk of death from lung

cancer among smokers, it also indicated there was also an increased risk of death from other asbestos-related diseases, including asbestosis, among nonsmokers (17). Data also suggest that the high risk of mesotheliomas (cancers of the pleura and peritoneum) from asbestos exposure appears to be unrelated to smoking (18, 6).

(2) A distributor of fireplaces and fireplace equipment doubts there is a hazard associated with emberizing materials because the fibers used in emberizing materials are relatively large and fibers which would become airborne would be pulled up the fireplace flue.

While it is true that the large asbestos fiber bundles pose little risk of inhalation, the fiber bundles release individual fibers which in turn, can break longitudinally into microscopic fibrils (57). Fibers could become airborne under normal use, installation, and handling conditions, as well as from room drafts. Once the fibers become airborne, they can remain suspended over long periods of time, eventually settling out on items of furniture, draperies, etc., only to become airborne and available for respiration with use of these items. As long as the free-form asbestos emberizing material remains loose on the fireplace floor, there is a possibility that it could become airborne and thus respired.

(3) A manufacturer states that since Commission data are based on occupational statistics, it is difficult to document the Commission's view, in the proposal that, "for many people the major exposure to inhalable asbestos is in the home."

While it is true that much of the Commission data on asbestos-related disease are based on occupational statistics, a risk assessment was made of consumer exposure to respirable asbestos in patching compounds during mixing, sanding and cleanup operations which estimated the increased risk of lung cancer from such exposure in the home. A report of asbestos in consumer patching compounds indicated that significant levels of respirable free-form asbestos fibers were detected in rooms adjacent to that where the actual patching and sanding operations had occurred so that other household members could be exposed as well as the individual performing the patching job (36). In many areas of the country (nonurban), there appears to be a relatively low background level of asbestos (52). Therefore, exposure in the home to asbestos fibers released from consumer products could represent the major exposure. As noted in the proposal, Dr. Paul Kotin, Johns-Manville, stated in a presentation before the Commission, June 9, 1977, that young children are particularly vulnerable to exposure to carcinogens and clearly their major exposure to inhalable asbestos would be in the home. The Commission therefore feels it is essential to minimize, to the extent possible, exposure to respirable asbestos.

(4) A commenter questions Commission reliance on OSHA's proposed amendment of October 9, 1975 to occu-

pational exposure to asbestos as the basis for the Commission proposal. The commenter believes that portions of the OSHA review of October 1975 are scientifically inaccurate.

The Commission notes that most of the information on hazards associated with inhalation of asbestos is based on occupational exposure. It can be said that the body of scientific literature in the OSHA proposal has already been subjected to public scrutiny. During preparation of the Commission proposal, Commission staff conferred with OSHA. As a result, the Commission proposal deleted references to studies which OSHA termed to be of questionable validity.

As pointed out in the Commission proposal, there had been only one report of consumer exposure to asbestos in the scientific literature prior to the proposal. Based on the data from that study, a Commission assessment was made of the potential increased risk of respiratory cancer associated with use of consumer patching compounds containing asbestos fibers.

The Commission also based its proposal on direct and indirect evidence of asbestos inhalation in non-occupationally exposed individuals, including reports from autopsy findings of asbestos fibers in lung tissues and from epidemiological studies.

(5) In assessing the degree and nature of the risk of injury to consumers from patching compounds, the Commission reviewed experimental data and human experience information. In addition, on the basis of data by Rohl on exposure to asbestos during the use of consumer patching compounds (36), the Commission's Health Sciences staff calculated an assessment of the risk which was described in the proposal. The calculations were based on the application of a theoretical model similar to that described by Enterline and Henderson (11). Several highly technical comments were received in response to the risk assessment. The significant issues raised in these comments are discussed below.

(a) Two commenters questioned the assumption in the risk assessment that exposure to asbestos is cumulative over the lifetime of a person, and whether intermittent exposure over several years has the same effect as if the same exposure had taken place in a single year. In reviewing the literature on asbestos exposure, the Commission finds that asbestos fibers are unlike many chemicals and other materials which the body may metabolize and excrete. Body clearance of asbestos fibers is much less effective. They have been found not only to remain in the body but to accumulate (55). Since the data tend to show that intermittent exposure can lead to cumulative buildup of asbestos fibers, it appears to the Commission that intermittent exposure over several years could have the same hazardous effect as if the total intermittent exposure had taken place within one year.

(b) Two commenters indicated that the hazard from applying patching compounds could differ in different circum-

stances. They indicate that persons of differing skills may release different amounts of inhalable asbestos into the air. Although these differences occur, a consumer would likely release more asbestos into the air because he or she may be less skilled in the process than a professional applicator. The Commission recognizes as these commenters point out that some products have a smaller percentage of asbestos than those which were used for exposure data in the Commission risk assessment. For example, one commenter submitted asbestos exposure data from a study he conducted using a compound that contained a smaller amount of asbestos. Based on this commenter's exposure data, another risk assessment was conducted. The results suggest that use of a patching compound containing less asbestos may reduce but does not eliminate an excess of deaths due to exposure to asbestos in patching compounds. The range is from 1 death per million persons exposed for the projected five years exposure using one model and up to 226 lifetime excess cancer respiratory deaths per million persons exposed during another model (53). It should be noted here that while asbestos levels may vary, they do not change the fact that there is no known level below which inhalable asbestos may be considered safe.

(c) Another commenter says that using a premixed compound reduces the consumer's exposure to asbestos. The commenter also thought that the Commission's estimate of consumer exposure was too high. The Commission's risk assessment analysis did take into consideration the exposure during the mixing of a patching compound. While exposure to asbestos fibers would be negligible during slight stirring of a premixed compound, the exposure during the sanding and cleaning operations involved would be the same as for the dry compound. Consequently, the risk assessment values would not be significantly reduced. As for the four-day, eight-hour exposure being too high an estimate, no data were submitted to substantiate that contention. As stated in the proposal, therefore, it appears to the Commission that although the exposure may be high, it is a reasonably foreseeable exposure.

D. *Substitutes for asbestos.* The July 29, 1977 proposal notes that substitutes for asbestos are already being used in patching compounds. One of the most common substitutes is attapulgite, a fibrous clay. Other substitutes of a fibrous nature are wollastonite, kaolinite, sepiolite and bentonite. Several comments express concern that materials used as substitutes for asbestos may also pose hazards.

The Commission shares this concern. Substitutes for asbestos have been under consideration for only a short time. Little data are available on which to evaluate the safety of substitute materials. Experimental findings of Stanton (58) indicate that many mineral fibers (in addition to asbestos) of small respirable di-

mentations are biologically active under experimental conditions.

According to correspondence dated July 26, 1977 from Dr. Paul Kotin of the Johns-Manville Co. with environmental consultant Barry Castleman, a Johns-Manville study is under way to assess the potential inhalation hazard of certain naturally-occurring or man-made mineral fibers such as ceramic fibers. Ceramic fibers are a potential substitute for artificial emberizing materials.

Human exposure data to substitutes are extremely limited. Occupational exposure data to certain clay mineral fibers which are proposed asbestos substitutes are scheduled to be presented at a Symposium on Occupational Exposure to Fibrous and Particulate Dust and their Extension into the Environment, in December 1977. These data are expected to indicate the extent of exposure, rather than human experience findings on results of such exposure. Data on the results of human exposure to asbestos substitutes will not, in all likelihood, be available in the near future.

(1) A commenter suggests that substitutes, since they would be fibrous, would present a risk.

In assessing asbestos substitutes, data available to the Commission indicates that a number of substances may be used which are not fibrous such as calcium carbonate, clay, resins and mica. For the fibrous clay minerals which may be used as asbestos substitutes such as wollastonite, kaolinite, sepiolite and bentonite, the Commission is aware that there is a lack of conclusive data on the hazard potential associated with these minerals. Additional study is needed to evaluate the risk of inhalation exposure to such small mineral fibers. Nevertheless, the Commission believes that the known risk from inhalable asbestos requires the banning of these products at this time.

(2) A comment questions a statement in the proposal that fibrous glass could be considered a substitute for chrysotile in emberizing materials.

The Commission concurs with this comment; it is currently unaware of any manufacturers or distributors who use or know of the use of fibrous glass for this purpose. In addition, from a technical viewpoint, glass fibers are not similar in size and shape to chrysotile. Unlike the rod-like glass fibers, chrysotile tends to be curved, or be of curly fibers or fiber bundles, comprised of extremely small-diametered fibrils. However, glass fibers are similar—at least in shape—to some of the amphibole asbestos minerals. The diameter of most fibrous glass is reportedly greater than 3-5 microns and considered too large to be respirable. However, glass fibers are not of uniform dimensions and a small percentage may be of respirable size. Additional study is needed to assess the pathologic effects of inhaled fibers, including fibrous glass.

E. *Economic considerations.* Six commenters expressed concern that the ban would have an adverse economic impact on the industry. Five of the six are manufacturers who commented on patching

compounds. The sixth is a distributor of gas fireplace logs.

One patching compound manufacturer claimed that some firms in that industry will go out of business should the ban be promulgated. As noted below, our studies indicate that some small producers may not have the technical capability to reformulate their products satisfactorily or may be unable to obtain necessary raw materials by the effective date of the ban. Thus, some may cease production temporarily, until such reformulation is achieved. Some of the large manufacturers have indicated a willingness to license their asbestos-free formulations (or parts of them) to smaller firms.

Two commenters discussed potential cost effects of the ban on patching compounds other than those relating to the product itself. One patching compound producer estimated at 60 percent the increased "workload" associated with the professional application of non-asbestos formulations because of different performance characteristics. The Commission has investigated the potential increase in direct labor costs associated with existing asbestos and non-asbestos formulations; it estimates an initial 10 to 25 percent average increase as a result of switching from the former to the latter. Other costs may accrue to professional users of the product should different application tools be needed or should some jobs have to be redone because of the relatively poor shrink- and crack-resistance of some non-asbestos formulations. These increased costs are expected to diminish over time as formulations improve and as applicators become more accustomed to using non-asbestos formulations.

One company which may be adversely affected by the proposed ban reports that attapulgite, one of the prime substitutes for asbestos in patching compounds, is in "limited supply" and that some small manufacturers may have difficulty in obtaining that material. Other industry sources have reported this same problem. The larger patching compound producers, who already have asbestos-free formulations on the market, are not expected to have as much difficulty in obtaining substitute materials.

Two manufacturers discussed the ban's potential adverse effect on the utility of the product. One expressed a belief that non-asbestos formulations are inferior in performance to asbestos formulations. Another reinforced that belief, reporting that the absence of asbestos formulations may prompt workmen to add their own asbestos to the product to help prevent cracking when wall joints are covered. However, the addition of asbestos would be tantamount to manufacture of the banned product and would thus be prohibited. It appears that at least some existing non-asbestos formulations may be less desirable, from a performance standpoint, to professional contractors; most consumer applicators are not ex-

pected to perceive a significant difference in the product's performance.

As is indicated in the proposal, the Commission is aware that economic impacts of varying degrees will occur as a result of the ban on inhalable asbestos containing patching compounds and emberizing materials containing respirable free-form asbestos. Also, the Commission is aware that technology for producing asbestos-free patching-compound formulations is becoming more generally available. The economic impact will tend to be reduced over time as non-asbestos formulation technology becomes more widespread and as existing recent formulations are improved by manufacturers. The nature and extent of the effects on the industries are discussed in the Environmental and Economic Assessments now on file in the Office of the Secretary and were considered by the Commission during this rulemaking process.

F. Other comments. (1) Several commenters suggested that the Commission should investigate other products containing asbestos in order to determine the existence of possible hazards.

In the proposal, the Commission noted that information on other products containing inhalable asbestos would continue to be developed in order to determine whether further regulation is necessary. Accordingly, the staff has begun to develop plans for collecting such information.

(2) One commenter suggested that the Commission issue a rule that would prohibit stockpiling of the banned products.

Section 9(d) (2) of the CPSA provides that the Commission may, by notice and comment rulemaking, prohibit a manufacturer from stockpiling a product for which a consumer product safety rule has been promulgated. In this case, the ban on consumer patching compounds covers the manufacture and initial introduction of products into commerce 30 days after promulgation; the ban on artificial emberizing materials covers products in commerce on the date of promulgation. Therefore, in practical effect, there would not be time for manufacturers to stockpile; nor would there be time prior to these effective dates for notice and comment rulemaking.

(3) A commenter expressed concern that the banned products be kept out of international commerce.

The Commission notes that this comment is directed not to the proposed rule but to its enforcement. If this matter should become a problem it would be considered in the context of enforcement.

(4) Several comments suggested editorial changes in the proposal. These suggestions were considered and, where appropriate, have been included herein.

DESCRIPTION OF THE BAN

The banned products. Parts 1304 and 1305 declare, respectively, that consumer patching compounds and artificial emberizing materials (embers and ash)

containing respirable free-form asbestos are banned hazardous products under section 8 of the Consumer Product Safety Act.

Scope and application. The rules apply to the named consumer products that are customarily produced or distributed for sale to or for the personal use, consumption or enjoyment of consumers in or around a household or residence, a school, in recreation or otherwise. In addition to those products which can be sold directly to consumers, the ban applies to the named consumer products which are used and enjoyed by consumers, such as those used in residences, schools, hospitals, public buildings or other areas where consumers have customary access, whether the patching compounds are applied professionally or by consumers. Only consumer products are subject to this regulation. Patching compounds which are consumer products include those which a consumer can purchase. Merely labeling a patching compound for industrial use would not exclude such articles from the ban. If the sale or use of the product to consumers is facilitated, it is subject to the ban. Patching compounds which are labeled as, marketed, and sold solely for industrial use in non-consumer environments are not subject to the ban. The ban applies to patching compounds containing intentionally-added respirable free-form asbestos sold directly to consumers and to those which are used in residences, schools, hospitals, public buildings or other areas where consumers have customary access.

Effective dates. (1) The rule at Part 1304 below applies to consumer patching compounds containing respirable free-form asbestos that are manufactured or initially introduced into commerce on January 16, 1978, or after that date. For all other consumer patching compounds containing respirable free-form asbestos, no matter when manufactured or initially introduced into commerce the rule at Part 1304 applies on June 12, 1978, and after that date. This means that 30 days after publication of this rule, manufacturers are prohibited from manufacturing or shipping the product to distributors, retailers, consumers or to others for application in consumer environments. Further, 180 days after publication of this rule, distributors and retailers will be prohibited from selling, offering for sale or distributing in commerce the described products, no matter when manufactured or initially introduced into commerce, to distributors, retailers, and users.

(2) The rule at Part 1305 below applies to artificial emberizing materials (embers and ash) containing respirable free-form asbestos that are in commerce on December 15, 1977, or after that date. This prohibition applies to products in inventory as well as to those manufactured on or after the effective date.

The Administrative Procedure Act (5 U.S.C. 553) which governs the matter of effective date for banning rules under the

CPSA, provides that a rule should be published 30 days before its effective date unless the Commission provides otherwise for good cause found and published with the rule.

As described in the discussion above on effective date, the Commission is concerned that ordinary household air currents in homes that contain artificial emberizing materials, can cause continuing exposure of consumers to the respirable free-form asbestos in artificial embers and ash. It appears to the Commission, therefore, that these products should be removed from commerce as expeditiously as possible in order to avoid having additional numbers of consumers unwittingly purchase these materials. The Commission finds there is good cause to issue the rule on artificial emberizing materials effective on the date of publication.

FINDINGS

1. CPSA Section 8. Section 8 (1) and (2) of the CPSA require that, before issuing a consumer product safety rule declaring a product to be a banned hazardous product, the Commission must find (1) that the product presents an unreasonable risk of injury and (2) that no feasible safety standard can adequately protect the public from the unreasonable risk of injury associated with the product.

(a) *Unreasonable risk of injury.* The regulations are intended to reduce or eliminate the unreasonable risk of injury to the public from cancers such as lung cancer and mesothelioma. The risk is associated with asbestos fibers which are not tightly bound into or encapsulated in the composition of a product. The health risk occurs when asbestos fibers become airborne such as by mixing, sanding, or cleanup operations when using patching compounds, or by the effect of ordinary household air currents on artificial emberizing materials in fireplaces. Tests show that certain malignancies are related to asbestiform minerals; these can arise 20 or more years after occupational exposure. However, also reported are malignancies from direct, non-occupational exposure. In a recent case, the court recognized a study on asbestos exposure cited by the Environmental Protection Agency at 40 FR 48295, showing "new biological evidence supporting the significance of single short-term exposures . . . One-day inhalation exposures in animal experiments have produced an increase in the incidence of mesothelioma." *National Association of Demolition Contractors v. Environmental Protection Agency*, Civ. Nos. 74-1545, 75-2078, D.C. Cir., October 13, 1977.

The information on which the Commission made the determination of unreasonable risk consists primarily of data on exposure of industrial workers to respirable free-form asbestos. Information on exposure of the public to inhalable asbestos in individual consumer products is limited. However, as is evident from the extensive bibliography included herein there is general scientific

and medical agreement that there is no known threshold level below which it is safe for people to be exposed to respirable free-form asbestos.

As noted in the proposal, inhalable asbestos in the household from consumer patching compounds and artificial emberizing materials presents a great risk due to the presence in the household of persons, such as children, who may be particularly vulnerable to carcinogens. Because of the long latency period, exposure to inhalable asbestos in the home can be life shortening for children. The Commission notes that consumers are exposed to asbestos from sources other than the banned products. However, consumers who are exposed to asbestos fibers from patching compounds and artificial embers and ash receive additional doses of asbestos and can be assumed to face a greater risk than persons not so exposed, and a greater cumulative risk than if no asbestos were present in the general environment.

In determining that the risk of cancers is unreasonable, the Commission concludes that the degree and nature of the risk of injury and the probability that the risk will result in harm outweighs the rules' effect on the products' utility, cost and availability to the consumer.

(b) *No feasible safety standard.* The Commission is not aware of a technically feasible procedure for removing the hazards of cancer from respirable free-form asbestos in the named products. The Commission believes that not all patching compounds present an unreasonable risk of injury to the public, only patching compounds containing respirable free-form asbestos. The hazard associated with this product is caused by the free form in which the asbestos appears. A safe level of exposure to free-form asbestos is not known. Therefore, it does not appear that a standard for patching compounds containing respirable free-form asbestos is feasible.

The product artificial emberizing materials for fireplaces, containing respirable free-form asbestos is used only in dry form. Thus individual asbestos fibers are never bound together. If the asbestos fibers were coated by another material to bind the fibers, it would no longer be the same product and would not give the desired decorative effect. In considering the dry character of the product and the fact that a safe level of exposure to respirable free-form asbestos is not known, it does not appear that a standard for artificial emberizing materials containing respirable free-form asbestos is feasible.

The Commission believes that no standard can render the defined products non-hazardous and concludes that only banning these products can adequately protect the public from unreasonable risks of injury associated with them.

2. *CPSA Section 9(b).* Section 9(b) of the CPSA, 15 U.S.C. 2058(b), as amended, requires the Commission to consider and take into account in the promulgation of a rule the special needs of elderly and

handicapped persons to determine the extent to which such persons may be adversely affected by such rule. The Commission has considered these needs and has determined that no adverse effect on elderly or handicapped persons will result from this regulation. It is in the best interest of the entire public, including the elderly and handicapped, that these hazards be reduced.

3. *CPSA Section 9(c).* Section 9(c) of the CPSA requires that prior to promulgating a consumer product safety rule the Commission shall consider and shall make appropriate findings for inclusion in such a rule as to: (1) The degree and nature of the risk of injury the rule is designed to eliminate or reduce; (2) the approximate number of consumer products, or types or classes thereof, subject to such rule; (3) the need of the public for the consumer products subject to such rule, and the probable effect of such rule upon the utility, cost, or availability of such products to meet such need; (4) any means of achieving the effect of the order while minimizing adverse effects on competition or disruption or dislocation of manufacturing and other commercial practices consistent with the public health and safety; (5) that the rule is reasonably necessary to eliminate or reduce an unreasonable risk associated with such product; and (6) that the promulgation of the rule is in the public interest (15 U.S.C. 2058(c)).

The findings required by Section 9(c) of the act have been described generally in the preamble and are incorporated in §§ 1304.5 and 1305.5 of the rules below.

BIBLIOGRAPHY

1. Anderson, H. A., Lillis, R., Daum, S., Fischbein, A. S. and Selikoff, I. J.: Household-Contact Asbestos Neoplastic Risk. *Ann. N.Y. Acad. Sci.* 271:311-323 (1978).
2. Asbestos Information Assoc.: Information from Representative of the Asbestos International Association Conference, Hamburg, Germany, 1976, June 27, 1977 memo.
3. Borrow, M., Conston, A., Livornese, L. I., and Schiet, N.: Mesothelioma and Its Association With Asbestos. *JAMA* (8): 93-97 (1967).
4. Canada, Consumer and Corporate Affairs, Consumer Standards Directorate, Product Safety Branch, Asbestos in Toys and Modelling Materials Issue No. 2, June, 1976.
5. Department of Labor, Occupational Safety and Health Administration: Asbestos Dust Standard, 29 CFR 1910.93a.
6. Department of Labor, Occupational Safety and Health Administration: Occupational Exposure to Asbestos, Notice of Proposed Rulemaking, FR Vol. 40, No. 197, pp. 47652-57665, (Oct. 9, 1975).
7. Department of Labor, Occupational Safety and Health Administration: Asbestos Dust in the Construction Industry. Preliminary Draft: Technical Feasibility Assessment, Spackling and Drywall Joint Compounds, p. 112, (1977).
8. Edge, J. R.: Asbestos Related Disease in Barrow In Furness Env. Res. 11:244-247 (1976).
9. Elmes, P. C. and Simpson, M. J. C.: Insulation Workers in Belfast 3. Mortality 1940-66. *Br. J. Ind. Med.* 28: 226-236 (1971).
10. England, Health and Safety Exec. Dept. of Prices and Consumer Protection. Asbestos Labeling Scheme. April 1978.
11. Enterline, P., and Henderson, V.: Model for Extrapolating to Low Levels of Asbestos Exposure. Presented at Conference on Problems of Extrapolating the Results of Laboratory Animal Data to Men and Extrapolating the Results from High Dose Level Experiments to Low Dose Level. Pinehurst, N.C. (March 1976).
12. Enterline, P., DeCouffe, P., and Henderson, V.: Mortality in Relation to Occupational Exposure in the Asbestos Industry. *J. of Occupational Medicine* 14 (12): 897-903 (1972).
13. Enticnap, J. B., and Smither, W.: Peritoneal Tumours in Asbestosis. *Br. J. Ind. Med.* 21:20-31 (1964).
14. Environmental Defense Fund: Petition for Action under section 12 of the CPSA against fireplace ashes and Logs Containing Asbestos. Footnote 1, May 12, 1977.
15. Fletcher, D. C.: A Mortality Study of Shipyard Workers and Pleural Plaques. *Br. J. Ind. Med.* 29:142-145 (1972).
16. Greenberg, M., and Davies, R.: Mesothelioma Register 19678, *Br. J. Ind. Med.* 31:91-104 (1974).
17. Hammond, E. C., Selikoff, I. J., and Churg, J.: Neoplasia Among Insulation Workers in the United States with Special Reference to Intra Abdominal Neoplasia. *Ann. N.Y. Acad. Sci.* 132:519-525 (1965).
18. Hammond, E. C., and Selikoff, I. J.: Relation of Cigarette Smoking to Risk of Death of Asbestos Associated Disease Among Insulation Workers in the United States, pp. 312-317 International Agency for Research on Cancer (1973).
19. Herries, P. G.: Asbestos Hazard in Ship Dockyards. *Ann. Occup. Hyg.* 11:134-135 (1968).
20. Hasan, Faysal M. et al: The Significance of Asbestos Exposure in the Diagnosis of Mesothelioma: A 28 year Experience from a Major Urban Hospital. *Amer. Rev. Resp. Dis.* 115:761-768 (1977).
21. Huff, J. E., Hammons, A. S., Ding, A., Whitfield, B. L., and Urickson, J.: Asbestos: An Overview. *Env. Chemicals Human and Animal Health 3rd Annual Conference Proceedings.*
22. IARC Working Group on the Evaluation of the Carcinogenic Risk of Chemicals to Man. IARC Monographs on the Evaluation of the Carcinogenic Risk to Man: Asbestos. International Agency for Research on Cancer, 1977.
23. Interagency Collaborative Group on Environmental Carcinogens, 19th Meeting, NIH, Aug. 14, 1975.
24. Jones, H. B., and Grindon, A.: Environmental Factors in the Origin of Cancer and Estimation of the Possible Hazard to Man. *Fd. Cosmet. Toxicol.* 18:251-268 (1975).
25. Lillingston, G. A. et al: Conjugal Malignant Mesothelioma. *New Eng. J. Med.* 291 (11): 583-584 (Sept. 12, 1974).
26. McDonald, J. C., McDonald, A. D., Gibson, A. W., et al: The Health of Chrysotile Asbestos Mine and Mill Workers of Quebec. *Arch. Env. Health* 28:61 1974.
27. McEwen, J., Finlayson, A., Mair, A., and Gibson, A. A. M.: Mesothelioma in Scotland. *Br. Med. J.* 4:574-578 (1970).
28. Mereweather, E. R. A., and Price, C. W.: Report on the Effects of Asbestos Dust on the Lungs and Dust Suppression in Asbestos Industry. H.M. Stationery Office, London (1930).
29. National Institute for Occupational Safety and Health: Criteria for a Recommended Standard... Occupational Exposure to Asbestos. (1972).
30. Newhouse, M. L., and Berry G.: The Risk of Developing Mesothelioma Among Workers in an Asbestos Textile Factory. XVII International Congress on Occupational Health, Bristol, England (1975).
31. Newhouse, M. L., and Thompson, H.: Mesothelioma of Pleura and Peritoneum Fol-

- lowing Exposure to Asbestos in the London Area. *Brit. J. Ind. Med.* 22:261 (1965).
32. Newhouse, M.: Asbestos in the Work Place and the Community. *Ann. Occ. Hyg.* 16: 97-107 (1973).
33. Newhouse, M. L., and Berry, G.: Predictions of Mortality from Mesothelioma Tumours in Asbestos Factory Workers. *Br. J. Ind. Med.* 33:147-151 (1976).
34. Newhouse, M. L., and Berry G.: Asbestos and Laryngeal Carcinoma. *Lancet*. 2: 615 (1973).
35. Nicholson, W. J.: Case Study 1: Asbestos The TLV Approach. *N.Y. Acad. Sci.* 271: 152-169 (1976).
36. Rohl, A. N., et al.: Exposure to Asbestos in the Use of Consumer Spackling, Patching and Taping Compounds. *Science* 189:551-553 (Aug 15, 1975).
37. Selikoff, I. J.: Asbestos and Neoplasia. *Am. J. Med.* 42(4): 487-498 (1967).
38. Selikoff, I. J., and Hammond, E. C.: III Community Effects of Non-Occupational Environmental Asbestos Exposure. *Am. J. Pub. Health* 58(9):1658-1666 (1968).
39. Selikoff, I. J., Churg, J., and Hammond, E. C.: The Occurrence of Asbestosis Among Insulation Workers in the United States. *N.Y. Acad. of Sci.* 132:139-155 (1965).
40. Selikoff, I. J., Hammond, E. C., and Churg, J.: Asbestos Exposure, Smoking, and Neoplasia. *JAMA* 204(2):106-112 (1968).
41. Selikoff, I. J., Hammond, E. C., and Seidman, H.: Cancer Risk of Insulation Workers in the United States. pp. 209-216 International Agency for Research on Cancer (1973).
42. Selikoff, I. J., Hammond, E. C., and Churg, J.: Carcinogenicity of Amosite Asbestos. *Arch. Env. Health* 25:183-186 (1972).
43. Selikoff, I. J., Nicholson, W. J., and Langer, A. M.: "Asbestos Air Pollution". *Arch. Environ. Health*, 25:113, July 1972.
44. Sheers, G.: Effects of Asbestos in Dockyard Workers. *Br. Med. J.* 3:574-579 (1958).
45. Stell, P. M., and McGill, T.: Asbestos and Laryngeal Carcinoma. *Lancet* 2:416-417 (1973).
46. Stumpflus, J.: Epidemiology of Mesothelioma on Watchmen Island. *Br. J. Ind. Med.* 28:59-66 (1971).
47. Wagner, J. C., Sieggs, C. A., and Marchand, P.: Diffuse Pleural Mesothelioma and Asbestos Exposure in the North Western Cape Province. *Brit. J. Ind. Med.* 17:260-271 (1960).
48. Wagner, J. C., et al.: The Effects of the Inhalation of Asbestos in Rats. *Br. J. Cancer*, 29: 252-259 (1974).
49. Webster, I.: Asbestos and Malignancy. *SA Med. J.* 47:165-171 (1963).
50. Whitwell, P., and Rawcliffe, R. M.: Diffuse Malignant Pleural Mesothelioma and Asbestos Exposure. *Thorax* 26:622 (1971).
51. Kearney, A. T.: Economic Impact Assessment of the Proposed Ban of Asbestos Containing Patching Compounds, October 1977.
52. Rohl, A., Langer, A., and Selikoff, I.: Environmental Asbestos Pollution Related to Use of Quarried Serpentine Rock. *Science*, V. 196, pp. 1319-1322, June 17, 1977.
53. Bayard, S.: Memorandum, Risk of Respiratory Cancer Due to Low-Level Exposure to Asbestos from Spackling and Joint Taping Compounds. June 3, 1977.
54. Bayard, S.: Memorandum to File; Responses to Comments, October 1977.
55. Thompson, J. G., *Ann. of N.Y. Acad. Sci.* 132:196-214, 1965.
56. Dept. of Interior, Bureau of Mines: Selected Silicate Minerals and their Asbestiform Varieties. 1977.
57. Harrington, J. S., et al.: Mineral Fibers: Chemical, Physicochemical and Biological Properties. *Adv. Pharmacol. Chemother.* 12:291-402, 1975.
58. Stanton, M. D.: Some Etiological Considerations of Fiber Carcinogenesis. *Biological*

Effects of Asbestos. IARC Publication No. 8. pp. 289-294, Lyon, 1973.

CONCLUSION

Upon considering the published proposal, the oral and written responses to the proposal and other relevant material, the Commission bans consumer patching compounds and artificial emberizing materials (embers and ash) as set forth below.

Accordingly, pursuant to provisions of the Consumer Product Safety Act (sections 8 and 9, 86 Stat. 1215-17, as amended, 90 Stat. 506, 15 U.S.C. 2057, 2058), new Parts 1304 and 1305 are added to Title 16, Chapter II, Subchapter B, as follows:

PART 1304—BAN OF CONSUMER PATCHING COMPOUNDS CONTAINING RESPIRABLE FREEFORM ASBESTOS

Sec.

- 1304.1 Scope and application.
1304.2 Purpose.
1304.3 Definitions.
1304.4 Consumer patching compounds as banned hazardous products.
1304.5 Findings.

AUTHORITY: Sections 8, 9, 86 Stat. 1215-1217, as amended 90 Stat. 506, 15 U.S.C. 2057, 2058.

§ 1304.1 Scope and application.

(a) In this Part 1304 the Consumer Product Safety Commission declares that consumer patching compounds containing intentionally-added respirable free-form asbestos in such a manner that the asbestos fibers can become airborne under reasonably foreseeable conditions of use, are banned hazardous products under sections 8 and 9 of the Consumer Product Safety Act (CPSA) (15 U.S.C. 2057 and 2058). This ban applies to patching compounds which are (1) used to cover, seal or mask cracks, joints, holes and similar openings in the trim, walls, ceiling, etc. of building interiors, which after drying are sanded to a smooth finish and (2) are produced and distributed for sale to or for the personal use, consumption or enjoyment of a consumer in or around a permanent or temporary household or residence, a school, in recreation or otherwise.

(b) The Commission has found that (1) these patching compounds are being or will be distributed in commerce; (2) that they present an unreasonable risk of injury; and (3) that no feasible consumer product safety standard under the CPSA would adequately protect the public from the unreasonable risk of injury associated with these products. This rule applies to the banned hazardous products defined in section 1304.3 and described further in section 1304.4.

(c) Only consumer products are subject to this regulation. Patching compounds which are consumer products include those which a consumer can purchase. Merely labeling a patching compound for industrial use would not exclude such articles from the ban. If the sale or use of the product by consumers is facilitated, it is subject to the ban. Patching compounds which are labeled as, marketed, and sold solely for indus-

trial use in non-consumer environments are not subject to the ban. In addition to those products which can be sold directly to consumers, the ban applies to patching compounds containing respirable free-form asbestos which are used in residences, schools, hospitals, public buildings or other areas where consumers have customary access.

§ 1304.2 Purpose.

The purpose of this rule is to ban consumer patching compounds containing intentionally added respirable, free-form asbestos. These products present an unreasonable risk of injury due to inhalation of fibers which increase the risk of developing cancer, including lung cancer and mesothelioma, diseases which have been demonstrated to be caused by exposure to asbestos fibers.

§ 1304.3 Definitions.

(a) The definitions in section 3 of the Consumer Product Safety Act (15 U.S.C. 2052) apply to this Part 1304.

(b) "Asbestos" means a group of mineral fibers composed of hydrated silicates, oxygen, hydrogen, and other elements such as sodium, iron, magnesium, and calcium in diverse combinations and are: Amosite, chrysotile, crocidolite, anthophyllite asbestos, actinolite asbestos, and tremolite asbestos.

(c) "Free-form asbestos" is that which is not bound, or otherwise "locked-in" to a product by resins or other bonding agents, or which can readily become airborne with any reasonably foreseeable use.

(d) "Patching compounds" are mixtures of talc, pigments, clays, casein, ground marble, mica or other similar materials and a binding material such as asbestos which are sold in a dry form ready to be mixed with water, or such combinations in ready-mix paste form.

(e) "Consumer patching compounds" are those that are customarily produced or distributed for sale to or for the personal use, consumption or enjoyment of consumers in or around a permanent or temporary household or residence, a school, in recreation or otherwise. The Commission considers that patching compounds for application in these consumer environments are either distributed for sale to or are for the personal use or enjoyment of consumers.

(f) "Intentionally-added asbestos" is asbestos which is (1) added deliberately as an ingredient intended to impart specific characteristics; or, (2) contained in the final product as the result of knowingly using a raw material containing asbestos. Whenever a manufacturer finds out that the finished product contains asbestos, the manufacturer will be considered as knowingly using a raw material containing asbestos, unless the manufacturer takes steps to reduce the asbestos to the maximum extent feasible.

(g) "Initial introduction into commerce" occurs when the manufacturer ships a product covered by this regulation from a facility of the manufacturer to a distributor, retailer, or user.

§ 1304.4 Consumer patching compounds as banned hazardous products.

On the basis that airborne asbestos fibers present the hazards of cancer, including lung cancer and mesothelioma to the public, consumer patching compounds containing intentionally-added, respirable free-form asbestos, which have been manufactured or initially introduced into commerce after January 16, 1978, are banned hazardous products. In addition, all other consumer patching compounds containing intentionally-added, respirable free-form asbestos, no matter when manufactured or initially introduced into commerce, are banned hazardous products after June 11, 1978.

§ 1304.5 Findings.

(a) *The degree and nature of the risk of injury.* The Commission finds that the risk of injury which this regulation is designed to eliminate or reduce is from cancer, including lung cancer and mesothelioma. In assessing the degree and nature of the risk of injury to consumers, the Commission has reviewed experimental data and human experience information. The Commission noted that in the scientific literature, there is general agreement that there is no known threshold level below which exposure to respirable free-form asbestos would be considered safe. Further on the basis of such scientific opinion, it appears to the Commission that children are particularly vulnerable to carcinogens because of their longer potential lifetime and their rapid rate of growth. In areas of the country where asbestos may not be prevalent in the environment, the major risk of exposure for children and others may occur in the household. In areas of the country where more asbestos fibers are present in the environment, the public is exposed to additional risks from the presence of asbestos fibers in households and other consumer environments, the Commission concluded on the basis of these factors that consumer patching compounds containing respirable free-form asbestos present an unreasonable risk of injury to the public. In addition, a risk assessment was made. For purposes of this assessment, the Commission considered the use of patching compounds by the consumer, for six hours a day four times a year, to be a high yet reasonably foreseeable exposure. The increased risk of death from respiratory cancer induced by this exposure is estimated at between 10 and 2,000 per million. For five years of exposure at these levels, the risk increases geometrically and is estimated at between 1,000 and 12,000 per million. The lower estimate of 10 per million is closer to the actual risk for a one-year exposure. Nevertheless, in view of the seriousness of the injury and the cumulative effects of asbestos exposure, even this minimum figure represents an unacceptable risk. The Commission believes that reducing exposure to respirable free-form asbestos in the home represents a substantial decrease in risk to consumers, since, for many people, the major ex-

posure to inhalable asbestos is in the home.

(b) *Products subject to the ban.* Consumer patching compounds as defined in § 1034.3 (d), (e), (f) include such products as drywall spackling compounds and tape joint compounds (commonly known as "joint cement" or "tape joint mud"). The Commission estimates annual shipments of patching compounds subject to the ban at approximately 30-50 million "units," or individual packages, of various sizes from 0.5 to 25 pounds (dry) or 0.5 to 5 gallons (wet). The Commission believes that about half the patching compounds sold in 1977, and intended for sale to or use or enjoyment by consumers, were formulated with asbestos. Many others containing significant levels of asbestos contamination will also be affected by the ban.

(c) *Need of the public for the products and effects of the rule on their utility, cost and availability.* Patching compounds, though used primarily by commercial construction workers, are also used by consumers, and are used for the patching and sealing of cracks and joints in and around the household and in other consumer environments either by consumers or professional applicators. The compounds are used to cover areas on gypsum drywall which might otherwise be aesthetically undesirable or which might lead to structural damage, energy loss or lower property value. The asbestos in these compounds acts as a structural reinforcing agent which helps to reduce cracking and shrinkage of the compound over time, and which renders the compound more pliable or "workable" upon application.

(1) *Utility.* The elimination of asbestos from these products may result in the increased use or new development of substitutes which have similar properties to those of asbestos, or which impart similar qualities to the product. In current reformulations, asbestos is replaced by a combination of substances, of which the most common is attapulgite, a fibrous clay. Some non-asbestos formulations are reportedly not as effective as those containing asbestos in controlling shrinkage and cracking over time. The workability of some compounds may be diminished as well. This may adversely affect the utility derived from the product by consumers, and by professional contractors until such time as improved formulations are developed and available to end-users.

(2) *Cost.* Asbestos-free patching compound formulations may require more time to use. This would tend to increase the direct labor costs of residential and other construction and renovation. The expected increase is between 10 and 25 percent. The Commission estimates that the annual labor cost of drywall finishing in these consumer environments is on the order of \$1 billion. The use of non-asbestos patching compound formulations in all applications may increase this cost by \$50-\$125 million, assuming that roughly half the current labor costs (i.e., that portion now associated with the use

of asbestos formulations) are affected by the 10-25 percent increase. The burden of this cost is expected to fall directly on owners of existing homes who may engage in some renovation, and on purchasers of newly-renovated or newly constructed homes. These increased costs are expected to diminish over time as formulations improve and as applicators become more accustomed to using non-asbestos formulations. The use of asbestos substitutes may also lead to cost increases in the manufacture of patching compounds. The Commission estimates this cost, which may vary widely from firm to firm, at an average of 5-15 percent. This is made up primarily of increased costs of raw materials and of formulation research and development. It is expected that the price of many patching compounds may rise as a result. Producers, distributors, and retailers of patching compounds may also have to incur costs associated with the disposal of products in inventory. The Commission estimates that the wholesale value of manufacturers' and distributors' inventories at the time the ban becomes effective will be approximately \$15 million. These costs may be reflected in the prices charged for asbestos-free patching compound formulations, and in the prices of other drywall and paint products. It appears that, because of competitive pressure from asbestos-containing compounds, producers of asbestos-free formulations have not yet passed on to purchasers their increased costs. If the increased production costs of asbestos-free formulations can be passed on completely as a result of the ban, the total annual price effect for the year following the issuance of the ban may be \$10-\$60 million. The magnitude of this effect may be reduced significantly in successive years following the issuance of the ban as producers' development costs are amortized, as raw materials become more widely available, and as price competition is strengthened because of market pressure and economies of scale associated with production.

(3) *Availability.* The supply of asbestos substitutes, particularly attapulgite clay and relatively uncontaminated talc, for use in the manufacture of patching compounds may be insufficient to meet the short-run demand which is expected to be stimulated by the promulgation of the ban. Further, many small producers probably lack the technical capability to reformulate their products, and may be forced to cease production, at least until formulations of satisfactory cost and performance are developed. This may affect some professional contractors. In the short run, consumers may be indirectly affected by delays in drywall finishing and building completion.

(d) *Any means of achieving the objective of the ban while minimizing adverse effects on competition or disruption or dislocation of manufacturing and other commercial practices consistent with the public health and safety.* The adverse effects of the ban on patching compounds containing asbestos is reduced by

limiting the ban to intentionally added asbestos. Other alternatives such as limiting the scope of the ban only to products purchased and used by consumers or to issuing a ban with a later effective date, were considered by the Commission. However, none was found that would cause less disruption or dislocation of manufacturing and other commercial practices, consistent with public health and safety.

Conclusion. The Commission finds that this rule, including its effective date is reasonably necessary to eliminate or reduce the unreasonable risk of injury from cancers such as lung cancer and mesothelioma that are associated with the banned products described herein, that no feasible consumer product safety standard under the Consumer Product Safety Act can adequately protect the public from this risk, and that promulgation of this rule is in the public interest.

PART 1305—BAN OF ARTIFICIAL EMBERIZING MATERIALS (ASH AND EMBERS) CONTAINING RESPIRABLE FREE-FORM ASBESTOS

Sec.

1305.1 Scope and application.

1305.2 Purpose.

1305.3 Definitions.

1305.4 Artificial fireplace ash and embers as banned hazardous products.

1305.5 Findings.

AUTHORITY: Secs. 8, 9, 30(d), Pub. L. 89-573, as amended, Pub. L. 94-284; 86 Stat. 1215-17, as amended, 90 Stat. 508 (15 U.S.C. 2057, 2058).

§ 1305.1 Scope and application.

In this Part 1305 the Consumer Product Safety Commission declares that artificial emberizing materials (ash and embers) containing respirable free-form asbestos generally packaged in an emberizing kit for use in fireplaces, and designed for use in such a manner that the asbestos fibers can become airborne under reasonably foreseeable conditions of use are banned hazardous products under sections 8 and 9 of the Consumer Product Safety Act (CPSA) (15 U.S.C. 2057 and 2058). This ban applies to artificial emberizing materials available in separate kits or with artificial fireplace logs for use in fireplaces and sprinkled or coated by consumers on the artificial logs to simulate live embers and ashes and give a glowing appearance when subjected to high temperatures. Bags of material containing asbestos that are sold separately to be sprinkled on and under artificial logs to simulate burning and glowing ashes also come within the scope of this ban.

§ 1305.2 Purpose.

The purpose of this rule is to ban artificial emberizing materials containing respirable free-form asbestos. These products present an unreasonable risk of injury due to inhalation of fibers which increase the risk of developing cancers such as lung cancer and mesothelioma,

diseases which have been demonstrated to be caused by exposure to asbestos fibers.

§ 1305.3 Definitions.

(a) The definitions in section 3 of the Consumer Product Safety Act (15 U.S.C. 2052) apply to this Part 1305.

(b) "Asbestos" means a group of mineral fibers composed of hydrated silicates, oxygen, hydrogen and other elements such as sodium, iron, magnesium and calcium in diverse combinations and are: Amosite, chrysotile, crocidolite, anthophyllite asbestos, actinolite asbestos, and tremolite asbestos.

(c) "Free-form asbestos" is that which is not bound, woven, or otherwise "locked-in" to a product by resins or other bonding agents, or those from which fibers can readily become airborne with any reasonably foreseeable use.

(d) "Emberizing materials" means an asbestos-containing material generally packed in an "emberizing" kit to be placed under artificial logs in gas-burning fireplace systems or in artificial fireplaces for decorative purposes. The product is also glued to artificial logs, either at a factory or by a consumer using an emberizing kit. (Synthetic logs manufactured of cellulosic products which are consumed by flames are not included in this definition. Electric artificial logs and artificial ash beds used in electric fireplaces, which do not contain respirable free-form asbestos are not included in this definition.)

§ 1305.4 Artificial fireplace ash and embers as banned hazardous products.

On the basis that airborne asbestos fibers present the hazards of cancer such as lung cancer and mesothelioma to the public, artificial fireplace ash and embers containing respirable free-form asbestos are banned hazardous products.

§ 1305.5 Findings.

(a) *The degree and nature of the risk of injury.* The Commission finds that the risk of injury which this regulation is designed to eliminate or reduce is from cancer, including lung cancer and mesothelioma. Measurements are not available of the amounts of asbestos in the air from asbestos-containing emberizing materials in homes. However, it appears that the amount of airborne asbestos in such homes would increase when air currents in the home are created by drafts from a fireplace chimney or other activities that stir air in any room. Since emberizing materials may contain up to 50 percent asbestos, which if not permanently bound into artificial fireplace logs would be in respirable form, the risk associated with emberizing materials is considerable, especially since it continues to exist 24 hours a day.

(b) *Products subject to the ban.* Artificial emberizing materials are decorative simulated ashes or embers, used in certain gas-burning fireplace systems, which glow to give the appearance of real burning embers. The material is sprinkled on

or glued to gas logs, or sprinkled on fireplace floors.

(c) *Need of the public for the products and effects of the rule on their utility, cost, and availability.* Artificial fireplace emberizing material serves a strictly decorative purpose and does not materially affect the actual performance of the fireplace gas system in terms of its ability to provide heat. A certain degree of aesthetic desirability exists, however, since the product "system" itself (the gas log, ashes, and embers) is intended to simulate burning wooden logs. Gas logs may be sold with artificial emberizing material attached at the factory (the log commonly referred to as being "frosted"), or with the "embers" in a separate kit, often mixed with simulated "ashes." Virtually all gas logs are either frosted or packaged with an emberizing kit; however, the majority of gas logs produced in 1977 were packaged with non-asbestos-containing emberizing kits. The Commission estimates annual sales of artificial gas logs at approximately 100,000 units. Some 25,000-30,000 of these would be subject to the ban. Approximately 100,000 gas logs frosted or treated by consumers with asbestos are estimated to be in existence. The Commission believes that the majority of gas logs are sold with emberizing kits; this gives the consumer a choice as to whether or not to use the artificial embers and ashes.

(1) *Utility.* Manufacturers of artificial gas log emberizing material are currently using four substitutes for asbestos in their products: vermiculite, rock wool, mica, and a synthetic fiber. None of the four is claimed to be as aesthetically effective as asbestos. Thus, the utility derived by consumers from some gas-burning fireplace systems may be adversely affected.

(2) *Cost.* No effect on the overall price level of gas logs is anticipated as a result of the ban. The average price of emberizing kits may rise somewhat; the Commission estimates the total price effect of the ban on consumers at under \$25,000.

(3) *Availability.* The Commission believes that all producers of artificial emberizing material will have eliminated asbestos from their products by the time the ban becomes effective. No significant impact on the availability of asbestos substitutes to producers nor on the availability of gas logs or emberizing kits to retail dealers and consumers is expected as a result of the ban.

(d) *Any means of achieving the objective of the ban while minimizing adverse effects on competition or disruption or dislocation of manufacturing and other commercial practices consistent with the public health and safety.* The Commission believes that there will be minimal disruption to the market for artificial emberizing materials as a consequence of the ban and that no further reduction in adverse effects is feasible.

Conclusion. The Commission finds that this rule, including its effective date, is

reasonably necessary to eliminate or reduce the unreasonable risk of injury from cancers such as lung cancer and mesothelioma that are associated with the banned products described herein, that no feasible consumer product safety standard under the Consumer Product Safety Act can adequately protect the public from this risk, and that promulgation of this rule is in the public interest.

Effective Dates: Part 1304 becomes effective January 16, 1978.

Part 1305 becomes effective December 15, 1977.

Dated: December 12, 1977.

SHELDON D. BUTTS,
Assistant Secretary, Consumer
Product Safety Commission.

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EXHIBIT 40

REVIEW ARTICLE

The Hazards of Chrysotile Asbestos: A Critical Review

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Abstract: Chrysotile, or "white", asbestos is the dominant form of asbestos in international commerce today. It accounts for 99% of current world asbestos production of 2 million tonnes. Chrysotile is an extremely hazardous material. Clinical and epidemiologic studies have established incontrovertibly that chrysotile causes cancer of the lung, malignant mesothelioma of the pleura and peritoneum, cancer of the larynx and certain gastrointestinal cancers. Chrysotile also causes asbestosis, a progressive fibrous disease of the lungs. Risk of these diseases increases with cumulative lifetime exposure to chrysotile and rises also with increasing time interval (latency) since first exposure. Comparative analyses have established that chrysotile is 2 to 4 times less potent than crocidolite asbestos in its ability to cause malignant mesothelioma, but of equal potency of causation of lung cancer. The International Agency for Research on Cancer of the World Health Organization has declared chrysotile asbestos a proven human carcinogen. Sales of chrysotile asbestos have virtually ended in Western Europe and North America, because of widespread recognition of its health hazards. However, asbestos sales remain strong in Japan, across Asia and in developing nations worldwide. The claim has been made that chrysotile asbestos can be used "safely" under "certain conditions" in those nations. That claim is not accurate. The Collegium Ramazzini, an international learned society in environmental and occupational medicine, has called for an immediate worldwide ban on all sales and uses of all forms of asbestos, including chrysotile. The rationale for this ban is threefold: (1) that safer substitute materials are readily available, (2) that "controlled" use of asbestos is not possible, and (3) that the health risks of asbestos are not acceptable in either the industrialized or the newly industrializing nations.

Key words: Chrysotile, Asbestos-related diseases, Epidemiology, Risk evaluation, Human carcinogenicity, Malignant mesothelioma, Lung cancer

Introduction

Chrysotile asbestos is an important cause of human illness and death¹. Clinical and epidemiologic studies have established beyond all reasonable doubt that chrysotile asbestos causes cancer of the lung, malignant mesothelioma

of the pleura and peritoneum, cancer of the larynx and certain gastrointestinal cancers². Chrysotile also causes asbestosis, a progressive fibrotic disease of the lungs. The risk of these diseases increases with cumulative exposure to chrysotile and also with time since first exposure. Chrysotile asbestos has been declared a proven human carcinogen by the US Environmental Protection Agency (EPA)³, by the US Occupational Safety and Health Administration (OSHA)⁴,

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and by the International Agency for Research on Cancer of the World Health Organization⁹. The total number of deaths in the United States that will eventually be caused by exposure to asbestos, over 95% of it chrysotile asbestos, is estimated to exceed 400,000⁹.

Background

Asbestos is a term given to a group of minerals that crystallize in a fibrous habitat. Four fibrous minerals have commercial importance—chrysotile, amosite, crocidolite, and anthophyllite. Of these, chrysotile is the most important, accounting for more than 95% of current world production. The various minerals differ chemically and structurally, but all readily separate into extremely fine fibers, most of which are thinner than 1 μm in diameter. As such, they can easily become airborne during manufacturing processes or by abrasion or disturbance of asbestos-containing materials. Their thinness allows them to be readily inspired and carried into the lower regions of the human lung, where they can become lodged and cause damage.

The modern history of asbestos disease dates from the beginning of the twentieth century, when two cases of asbestotic lung scarring were briefly described in asbestos textile workers. The pulmonary disease resulting from such scarring was well described in subsequent publications and the term *asbestosis* applied to it in 1924. An association of bronchogenic carcinoma with asbestos was first suggested in the 1930s. Mesothelioma, a malignancy of the lining of the chest or abdomen, was clearly associated with asbestos in 1960.

Despite publication over the past four decades of a voluminous literature on the causal association between asbestos and disease in different populations, and despite extensive experimental demonstration of the carcinogenicity of all forms of asbestos in laboratory animals, there currently exists an extensive and often acrimonious debate concerning the carcinogenicity of chrysotile asbestos. Because of the continuing extensive sale and use of asbestos in South and Central America, Asia, and Africa and the continued widespread presence of asbestos materials in buildings in the United States and Europe, it is of vital importance that this unnecessary debate be brought to a swift conclusion.

This review considers epidemiologic studies of the health effects of asbestos in populations exposed to commercial chrysotile and to mixtures of chrysotile and other forms of asbestos. We show that evidence for the human carcinogenicity of chrysotile asbestos is incontrovertible. Claims have been made that chrysotile asbestos can be used

safely. These claims are not supported by valid data.

The Spectrum of Asbestos Diseases

A seminal study that established much of our current knowledge of the spectrum of asbestos diseases was conducted by Selikoff and Seidman¹⁾ (Table 1). It followed 17,800 heavily exposed asbestos insulation workers for 20 years and demonstrated the wide range of malignancies caused by asbestos. Of these malignant diseases, bronchogenic carcinoma and mesothelioma were the two most important, accounting for more than 90% of the increased cancer risk in this population. Nearly 24% of the deaths in this group of workers were due to bronchogenic carcinoma and 9% to mesothelioma. Lesser degrees of excess cancer mortality were seen at other sites including the esophagus, stomach, colon and rectum, larynx, pharynx and buccal cavity, gall bladder and bile ducts, and kidney. Overall, among insulators whose asbestos exposure began prior to 1968, 30.9% of deaths were excess cancer deaths resulting from one of the above malignancies, additionally another 8.6% of deaths in this population were due to asbestosis.

Although the mortality experience of this unusual group is extraordinary, the insulators were not alone either in their exposure to asbestos or in their risk of asbestos-associated cancer. In 1982 our group made estimates of the expected mortality in the United States from past occupational exposures to asbestos²⁾. Considering labor turnover since 1940, it was estimated that approximately 700 asbestos-related deaths occur each year among workers directly installing or removing insulation. Additionally, a much larger population of construction workers was also exposed to asbestos, albeit to lower levels. Because of the much greater number of construction workers, many more asbestos-related deaths are taking place among them. Thus it was estimated that approximately 7000 deaths are occurring each year in current or former shipyard and construction workers and in workers exposed to asbestos through maintaining insulation materials in plants and powerhouses. We estimated that the total mortality in the United States from the asbestos epidemic will exceed 400,000 deaths. Over 95% of the asbestos responsible for this exposure is chrysotile.

Many of the workers who are now dying of asbestos-related disease were exposed to asbestos in concentrations in excess of 10 fibers/ml of air. The current US standard, promulgated in 1994, is 100 times lower, 0.1 fiber/ml. Additionally, procedural standards now require enclosures and the use of air-supplied respirators in circumstances in which release

Table 1. Observed and expected deaths among 17,800 asbestos insulation workers, United States, 1967-1986*

Underlying cause of death	Observed, (n)	Expected, (n)	Standardized mortality ratio (SMR)
Total deaths, all sites	4951	3453.5	143
Total cancer, all sites	2295	761.4	301
Lung cancer	1168	268.7	435
Pleural mesothelioma	173	0	∞
Peritoneal mesothelioma	285	0	∞
Larynx	18	10.6	170
Oropharynx	48	22	218
Kidney	37	18.9	196
Pancreas	54	39.5	137
Esophagus	30	17.8	168
Stomach	38	29.4	129
Colon and Rectum	121	88.5	137
Gall bladder and bile ducts	14	5.4	261
Noninfectious pulmonary disease	507	144.8	350
Asbestosis	427	0	∞
All other causes	2149	2547.3	84

*From Selikoff and Seidman¹¹; with permission. +Based on all available information (autopsy, surgical, clinical, and death certificate).

of asbestos fibers is likely to occur, such as during removal of in-place asbestos. These standards were not in place in years past. If US regulations are followed, asbestos-related disease from future exposures will be sharply reduced. However, workers in other regions of the world, particularly in the developing nations in South America, Asia, and Africa, are not similarly protected. In some of these nations, chrysotile asbestos is not officially recognized as hazardous and controls on its use are often minimal.

Lung cancer

It is widely accepted that asbestos fibers, including chrysotile fibers, increase the existing risk of developing lung cancer in proportion to the cumulative exposure that occurred up to a time 10 years prior to evaluation⁹. The relationship can be expressed formally by the equation $I = I_0 (1 + K_L \cdot f \cdot d_{(t-10)})$, where I is the lung cancer incidence or mortality observed in a study population; I_0 is the age- and calendar year-specific lung cancer incidence or mortality observed expected in the absence of asbestos exposure (ideally, I and I_0 would explicitly consider smoking habits of each study individual); f is the intensity of asbestos exposure to fibers longer than 5 μm ; d is the duration of exposure in years up to a period 10 years prior to evaluation; and K_L is a proportionality constant that is a measure of the

carcinogenic potency of the asbestos exposure. K_L represents the fractional increase in lung cancer incidence or mortality that occurs from a 1-year exposure to 1 fiber/ml. The relative risk of lung cancer, I/I_0 , is independent of age and depends only on exposure characteristics.

Information is available that allows exposure-response relationships between asbestos and lung cancer to be considered in various exposure scenarios. Table 2 summarizes estimates of the percentage increase in lung cancer risk associated with a 1-year exposure to 1 fiber/ml that have been made by individual researchers or by national review groups⁹. There are obviously substantial uncertainties in estimates of K_L . This uncertainty arises first, because only limited data exist on workplace asbestos exposures prior to the mid 1960s. Also when available, the data were usually expressed in particle counts, rather than in fiber counts. The relationship between particle and fiber counts is highly uncertain. When early data were unavailable, estimates of exposure have had to be made, based on later fiber counts and on information on changes in control procedures and exposure conditions over time. These adjustments too, are uncertain. Finally, uncertainties exist in the expected lung cancer risks, which depend on smoking habits and, perhaps, on exposures to lung carcinogens other than asbestos. Despite all these uncertainties, many groups have made estimates

Table 2. Risks of lung cancer and mesothelioma in workers exposed to various asbestos minerals

Asbestos exposure and location	Type of asbestos	Percentage increase in lung cancer for a 1-y exposure to 1 f/ml of asbestos*
Textile manufacturing (South Carolina)	100% Chrysotile	2.6
Textile manufacturing (Rochdale, UK)	98% Chrysotile 2% Crocidolite	1
Textile manufacturing (Pennsylvania)	98% Chrysotile 1% Crocidolite 1% Amosite	1.4
Amosite insulation manufacturing (New Jersey)	100% Amosite	4.3
Insulation application (United States)	60% Chrysotile 40% Amosite	0.8
Asbestos products (United States)	80% Chrysotile 15% Amosite 5% Crocidolite	0.5
Asbestos cement products manufacturing (Louisiana and Ontario)	89% Chrysotile 10% Crocidolite 1% Amosite	1.8
Crocidolite mining	100% Crocidolite	1
Chrysotile mining	100% Chrysotile	0.1

*Details of the calculation of these unit exposure risks are described by the Environmental Protection Agency²¹.

Chrysotile as mined in Canada is contaminated by a small amount of tremolite (generally less than 1%). This contaminant is carried over into fiber used in different industries. The percentages in the column refer to the percentage of commercially sold fiber, including the contamination. *The percentages of the various fibers used in the plants studied were not given. The estimates are based on published product compositions.

of risk parameters. The results (Table 2) indicate remarkable consistency within an industry and even across industries. The risk of lung cancer per cumulative fiber exposure is very similar for all exposure circumstances except chrysotile mining and milling. Risks in the three chrysotile textile manufacturing studies ranged from 1% to 2.6% per 1-year exposure to 1 fiber/ml. These risks are not statistically different from one another and cannot be attributed to the small use of commercial amphibole asbestos in two of the textile plants. Indeed, the highest lung cancer risk was found in the textile plant that used no commercial amphiboles.

Among the remaining nonmining studies, the percentage increase in lung cancer for each year of exposure to 1 fiber/ml ranged from 0.5% to more than 4%, irrespective of the type of fibers used in the production process. The only exceptions were two studies of friction product manufacturing and one of asbestos cement production. In each of these three studies, severe uncertainties limit the validity of the lower risks reported. All remaining risks, involving substantial amphibole exposure, are similar to those of predominantly chrysotile exposures, within the statistical uncertainties of the data. Even a pure crocidolite exposure

in mining demonstrated an increased risk of only 1% for each year of exposure to 1 fiber/ml²¹.

Although studies of chrysotile mining and milling demonstrate an excess risk of lung cancer, the risk is more than 10 times lower than that seen in studies of asbestos production workers exposed only to chrysotile or to 97% to 98% pure chrysotile. The origin of this lower risk in the miners and millers is not fully understood. Part of the difference may reflect the different fiber size distributions between the mining and milling operations and the textile plants and other production facilities. Fibers are presumably clumped together and are larger in mining and milling, but more fragmented and smaller in the user industries.

In summary, the available data on workers employed in the production of asbestos products strongly indicate a lung cancer risk for chrysotile similar to that seen in workers exposed to amosite and crocidolite asbestos. The best estimate of lifetime lung cancer risk for worker exposure to chrysotile in the using industries (as opposed to the mining and milling industries), is an increase of 1% in lung cancer risk for each year of exposure to 1 fiber/ml ($K_L = 0.01$). Higher fiber exposure circumstances or longer periods of

Table 3. Ratio of mesothelioma to adjusted excess lung cancer according to type of asbestos exposure**

Type of exposure	Studies (n)	Mesothelioma/excess lung cancer	
		Pleural cases	All cases
Chrysotile	8	0.13	0.14
Predominantly chrysotile	6	0.24	0.48
Amosite	2	0.13	0.22
Predominantly crocidolite	6	0.47	0.61
Anthophyllite	1	0	0
Talc (tremolite)	2	0	0.08
Mixed exposures	16	0.19	0.4

*From Environmental Protection Agency³¹. **Adjusted to the US male cancer rates in 1970.

exposure would give directly proportional higher risks. In certain textile operations, the unit exposure risk appears to be as much as three times higher than this lower limit. No data are available to indicate the presence of a threshold below which there is no risk from exposure to any asbestos mineral.

Malignant mesothelioma

The risk of mesothelioma by asbestos fiber type can be analyzed in several ways. First, because the risk of lung cancer is very similar across all exposures to all fiber types, excluding mining and milling of chrysotile, one can use the excess number of lung cancers as a measure of cumulative fiber exposure. With comparable follow-up periods, the ratio of the number of mesotheliomas to excess lung cancer is then a measure of the relative risk of mesothelioma at a given level of fiber exposure. Were mesotheliomas produced only by amphiboles, one would expect large differences in the mesothelioma: lung cancer ratio between populations with pure chrysotile exposure and those with extensive amphibole exposure. Table 3 summarizes this ratio by fiber type usage for more than 40 studies.

The ratio of mesothelioma to lung cancer is seen in this analysis to be the same, within statistical uncertainty, for exposures to 100% chrysotile, 97%+ chrysotile, 100% amosite, and mixtures of chrysotile, amosite, and crocidolite. Only 100% crocidolite exposures appear to have a greater ratio, about two to four times above that of predominantly chrysotile exposures. This relatively small difference in the potential for crocidolite to produce mesotheliomas cannot explain the high mesothelioma risk seen in chrysotile exposures that are accompanied by only a very small exposure to crocidolite. Canadian chrysotile that is amphibole-free

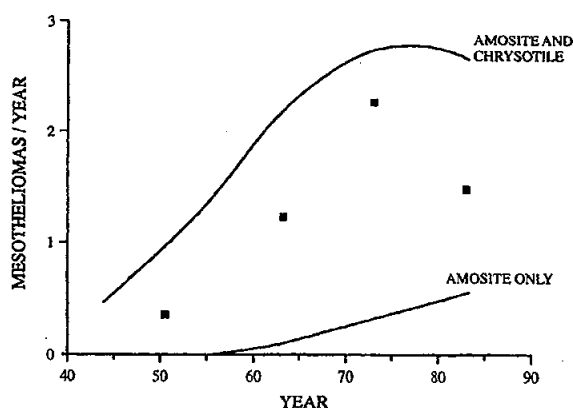


Fig. 1. Estimated and observed cases of mesothelioma/year. 1943–1987 for insulators exposed to amosite alone and amosite/chrysotile. Estimated numbers (smooth curves) are from models of asbestos cancer risk. The solid square represents the number of mesothelioma cases actually observed.

still is associated with mesothelioma⁸). These data strongly suggest therefore that much of the mesothelioma risk in populations with predominantly chrysotile exposures is due to chrysotile².

The mortality risk of mesothelioma from exposure to asbestos can be described by a widely accepted mathematical model (Fig. 1). In this model there is a very low risk of mesothelioma for approximately 20 years from first exposure to asbestos. Thereafter, however, the risk rises very rapidly such that in long-term asbestos-exposed populations mesothelioma may actually become the dominant cancer risk.

Chronologic information is available from two groups of

insulation workers that allows consideration of the contribution of chrysotile to mesothelioma risk. The essence of this analysis is a comparison of the time-course of appearance of mesotheliomas with the time-course of use of (1) chrysotile and (2) other types of asbestos. The analysis takes advantage of the fact that prior to 1935 insulation workers in the United States were exposed only to chrysotile. From 1935 until 1940 they were exposed mainly to chrysotile and only occasionally to amosite. Regular exposure to mixtures of chrysotile and amosite began only after 1940. Because of the strong dependence of mesothelioma risk to time elapsed since exposure, exposures to amosite would not therefore be expected to contribute substantially to a mesothelioma risk in this workforce before the mid-1950s. Observations of mortality from mesothelioma prior to that time would relate directly to chrysotile.

The analysis was undertaken in the 632 members of the New York and New Jersey locals of the Insulator's Union who were members on January 1, 1943². The majority of the group were first employed prior to 1923; for two

individuals first employment as an insulator began in 1888. Follow-up of the group has continued from 1943 until the present. Through 1992, all but 40 of the 632 were deceased.

The model given above for mesothelioma risk and for estimates of insulation workers' exposure was used to calculate the expected numbers of mesotheliomas for the period from 1943 to 1987 among this cohort. This calculation was done for two periods of time. In one calculation, only exposures subsequent to 1935 were considered ("amosite period") in the other, all asbestos exposures to individuals in the group were considered, from their first exposure to chrysotile asbestos until termination of employment or death ("total period"). The numbers of mesothelioma deaths observed were compared to the number that would be expected if amosite were the sole cause of the disease.

Figure 2 shows the results of these calculations. The principal finding is that the time course of mesothelioma risk is totally incompatible with an exposure pattern that begins only in the late 1930s. Indeed, the 95% confidence limits on three of the four data points do not intercept the distribution that would be expected, were amosite exposure responsible for mesothelioma in this population. Barring undiscovered exposures to amphiboles prior to 1935, these data present strong evidence that chrysotile is the substantial, indeed the dominant contributor to the mesothelioma risk experienced by this group of insulation workers².

The study by Selikoff *et al.*¹⁰ of the entire union membership of US and Canadian insulators also strongly indicates the existence of a mesothelioma risk associated with exposure to chrysotile. Follow-up for this study began in 1967, 30 years after the earliest incorporation of amosite by insulation manufacturers into their products. However, the risk of mesothelioma rises steeply with time from first exposure for a period of at least 50 years. Were only amosite contributing to risk, this pattern would not be expected. The pattern relates clearly to chrysotile.

One can also estimate risk of mesothelioma due to chrysotile through direct calculations in mixed-exposure circumstances (Table 4). These analyses show that risk of

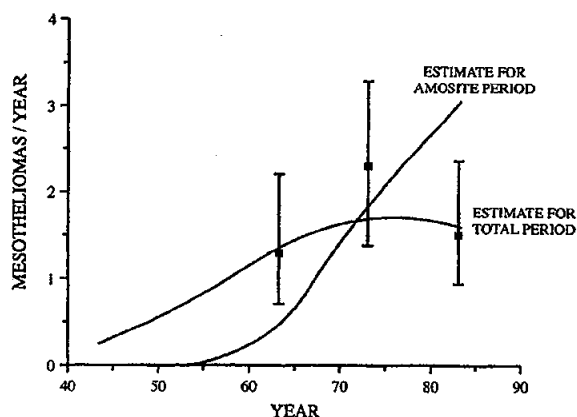


Fig. 2. Estimated and observed cases of mesothelioma/year, 1943–1987. Estimated mesothelioma risk (cases/year) adjusted to yield 56 deaths. The solid squares represent the number of mesothelioma cases actually observed.

Table 4. Risks of mesothelioma in workers exposed to various asbestos minerals

Asbestos exposure and location	Type of asbestos	Risk coefficient
Textile production (Rochdale, UK)	Chrysotile	1×10^{-8}
Insulation workers (United States)	Chrysotile and Amosite	1.5×10^{-8}
Factory workers (Paterson, NJ)	Amosite	3.2×10^{-8}
Miners and millers	Crocidolite	13.4×10^{-8}
Cement workers (Ontario, Canada)	Chrysotile and crocidolite	12×10^{-8}

mesothelioma/fiber exposure, as measured by K_M , is virtually the same for exposures to 98% chrysotile + 2% crocidolite, 60% chrysotile + 40% amosite, and 100% amosite. The value of K_M from the study of Canadian cement workers is higher than the chrysotile-amosite exposures, as was a value of K_L in the same group of workers. The value for a pure crocidolite exposure, as calculated by de Klerk and Armstrong⁷ for the mining population of Australia, is about 10 times greater. As with the values of K_L in Table 1, K_M is not definite because of uncertainties of exposures in the early exposure years of the groups under study and from uncertainties of small numbers. Indeed, from a consideration of the ratios of mesothelioma to excess lung cancer, the mesothelioma potency of crocidolite would appear to be only two to four times greater than chrysotile or amosite mesothelioma potency.

The problem of mesothelioma from exposure to chrysotile continues to the present time. Peto *et al.*¹⁰ predict that deaths from mesothelioma among men in Western Europe will increase from just over 5,000 in 1998 to about 9,000 by the year 2018. In Western Europe alone, past asbestos exposure will cause a quarter of a million deaths from mesothelioma over the next 35 years. The number of lung cancer deaths in Western Europe over the next 35 years¹⁰. In Sweden, Jarvholm has reported that the number of deaths caused each year by malignant mesothelioma is greater than the number of deaths caused in that country by all workplace injuries.

Current World Uses of Asbestos¹³

Asbestos usage worldwide is extensive, but there have been dramatic changes in the production and use of asbestos in recent years. Table 5 gives representative production data for the past three decades¹⁴; these data have substantial

Table 5. World production of asbestos

Year	Production (tonnes)
1963	2,922,000
1973	4,614,000
1978	5,159,000
1983	4,276,000
1988	4,323,000
1993	2,650,000
1994	2,410,000
1995	2,308,300 (a)
1996	2,140,000 (a)

(a) Chrysotile only.

uncertainties because of limited information on Russian production. The data clearly indicate a rising world production until the late 1970's. After that time a steady decline ensued. Between 1963 and the middle 1970's amphibole mineral constituted from 5% to 7% of the total asbestos production. In subsequent years, the percentage drop in amphibole usage was considerably greater than that for chrysotile. For example, at peak production South Africa mined 269,000 tons of amphibole in 1978, but less than 47,000 in 1991, of which 20,000 was crocidolite. Amosite production ceased in 1992.

Currently over 95% of all asbestos used worldwide is chrysotile, with crocidolite being used only for very specialized purposes. Table 6 shows the 17 top chrysotile consuming nations in 1994¹⁵. France and other European nations have since banned asbestos from use. The current primary users of chrysotile are countries in Asia and Central/South America. Substantial use also continues in the Middle East and Eastern Europe. While there has been an overall decline in chrysotile asbestos usage, a decline has not occurred in all countries. The decline has been substantial in Western Europe and the United States, but an increase has taken place in Asian nations. Some of these changes with over time can be seen in the data on annual imports and production of asbestos in selected nations (Table 7)¹⁴.

Parallel with the dramatic changes in the global distribution of asbestos, there have occurred changes in its uses.

Table 6. Principal chrysotile consuming countries in 1994

Nation	Annual usage (tonnes)
Commonwealth of Independent States	700,000
China	220,000
Japan	195,000
Brazil	190,000
Thailand	164,000
India	123,000
South Korea	85,000
Iran	65,000
France	44,000
Indonesia	43,000
Mexico	38,000
Columbia	30,000
Spain	29,000
USA	29,000
Turkey	25,000
Malaysia	21,000
South Africa	20,000
Total	2,021,000

Table 7. Annual imports and production of asbestos, in tonnes, in selected countries, by year

Country	1970	1975	1980	1985	1994 (b)
Japan	311,274	261,841	309,305	264,619	195,000
Thailand	21,271	43,024	58,756	75,516	164,000
India	56,008	63,240	99,010	123,000	
South Korea	35,292	56,960	36,787	57,143	85,000
Taiwan	6,589	13,363	31,247	24,519	
Mexico	40,460	60,981		54,871	38,000
France	151,846	138,637	127,123	68,827	44,000
United States	660,000	538,000	162,000	29,000	

(b) Chrysotile only; from reference (15).

Previously, asbestos was used in a wide variety of products. Now, however, asbestos use is largely concentrated in relatively few products, which vary from nation to nation. Worldwide, the dominant use of asbestos is in cement products. For example, in Japan 93% of all asbestos is used in various fire-retardant wallboards and 3.6% in friction products. In developing nations, such as those in Southeast Asia, asbestos-cement pipes are of importance for water systems. South Korea, on the other hand, has extensive asbestos textile and friction product industries and ships the finished products to Japan, West Europe and the United States¹⁶.

There are also differences in national responses to the health hazards of asbestos. Scandinavian and other Western European nations have prohibited all new uses of asbestos. In the United States the permissible exposure level is 0.1 f/ml. In contrast, Japan and South Korea each have a standard of 2 f/ml for chrysotile; amosite and crocidolite use are prohibited in Japan, but lower standards apply in South Korea for amosite (0.5 f/ml) and crocidolite (0.2 f/ml). Generally, developing nations have permissible exposure levels greater than 1 f/ml.

At the international level, the International Labour Organization¹⁷ has published a Recommendation Concerning Safety in the use of Asbestos in which they advocate the banning of new uses of crocidolite and urge controls on the use of other asbestos minerals. They particularly advocate the use of substitute materials and alternative technologies.

With the use of asbestos being predominantly in cement products, a good opportunity for control of workplace and environmental exposures exists. During normal use of such products there is limited release of fibers, and during installation exposures can be well controlled with the use of appropriate dust collectors. However, this may not always

be done and workplace monitoring by regulatory agencies is important. Uncontrolled sawing can produce concentrations in excess of ten f/ml.

Conclusion: The Need for an International Ban on Chrysotile Asbestos

Chrysotile is the dominant form of asbestos in use today around the world. Evidence is incontrovertible that chrysotile asbestos is a potent cause of both lung cancer and malignant mesothelioma³⁻⁹. Data to support this case derive from more than 40 studies of different exposure circumstances. Chrysotile is shown to be a powerful carcinogen when the time course of risk is considered in mixed fiber exposures. Chrysotile is shown also to be a potent human carcinogen in direct calculations of risk. All available data suggest that chrysotile dominates the risk in those circumstances in which it is the principal fiber used. The risk of chrysotile in producing mesothelioma is similar to that of amosite on a per fiber exposure basis. Crocidolite would appear to have a potential two to four times greater to produce mesothelioma for equal exposure than chrysotile².

The Collegium Ramazzini, an independent international scholarly society in occupational medicine has called for an immediate international ban on the mining and use of chrysotile and all other forms of asbestos. We strongly support that call.

An immediate international ban on the mining and use of chrysotile and all other forms of asbestos is necessary because the risks cannot be controlled by technology or by regulation of work practices. The strictest occupational exposure limits in the world for chrysotile asbestos (0.1 f/ml) are estimated to be associated with lifetime risks of 2.3/1,000 for lung cancer and 0.8/1,000 for asbestosis¹⁸. These exposure limits

can be technically achieved in the United States and in a few other highly industrialized countries, but the residual risks still are too high to be acceptable. In newly industrializing countries engaged in mining, manufacturing, and construction, asbestos exposures are often much higher, and the potential for epidemics of asbestos disease is greatly increased^{18, 19}.

Scientists and policy makers in these countries should be wary of claims that asbestos can be used "safely". Those claims are not supported by data. Moreover, even the best workplace controls cannot prevent occupational and environmental exposures to products in use or to waste asbestos. Environmental exposure from the continued use of asbestos is also a serious and continuing problem. A recent study of women residing in communities in Canadian chrysotile mining areas found a seven-fold increase in the mortality rate from pleural cancer²¹. Large quantities of asbestos remain as a legacy of past construction practices in many thousands of schools, homes and commercial buildings in developed countries, and are now accumulating in thousands of communities in developing countries.

An immediate international ban on mining and use of all forms of asbestos is necessary because country-by-country actions have shifted rather than eliminated the health risks of asbestos. The asbestos industry has a powerful influence over public policy in many countries. In the United States, the asbestos industry succeeded in 1991 in overturning the EPA's recommended ban and phase-out of asbestos by a technical ruling in the courts. Canada, Russia, and other asbestos-exporting countries have developed major markets in the newly industrializing nations. Conditions of current asbestos use in developing countries now resemble those that existed in the industrialized countries before the dangers of asbestos were widely recognized.

The grave health hazards of asbestos are entirely preventable. The health risks of asbestos exposure are not acceptable in either industrially developed or newly industrializing nations. Moreover, suitable, safe substitutes for asbestos are available. An immediate worldwide ban on the production and use of asbestos is long overdue, fully justified and absolutely necessary.

References

- 1) Selikoff IJ, Seidman H (1991) Asbestos associated deaths among insulation workers in the United States and Canada. 1967-1987. *Ann N Y Acad Sci* **643**, 1-14.
- 2) Nicholson WJ, Landrigan PJ (1996) Asbestos: A status report. *Current Issues in Public Health* **2**, 118-23.
- 3) US Environmental Protection Agency (1986) Airborne Asbestos Health Assessment Update. EPA/6000/8-84/003F, June.
- 4) US Department of Labor, Occupational Safety and Health Administration (1994) Occupational Exposure to Asbestos; Final Rule. Federal Register 29 CFR Parts 1910 et al. August 10, 1994.
- 5) International Agency for Research on Cancer (1987) IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Lyon: IARC Monograph Supplement 7, 106-16.
- 6) Nicholson WJ, Perkel G, Selikoff IJ (1982) Occupational exposure to asbestos: population at risk and projected mortality, 1980-2030, *Am J Ind Med* **3**, 259-311.
- 7) de Klerk NH, Armstrong BK, Musk AW, Hobbs MST (1989) Cancer mortality in relation to measures of occupational exposure to crocidolite at Wittenoom Gorge in Western Australia. *Br J Ind Med* **46**, 529-36.
- 8) Frank AL, Dadson RF, Williams MG (1998) Carcinogenic implications of the lack of tremolite in UICC reference chrysotile, *Am J Ind Med* **34**, 314-7.
- 9) Selikoff IJ, Churg J, Hammond EC (1964) Asbestos exposure and neoplasia. *J Am Med Assoc* **188**, 22-6.
- 10) Selikoff IJ, Hammond EC, Seidman H (1979) Mortality experience of insulation workers in the United States and Canada. *Ann N Y Acad Sci* **330**, 91-116.
- 11) Peto J, Frvstli S, La Vecchia C, Levi F, Negri E (1999) The European mesothelioma epidemic, *British Journal of Cancer* **79**, 566-72.
- 12) Jarvholm B, Englund E, Albin M (1999) Pleural mesothelioma in Sweden: an analysis of the incidence according to the use of asbestos. *Occup Environ Med* **56**, 110-3.
- 13) Portions of the text on current world uses of asbestos are taken from: Proceedings of the Asbestos Symposium for Countries of Central and Eastern Europe. People and Work: Research Reports 19, Finnish Institute of Occupational Health.
- 14) US Bureau of Mines, Minerals Yearbook, 1995.
- 15) Chrysotile Asbestos: An Overview, Asbestos Institute. Montreal, Quebec, Canada, 1997.
- 16) Johanning E, Goldberg M, Kim R (1994) Asbestos Hazard Evaluation in South Korean Textile Production. *Int J Health Services* **24**, 131-43.
- 17) International Labour Organization: Sfety in the use of

- asbestos, Geneva, Switzerland, 1984.
- 18) US Department of Labor, Occupational Safety and Health Administration (1986) Occupation Exposure to Asbestos, Tremolite, Anthophyllite, and Actinolite; Final Rules. Federal Register 29 CFR Parts 1910 and 1926, p 22644. June 20.
 - 19) Giannasi F, Thebaud-Mony A (1997) Occupational exposures to asbestos in Brazil. *Int J Occup Environ Health* 3, 150-7.
 - 20) Izmerov N, Flovskaya L, Kovalevsky E (1998) Working with asbestos in Russia. Castleman BI: *Int J Occup Environ Health* 4, 59-61 (letter).
 - 21) Camus M, Siemiatycki J, Meek B (1998) Nonoccupational exposure to chrysotile asbestos and the risk of lung cancer. *N Engl J Med* 338, 1565-71.

EXHIBIT 41

REVIEW

Mesothelioma: cases associated with non-occupational and low dose exposures

Gunnar Hillerdal

Abstract

Objectives—To estimate the importance of low dose exposure to asbestos on the risk of mesothelioma.

Methods—A review of the literature.

Results and conclusions—There is no evidence of a threshold level below which there is no risk of mesothelioma. Low level exposure more often than not contains peak concentrations which can be very high for short periods. There might exist a background level of mesothelioma occurring in the absence of exposure of asbestos, but there is no proof of this and this "natural level" is probably much lower than the 1-2/million/year which has been often cited.

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Keywords: low exposure; asbestos; mesothelioma

Mesothelioma is an incurable disease which is almost exclusively due to inhalation of asbestos fibres. Asbestos has been extensively used in industry and construction in the 20th century, especially during and after the second world war, and even if the mineral is no longer used in most rich western countries the total world production remains high. There is a worldwide pollution with asbestos, as indicated by the finding of the mineral in samples of Greenland ice¹ and on the Yorkshire Moors,² and every citizen in the world has been exposed to some extent. Consequently, asbestos fibres can be found in most lungs at necropsy.³ It is thus understandable that there is concern about the risk of mesothelioma for the general population.

However, it should be remembered that mesothelioma is a rare disease with incidence in industrialised countries ranging from 1 to 5/million/year among women and values for

men 5-10 times higher (see table 3). Even in cohorts with a very heavy exposure to asbestos most people will die from other causes. In people with certified asbestosis—that is, with a heavy exposure—up to 10% will develop mesothelioma; among insulators in the United States and Canada, also a heavily exposed group, 9.3% of the deaths have been due to this disease; and in amphibole miners in South Africa or Australia, this figure is 2-4% (table 1). Clearly, with exposure concentrations several magnitudes lower, as occurs in the general population, the risk is very small, often impossible to measure.

A discussion of the risks from low exposure must include the dose-response curve; the existence or non-existence of a threshold, and thus a background concentration; and should try to define low exposure and estimate to what degree that really means a low concentration. From conflicting findings and opinions attempts must be made to make a meaningful conclusion.

The different types of asbestos seem to differ considerably in their ability to cause mesotheliomas. Chrysotile is considered by many authors to be a weak carcinogen in humans,¹¹ whereas the two amphiboles crocidolite and tremolite are much more dangerous according to many studies.¹² The third of the more important amphiboles, anthophyllite, was long considered not to cause mesothelioma, but such tumours have now been reported although the risk seems to be small.¹³ There is, none the less, a minority opinion that chrysotile is in fact responsible for most of the pleural mesotheliomas in society¹⁴ or should at least be considered to carry the same risk.¹⁵ This discussion, however, falls outside the present review and is not important for the conclusions drawn here.

Definition and diagnosis of mesothelioma

Mesotheliomas are, by definition, tumours that arise from mesothelial cells and can thus arise from any body cavity: the pleura, the peritoneum, the pericardial sac, and even the tunica vaginalis testis. Pleural mesotheliomas are the most common and pathologically the best defined ones. Pleural mesotheliomas have a male to female rate of about five to one, whereas for peritoneal tumours this ratio is 1.5 to 1.¹⁶ Thus, either the aetiology is different, the

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Table 1 Proportionate mortality from mesothelioma in various cohorts

Cohort	Deaths (n)	Deaths due to mesothelioma (%)	Reference
Amphibole miners	1225	2	4
Crocidolite miners	118	4	5
		6	6
Insulation workers	4951	9	7
Patients with asbestosis	283	9	8
	40	10	9
	59	10	10

Table 3 Incidence or mortality of mesothelioma in various countries and areas over time (/ million inhabitants / year)

Country or area	Year	Male	Female	Reference
United States	1968-81	2.1	0.8	33
North America	1972	2.8	0.7	34
Nantes-Saint-Nazaire, France	1956-74	5.2	0.2	35
Texas	1976-80	5.8	2.1	36
Selected cities, United States	1970s	4.4-11.1	1.2-3.8	37
United States	1986	7-13	1-2	38
Barcelona, Spain	1983-90	8.3	4.7	39
Great Britain	1968-71	8.4	2.3	40
Finland	1990-94	10	2.9	41
Great Britain	1972-76	12.6	2.8	40
Nantes-Saint-Nazaire, France	1975-84	17.2	0.8	35
United Kingdom	1983	17.5	3.2	16
Denmark	1978-80	14.7	7.0	42
Nantes-Saint-Nazaire, France	1985-92	19.4	4.0	35
Great Britain	1968-71	20.7	4.3	40
Australia	1982-88	28.3	3.3	43
Great Britain	1982-86	30.5	4.9	40
Great Britain	1987-91	44.0	6.4	40
Australia	1994	49.9	4.8	44

would increase steeply with time, making early childhood exposure of great importance.⁵⁰ However, there are clear indications that mineral fibres clear from the lung, albeit with different half lives for the different types of asbestos. Chrysotile has the shortest half life, and crocidolite is generally accepted to have the longest. The half life of crocidolite has been estimated to 7-8 years.⁵¹ This clearing of fibres would, at least theoretically, tend to actually decrease the risk of mesothelioma and other diseases with time.

In conclusion, the value of the cubic residence-time formula is in practice low and it should not be used for extrapolations, at least not at the extreme ends of exposure.

The latency time varies in different cohorts, and is dependent on how long a cohort is followed up. In 370 necropsy cases from Italy, latency time could be calculated in 312.⁵² Latency time was also dependent on exposure, varying from 29.6 years for insulators (with the highest exposure) to 51.7 in women with domestic exposure.

The threshold value and the background concentration

There have been strong arguments for the existence of a threshold value (a minimal exposure required for development of a mesothelioma).⁵³⁻⁵⁵ In most studies, several patients with mesothelioma do not report any occupational or other exposure to asbestos,^{33 56-60} and thus there seems to be a small spontaneous basal or background incidence of the tumour. In a large study from England, consisting of 185 cases and 159 controls who were very carefully interviewed, 5% of the cases (and 27% of the controls) seemed not to have any kind of exposure to asbestos.⁵⁹ This included domestic and even residential exposure. However, it is of course possible that some of these background cases might in fact be due to occupational, domestic, or even environmental exposure, unknown to (or forgotten by) the patients themselves.

There are authors who claim that the presumed background level must be very low, and retrospective searches for the tumour in the medical literature yield no convincing cases

of mesothelioma before 1946,⁶¹ although such negative evidence is of questionable value. McDonald and McDonald, in a recent review, estimated the background level to be 1-2/ million/year; they came to this figure by extrapolating backwards from epidemiological studies from various countries.⁶²

Malignant mesothelioma can occur in children,⁶³ and such cases can be considered as proof of non-asbestos (spontaneous) aetiology, as the latency time with necessity must be very short in these cases. Asbestos fibres have, however, been reported in the lungs of children, even in stillborn ones,^{64 65} showing that asbestos fibres spread in the human body and even penetrate through the placenta. Even if a latency time of only a few years is extremely rare in mesothelioma related to asbestos,⁶⁶ it can occur. There are some published examples of latency times of only 5 years.⁶⁶

Mesotheliomas also occur in animals, from baboons⁶⁷ and domestic dogs⁶⁸⁻⁷⁰ to fish.⁷¹ Dogs are exposed environmentally to asbestos just like their human masters, which might explain some of the tumours,^{68 69 72} but in fish it would be difficult to blame asbestos for the tumour. Thus, as in other animals, there is probably a background level of spontaneous mesotheliomas in humans.

Levels of exposure

Although many authors write about low level exposure to asbestos, there is rarely a definition of this term. In fact, in many articles low level exposure seems to be synonymous to non-occupational exposure, which, as described later, is certainly not true in many cases. Occupational as well as non-occupational exposure can be anything from very heavy to very low.

Occupational exposure to asbestos

It must be realised that occupational exposure to asbestos occurs or has occurred not only in the "classic" industries, such as asbestos mines and factories, shipyards, insulating business, asbestos cement industry, building and construction etc, but also in very many other occupations and trades. Examples are pulp and paper industry,⁷³ oil refineries,⁷⁴ electrical industry,⁷⁵ jewellery workers,⁷⁶ sugar refineries,⁷⁷ and cigarette filter workers.⁷⁸ Seamen and fishermen can have been exposed to asbestos used as insulation in their boats. In the reprocessed textile industry, bags heavily contaminated with asbestos could be reused for various other purposes, for instance covering heaps of rags; in an Italian investigation of such an industry, mesotheliomas and lung cancer were found to be fairly common among rag sorters.⁷⁹

Given the extensive use of the mineral, many people have been occupationally exposed to asbestos. This exposure can have been only brief but perhaps intense during that short period. In many or most instances the workers have no idea of the exposure and it can be impossible or almost impossible to elucidate it. Also, the level of exposure is often very difficult to estimate, should the information be available.

Non-occupational exposure to asbestos

DOMESTIC EXPOSURE

The family of an asbestos worker could be exposed to considerable amounts of asbestos brought home on his working clothes, which all too often it was the duty of the wife or daughter to clean. Pleural thickening, calcifications, and pulmonary fibrosis have been described in such cases, as well as mesotheliomas.⁸⁰⁻⁸²

AIR POLLUTION FROM ASBESTOS MINES, FACTORIES, DOCK YARDS, ETC

Asbestos mines used to be great environmental nuisances. They could be seen from a distance because of the dust cloud. Asbestos fibres can spread over a distance many kilometres from a mine, and the tailings from the mines were used for paving roads, parking areas, playgrounds, etc. In the crocidolite mining areas in South Africa, the incidence of mesotheliomas was increased to at least 10 times that expected even among women, proving a non-occupational exposure. However, whether some of this exposure was domestic (see later) is not clear.⁸³

Another example is the formerly active crocidolite mine at Wittenoom, Western Australia. At least 5000 people lived in the township of Wittenoom without working in the mines, and in 1993 27 cases of mesothelioma had occurred among these people.⁸⁴⁻⁸⁶ It has been estimated that 1.1% of child residents and 1.9% of the female residents of Wittenoom have died or will die from mesothelioma, whereas among the workforce this figure would be 6%.⁸⁶

Around the chrysotile mines in Quebec, Canada, there have been at least 53 occupational mesotheliomas from the mines, nine domestic, and two with general environmental exposure only.⁸⁵ In the nearby towns, the lungs of residents who have never worked in the mines have a fibre concentration which is 10 times higher than that of the average Canadian.⁸⁶

Mesotheliomas have also been reported from the surroundings of asbestos factories⁸⁷ and in people living near dockyards. However, the risk from residential exposure is probably low. In a large study from England, this factor accounted for only 3% of all the identified cases.⁵⁹

CONSUMER GOODS

Asbestos has been introduced into various goods used by the public. Examples are wall paints and spackling and jointing compounds. Another is a hand held hair drier, of which 13 million were sold in the United States and which has been described as a "small asbestos spray gun".⁸⁸ In commercially produced Kent filter cigarettes, crocidolite was used in the filters from 1952-6. The sale of these cigarettes was 11.7 billion, and in the commercials the health effects of this filter was emphasised.⁷⁸⁻⁸⁹

Once asbestos is introduced into a home, it will spread to all rooms and is almost impossible to remove even with a vacuum cleaner. It will easily be disturbed into the air from the slightest movement, and sedimentation is very slow.⁹⁰

URBAN AIR POLLUTION

The air in cities contains a very low concentration of asbestos. Near to construction or demolition work the concentrations are higher. It has been suggested that the air of London during the blitz was heavy with asbestos. Asbestos is also released on braking, and close to a motorway the fibre concentrations in the air will be higher than the background, but still well below the industrial threshold values. A risk not often appreciated is in dumps. In the vicinity of a waste disposal site the concentration of asbestos fibres can be 10-1000 times above the background concentration.⁹¹

Drinking water can contain asbestos or asbestiform fibres from natural sources or pollution. The use of asbestos cement pipes can cause a considerable number of fibres in the drinking water. Small amounts of asbestos can be found in some wines, beers, liquors, and other beverages, probably deriving from the filtration process. Fibres that are ingested will to some extent also enter the blood stream as seen from animal experiments.⁹²⁻⁹³ In humans, there are few reports. However, when amphibole fibres were found in drinking water from Lake Superior, a very small portion could be traced in urine,⁹⁴ and when chrysotile occurred in the drinking water, very small amounts were again found in urine.⁹⁵ However, most ingested mineral fibres will never be absorbed but will be cleared in the normal way, and the harmful effects of asbestos in drinking water or drinks is probably minuscule (and much smaller than the risk of drinking the alcohol).

Even if ingested asbestos is not dangerous, it has to be realised that it is only a very small portion of the tap water that we actually drink. Most of it is used for other purposes. Once the water has dried after washing, cleaning, taking showers etc the asbestos fibres will spread in the air. Such amounts are small but not insignificant and will add to the normal background exposure.⁹⁶

ASBESTOS IN PLACE = BUILDINGS CONTAINING ASBESTOS

A mixture containing asbestos was popular after the second world war for spraying on ceilings and walls for insulation and decoration. This was used well into the 1960s. There is now a public danger because of the plaster falling down from natural wear and tear, vandalism, or "artistic" carving in schools, etc. In many industrial buildings, asbestos was also used for spraying on the underside of the roof, and with natural wear and tear (and for instance birds building nests!)⁹⁷ there is now release of fibres to the surroundings. Asbestos was also extensively used in walls or around plumbing for insulation purposes, in cement to strengthen it, or just as a cheap filler.

In a modern city, asbestos can often be found in many places: in the cellar, where steam pipes are insulated; in storage or laundry rooms; in air conditioning sets; in theatres, museums, restaurants, etc.⁹⁸ Whenever there is damage to any construction or machine that contains asbestos, the possibilities of exposure, sometimes even fairly high, is there.

Table 4 Reported mesothelioma cases after exposure to "asbestos in place"

Occupation or exposure	Comments	Reference
School teachers	9/487 patients with mesothelioma 1 case each 4 cases	99 100-103 104
Attended school		102
Office clerk		102
Female office worker		105
Asbestos insulation at home	6/262 patients with mesothelioma	106

It has been claimed that up to 1000 premature deaths from lung cancer or mesothelioma will occur in the future among school children from schools where asbestos was used in the walls⁹⁹—calculations which, however, had to be built on extrapolations and assumptions. Several case reports have been published on patients with mesothelioma, in which the only exposure to asbestos that was reported was "in place" (table 4). From various cohorts with such exposure, significant increases in radiological findings from the lungs—such as pleural plaques—have also been reported, indicating exposure to asbestos, but these results are not undisputed and there is a probable overdiagnosis, as control groups are missing.¹⁰⁷

ENVIRONMENTAL MESOTHELIOMAS FROM LOCAL DEPOSITS OF FIBROUS MINERALS

"Endemic pleural plaques" were first described from Finland and since then many such findings have been reported. In these areas, there are small local pockets of asbestos which sometimes have been quarried, often for generations, for some local use. The most common use is whitewashing of houses with tremolite, which has resulted in an extremely high incidence of mesothelioma in some villages (table 5). When the exposure is due to whitewashing of the houses the risk will disappear when this procedure is stopped, but due to the long latency time this will take many decades.¹²²

A non-asbestos fibre, the zeolite erionite, has been found in some Turkish villages. Roads, buildings, etc., can contain this fibre in small amounts. Erionite is even more dangerous than crocidolite and the incidence of mesotheliomas in these unfortunate villages is extremely high.

Endemic plaques are of interest also in other countries, as many people born in these places and living there in their childhood and youth now have moved to other places, taking with them not only the plaques but also the risk of mesothelioma.¹³¹

Concentrations of exposure

OCCUPATIONAL CONCENTRATIONS

The concentration of exposure which the first workers exposed to asbestos have experienced can only be guessed. Estimated or recreated values from the past suggest fibre concentrations from 25 up to occasional values of 1000–2000 fibres/ml. With his own recalculations, Harries in 1970 estimated the fibre concentrations in the dockyard in 1951 as follows: sprayed asbestos insulation 171–322 fibres/cc; stripping asbestos 334; sweeping 353; adjacent passage 83; and in the passageway to the shower 25. Bagging debris 564; pipe lagging 194–200; removal of pipe lagging 171. Snap samples showed values up to 1000–2000 fibres/cc.¹³² These values are similar to the ones published by McMillan in 1983, who recreated values from the past: engine room 88; delagging in boilers room 171; bagging debris 353 f/ml.¹³³

Measurements from working places in the 1960s often showed peak doses of 20 fibres/ml and much less in more recent years. Where asbestos is still used, many countries have adopted a concentration of 1–2 fibres/ml as the upper legal concentration of exposure. These figures should be compared with the few available non-occupational measurements (table 6). A problem with the legal concentration is that most asbestos use today occurs in developing countries, many of which have adopted standards which they cannot enforce. As a result, actual exposures may be much higher than the standard in these countries.

NON-OCCUPATIONAL CONCENTRATIONS

The fibre concentrations in domestic exposure might in fact be as high as in occupational exposure. Brushing clothes might give peaks of ≥ 100 fibres/ml.⁵³ Ordinary vacuum cleaning is not effective in removing asbestos fibres, which

Table 5 Local deposits of mineral fibres (asbestos or erionite), occurrence of plaques, and of malignant mesothelioma

Country or area	Type of fibre	Plaques (% of investigated inhabitants)	Mesothelioma risk ($\times 10^4/y$)	Comment	Reference
Afghanistan	Tremolite	—	—	Case report only	108
Austria	Tremolite	5.3	Not increased	Vineyard and field workers	109 110
Bulgaria	Anthophyllite	2.8 women	Not increased	Tobacco growers	111 112
	Tremolite	5.6 men			
Corsica	Tremolite	41 (>50 y)	High	General pollution	113 114
Cyprus	Tremolite		High	General pollution	115
Czechoslovakia	Unknown	2.7–6.6	—	Farmers	116
Finland	Anthophyllite	6.5–9.0	Not increased		117 118
Greece:					
Metsovo	Tremolite	46.9	280 140 (1985–94)	White washing houses	119–121
SW Aridea, Macedonia		24.2 (>40 y)	High		122
New Caledonia $\times 2$			8.3* 300†	White washing houses	123 124
South Africa	Amosite crocidolite	2.5–6.6	High	Population around mine	125
Turkey	Tremolite	1.2–25	High	White washing houses	4
	Erionite	65		Farmers	126–128
USSR	Unknown	Locally high			19, 128, 129 130

*12 cases/145 000 inhabitants/10 y.

†Occurrence in local area.

Table 6 Fibre concentrations in air and lungs with non-occupational exposure to asbestos

Type of exposure	Fibres in air (f/ml)	Fibres in lungs (f/10 ⁶ g dry tissue)	Reference
Domestic exposure (paraoccupational)		5.3–319.5	11
		0.0049	102
Near asbestos mines, factories, etc:			
In Wittenoom:			48
When mine operating	0.5		
After closure of mine	0.01–0.21		
Farmers near mine in Canada		1.2–26.8	134
Local asbestos findings:			
Greece:			123
In the yard of an abandoned house	0.01		
In a newly whitewashed room	0.02–17.9		
Corsica	*	21±11	114
New Caledonia:			
While sweeping floor	78		124, 125
Road dust clouds	0.06–0.67		
Asbestos in place:			
Teacher's aid		0.0043	102
Female office worker		31 (TEM)	103

*39 ng/m³ (100 times higher than controls). TEM = transmission electron microscopy.

can remain for years in the house and be airborne again whenever disturbed. Thus, domestic exposure is not low exposure.

Environmental concentrations in the villages where whitewashing occurs, low values are reported when there is no disturbance, but in a newly whitewashed room and while sweeping floors, the concentrations can be quite considerable (table 6).

With asbestos in place, as long as the asbestos is undisturbed the concentrations in the air are very low (zero or hardly measurable: ≤ 0.001 fibres/ml), but once deterioration takes place values can go up to 15 fibres/ml, and when being removed there can be even higher values. In schools in the United States, the mean concentration was estimated to be 0.003 fibres/ml, and in federal buildings 0.006.¹³⁵

Thus, with so called non-occupational exposure, the typical exposure is a low or very low, almost unmeasurable, background concentration, but occasional high exposure when there is a disturbance of some kind. It follows, firstly, that retrospective estimation of cumulative exposure from history alone is an impossibility in most cases; but secondly, and perhaps more importantly, that any person living or working in (or even temporarily visiting) buildings where asbestos has been used in construction or otherwise might well have been exposed to high concentrations of airborne asbestos fibres once or many times in their lives, and in most instances unknowingly. This includes most of us!

A better way of estimating lifelong exposure might be analysis of fibres in the lungs, but as already mentioned fibres do clear from the lungs. How big the differences in clearance are between people is unknown. Thus, the correlation between lifetime cumulative exposure and fibre concentrations in the lungs is not excellent, but the findings from the lungs probably give a better estimation of exposure than even a careful retrospective analysis of the patient's history, at least in low grade exposure. In most studies, there is a clear dose-response relation between exposure and the number of fibres in the lungs.^{11 12 46 48 51}

Fibres in the lungs of patients with non-occupational mesothelioma

As has been mentioned, asbestos fibres can be found in the lungs of the general population without any known exposure. In Germany, the upper normal limit was estimated to be 300 000 fibres/g dry lung. In a large study of 324 malignant mesotheliomas, from which 46 lung samples were available, it was found that even at a fibre concentration of 100 000–200 000 fibres/g, there was a fivefold increased risk of mesothelioma, which was significant.¹³⁶ In this study (which has unfortunately only been published in German) as in many others, the mean number of fibres in the lungs of patients with malignant mesothelioma is much higher than the normal values, but there are usually patients with values that lie within the normal level.^{25 137–141}

Discussion

Any asbestos fibre found in a lung must have been inhaled. As far as is known, no truly unexposed group can be found in the world. There is no proof of a threshold value—that is, a minimal lower limit below which asbestos fibres cannot cause the tumour—and thus it is plausible that even such low exposure can cause mesothelioma (even if the risk is extremely low). Patients with mesothelioma whose lungs show fibre concentrations within the normal range cannot be dismissed as background cases,—that is, not due to asbestos. The only way to prove such a hypothesis would be to compare the incidence of mesothelioma in a group with such background exposure with the incidence in a truly non-exposed group. This is not possible, as no such group can be found.

It is nevertheless possible that there is a background level of mesothelioma,—that is, that the tumour can occur even in the complete absence of asbestos (or erionite) fibres. However, the data reviewed here indicate that if so, this background level must be very low—probably much <1 case/million people/year. This figure comes from studies of industrialised countries, where background exposure to asbestos is unavoidable. What the true figure is can only be guessed.

What, then, are the consequences for the public health? From the studies of non-occupational exposures it seems probable that the occasional high level exposure situations are the ones that are most important. Although the background, hardly measurable, concentrations of fibres in the air cannot be completely dismissed, the cumulative risk of these exposures is probably minor—and what is more, there is no way to reduce these concentrations. It is the high concentration situations which should be avoided. By knowing where asbestos occurs, such risks could be identified. Any source of pollution by asbestos which releases significant amounts of fibres should be eliminated as soon as it is discovered, using correct equipment and techniques. Correct techniques are also necessary whenever rebuilding or tearing down of structures containing asbestos to avoid asbestos pollution of the environment. If

the asbestos is well contained and not disturbed, it is usually better to leave it in place. In many instances, encapsulation is also better than removal.¹⁴²

- 1 Langer AM. Inorganic particles in human tissue and their association with neoplastic disease. *Environ Health Perspect* 1974;9:229-33.
- 2 Gloag D. Asbestos fibres and the environment. *BMJ* 1981; 282:623-6.
- 3 Churg A. Fiber counting and analysis in the diagnosis of asbestos-related disease. *Hum Pathol* 1982;13:381-92.
- 4 Sluis-Cremer GK, Liddell FDK, Logan WDP, et al. The mortality of amphibole miners in South Africa, 1946-80. *Br J Ind Med* 1992;49:566-75.
- 5 Cookson WOCM, Glancy JJ, de Klerk NH, et al. Benign and malignant pleural effusions in former Wittenoom miners and millers. *Aust N Z J Med* 1985;15:731-7.
- 6 Rogers A, Nevill M. Occupational and environmental mesotheliomas due to crocidolite mining activities in Wittenoom, Western Australia. *Scand J Work Environ Health* 1995;21:259-64.
- 7 Selikoff IJ, Seidman H. Asbestos-associated deaths among insulation workers in the United States and Canada, 1967-87. *Ann N Y Acad Sci* 1991;643:1-14.
- 8 Berry G. Mortality of workers certified by pneumoconiosis medical panels as having asbestosis. *Br J Ind Med* 1981;38: 130-7.
- 9 Navratil M. Schicksal von Patienten mit Asbestose in Verlauf einer 25jährigen präventiven Gesundheitspflege. *Zentralblatt Arbeitsmedizin und Arbeitsschutz* 1979;29:259-64.
- 10 Coutts II, Gilson JC. Mortality in cases of asbestosis diagnosed by a pneumoconiosis panel. *Thorax* 1987;42: 111-6.
- 11 Gibbs AR, Griffiths DM, Pooley FD, et al. Comparison of fibre types and size distributions in lung tissues of paraoccupational and occupational cases of malignant mesothelioma. *Br J Ind Med* 1990;47:621-6.
- 12 Rogers A, Leigh J, Berry G, et al. Relation between lung asbestos fiber type and concentration and relative risk of mesothelioma. A case-control study. *Cancer* 1991;67:1912-20.
- 13 Karjalainen A, Meurman LO, Pukkala E. Four cases of mesothelioma among Finnish anthophyllite miners. *Occup Environ Health* 1994;51:212-15.
- 14 Smith AH, Wright CC. Chrysotile asbestos is the main cause of pleural mesothelioma. *Am J Ind Med* 1996;30: 252-66.
- 15 Stayner LT, Dankovic DA, Lemen RA. Occupational exposure to chrysotile asbestos and cancer risk: a review of the amphibole hypothesis. *Am J Public Health* 1995;86:179-86.
- 16 Jones RD, Smith DM, Thomas PG. Mesothelioma in Great Britain in 1968-83. *Scand J Work Environ Health* 1988;14: 145-52.
- 17 Weiss SW, Tavassoli FA. Multicystic mesothelioma. An analysis of pathologic findings and biologic behaviour in 37 cases. *Am J Surg Pathol* 1988;12:737-46.
- 18 Hillerdal G. Malignant mesothelioma 1982: review of 4710 published cases. *Br J Dis Chest* 1983;77:321-43.
- 19 Baris YI, Simonato L, Artvinli M, et al. Epidemiological and environmental evidence of the health effects of exposure to erionite fibers: a four-year study in the Cappadocian region of Turkey. *Int J Cancer* 1987;39:10-17.
- 20 Hillerdal G, Bergh J. Malignant mesothelioma secondary to chronic inflammation and old scars. Two new cases and review of the literature. *Cancer* 1985;55:1968-72.
- 21 Cavazza A, Travis LB, Travis WD, et al. Post-irradiation malignant mesothelioma. *Cancer* 1996;77:1379-85.
- 22 Neugut AI, Ahsan H, Antman KH. Incidence of malignant pleural mesothelioma after thoracic radiotherapy. *Cancer* 1997;80:948-50.
- 23 Mizuki M, Yukishige K, Abe Y, et al. A case of malignant pleural mesothelioma following exposure to atomic radiation in Nagasaki. *Respirology* 1997;2:201-5.
- 24 Mårtensson G, Larsson S, Zettergren L. Malignant mesothelioma in two pairs of siblings: is there a hereditary predisposing factor? *Eur J Respir Dis* 1984;65:179-84.
- 25 Dawson A, Gibbs A, Browne K, et al. Familial mesothelioma: details of 17 cases with histopathologic findings and mineral analysis. *Cancer* 1992;70:1183-7.
- 26 Hirvonen A, Pelin K, Tammilehto L, et al. Inherited GSM1 and NAT2 defects as concurrent risk modifiers in asbestos-related human malignant mesothelioma. *Cancer Res* 1995;55:2981-3.
- 27 Huncharek M, Kelsey K, Muscat J, et al. Parental cancer and genetic predisposition in malignant pleural mesothelioma: a case-control study. *Cancer Lett* 1996;102: 205-8.
- 28 Behling CA, Wolf FL, Haghighi P. AIDS and malignant mesothelioma: is there a connection? *Chest* 1993;103: 1268-9.
- 29 Idemiyor V, Cherubin CB. Rapidly progressive mesothelioma in an HIV-positive patient. *Ann Pharmacother* 1992;26:429.
- 30 Schiffman M, Pickle LW, Fonham E, et al. Case-control study of diet and mesothelioma in Louisiana. *Cancer Res* 1988;48:2911-15.
- 31 Muscat JE, Huncharek M. Dietary intake and the risk of malignant mesothelioma. *Br J Cancer* 1996;73:1122-5.
- 32 Stenton SC. Asbestos, Simian virus 40 and malignant mesothelioma. *Thorax* 1997;52(suppl 3):S52-7.
- 33 Enterline PE, Henderson VL. Geographic patterns for pleural mesothelioma deaths in the United States, 1968-81. *J Natl Cancer Inst* 1987;79:31-7.
- 34 McDonald AD, McDonald JC. Malignant mesothelioma in North America. *Cancer* 1980;46:1650-6.
- 35 Chailleux E, Pioche D, Chopra S, et al. Épidémiologie du mésothéliome pleural malin dans la région de Nantes-Saint-Nazaire. Evolution 1956-92. *Rev Mal Respir* 1995; 12:353-7.
- 36 Weiss NS, Martin J, Suarez L, et al. Review of mesothelioma incidence and mortality in Texas. *Texas Med* 1988;84:44-8.
- 37 Hinds MW. Mesothelioma in the United States. Incidence in the 1970s. *J Occup Med* 1978;20:469-71.
- 38 Spirtas R, Beebe GW, Connolly RR. Recent trends in mesothelioma incidence in the United States. *Am J Ind Med* 1986;9:397-407.
- 39 Grupo de Estudio del Mesotelioma en Barcelona. Mortalidad por mesotelioma pleural en la provincia de Barcelona. *Med Clin (Barc)* 1993;101:565-9.
- 40 Peto J, Hodgson JT, Matthews FE, et al. Continuing increase in mesothelioma mortality in Britain. *Lancet* 1995;345: 535-9.
- 41 Karjalainen A, Pukkala E, Mattson K, et al. Trends in mesothelioma incidence and occupational mesotheliomas in Finland in 1960-95. *Scand J Work Environ Health* 1997;23: 266-70.
- 42 Andersson M, Olsen H. Trend and distribution of mesothelioma in Denmark. *Br J Cancer* 1985;51:699-705.
- 43 Leigh J, Corvalán CF, Grimwood A, et al. The incidence of malignant mesothelioma in Australia 1982-8. *Am J Ind Med* 1991;20:643-55.
- 44 Leigh J, Hull B, Davidsson P. Australian mesothelioma register report. The incidence of mesothelioma in Australia 1992-4. Sydney: National Institute of Occupational Health and Safety, 1996.
- 45 McDonald JC, Armstrong B, Case B, et al. Mesothelioma and asbestos fiber type. Evidence from lung tissue analyses. *Cancer* 1989;63:1544-7.
- 46 Roggli VL, Pratt PC, Brody AR. Asbestos content of lung tissue in asbestos related diseases: a study of 110 cases. *Br J Ind Med* 1986;43:18-28.
- 47 Churg A, Wright JL, Vedral S. Fiber burden and patterns of asbestos-related disease in chrysotile miners and millers. *Am Rev Respir Dis* 1993;148:25-31.
- 48 Hansen J, de Klerk NH, Musk AW, et al. Environmental exposure to crocidolite and mesothelioma. Exposure-response relationships. *Am J Respir Crit Care Med* 1998;157:69-75.
- 49 Doll R, Peto J. *Effects on health of exposure to asbestos. A report to the Health and Safety Commission*. London: The Stationery Office, 1985.
- 50 Landrigan PJ. A population of children at risk of exposure to asbestos in place. *Ann N Y Acad Sci* 1991;643:283-6.
- 51 de Klerk NH, Musk AW, Williams V, et al. Comparisons of measures of exposure to asbestos in former crocidolite workers from Wittenoom Gorge, W Australia. *Am J Ind Med* 1996;30:579-87.
- 52 Bianchi C, Giarelli L, Gamdi G, et al. Latency periods in asbestos-related mesothelioma of the pleura. *Eur J Cancer Prev* 1997;6:162-6.
- 53 Browne K. Asbestos-related mesothelioma: epidemiological evidence for asbestos as a promoter. *Arch Environ Health* 1983;38:261-6.
- 54 Ilgen EB, Wagner JC. Background incidence of mesothelioma: animal and human evidence. *Regul Toxicol Pharmacol* 1991;13:133-49.
- 55 Ilgen EB, Browne K. Asbestos-related mesothelioma: evidence for a threshold in animals and humans. *Regul Toxicol Pharmacol* 1991;13:116-32.
- 56 Ashcroft T. Epidemiological and quantitative relationships between mesothelioma and asbestos on Tyneside. *J Clin Pathol* 1973;26:832-40.
- 57 Chellini E, Fornaciari G, Merler E, et al. Pleural malignant mesothelioma in Tuscany, Italy (1970-88): II. Identification of occupational exposure to asbestos. *Am J Ind Med* 1992;49:599.
- 58 Spirtas R, Heinemann EF, Bernstein L, et al. Malignant mesothelioma: attributable risk of asbestos exposure. *Occup Environ Med* 1994;51:804-11.
- 59 Howell D, Arblaster L, Swinburne L, et al. Routes of asbestos exposure and the development of mesothelioma in an English region. *Occup Environ Med* 1997;54:403-9.
- 60 Yates DH, Corrin B, Stidolph PN, et al. Malignant mesothelioma in south east England: clinicopathological experience of 272 cases. *Thorax* 1997;52:507-12.
- 61 Mark EJ, Yokoi T. Absence of evidence for a significant background incidence of diffuse malignant mesothelioma apart from asbestos exposure. *Ann N Y Acad Sci* 1991;643: 196-204.
- 62 McDonald JC, McDonald AD. The epidemiology of mesothelioma in historical context. *Eur Respir J* 1996;9: 1932-42.
- 63 Fraite AE, Cooper S, Greenberg SD, et al. Mesothelioma of childhood. *Cancer* 1988;62:838-47.
- 64 Haque AK, Kutz MF. Asbestos bodies in children's lungs. *Arch Pathol Lab Med* 1988;112:514-18.
- 65 Haque AK, Vrazel DM, Burau K, et al. Is there transplacental transfer of asbestos? A study of 40 stillborn infants. *Ped Pathol Lab Med* 1996;16:877-92.
- 66 Booth SJ, Weaver EJM. Malignant pleural mesothelioma five years after domestic exposure to blue asbestos. *Lancet* 1986;i:435.

- 67 Fortman JD, Manaligod JR, Bennett BT. Malignant mesothelioma in an olive baboon (*Papio anubis*). *Lab Animal Sci* 1993;43:503-5.
- 68 Glickman LT, Domarski LM, Maguire TG, et al. Mesothelioma in pet dogs associated with exposure of their owners to asbestos. *Environ Res* 1983;32:305-13.
- 69 Harbison ML, Godleski JJ. Malignant mesothelioma in urban dogs. *Vet Pathol* 1983;20:531-40.
- 70 Smith DA, Hill FW. Metastatic malignant mesothelioma in a dog. *J Comp Pathol* 1989;100:97-101.
- 71 Herman RL. Mesothelioma in rainbow trout, *Salmo gairdneri* Richardson. *Journal of Fish Diseases* 1985;8:373-6.
- 72 Mirabella F. Studio epidemiologico del mesothelioma spontaneo canino: sua possibile utilita' in riferimento alla patologia umana. *Med Lavoro* 1987;78:28-32.
- 73 Järholm B, Malker H, Malker B, et al. Pleural mesothelioma and asbestos exposure in the pulp and paper industries: a new risk group identified by linkage of official registers. *Am J Ind Med* 1988;13:561-7.
- 74 Finkelstein MM. Asbestos-associated cancers in the Ontario refinery and petrochemical sector. *Am J Ind Med* 1996;30:610-15.
- 75 Imbemon E, Goldberg M, Bonenfant S, et al. Occupational respiratory cancer and exposure to asbestos: a case-control study in a cohort of workers in the electricity and gas industry. *Am J Ind Med* 1995;28:339-52.
- 76 Kern DG, Hanley KT, Roggli VL. Malignant mesothelioma in the jewelry industry. *Am J Ind Med* 1992;21:409-16.
- 77 Maltoni C, Pinto C, Valenti D, et al. Mesotheliomas following exposure to asbestos in sugar refineries: report of 11 Italian cases. In: A Mehlman, A Upton, eds. *Advances in modern environmental toxicology*. Vol XXII. The identification and control of environmental and occupational diseases: hazards and risks of chemicals in the oil refining industry. Princeton, NJ: Princeton Scientific, 1994:629-34.
- 78 Talcott JA, Thurber WA, Kantor AF, et al. Asbestos-associated disease in a cohort of cigarette-filter workers. *N Engl J Med* 1990;321:1220-5.
- 79 Quinn MM, Kriebel D, Buatti E, et al. An asbestos hazard in the reprocessed textile industry. *Am J Ind Med* 1987;11:255-67.
- 80 Kane MJ, Chahinina AP, Holland JF. Malignant mesothelioma in young adults. *Cancer* 1990;65:1449-55.
- 81 Magnani C, Terracini B, Ivaldi C, et al. A cohort study on mortality among wives of workers in the asbestos cement industry in Casale Monferrato, Italy. *Br J Ind Med* 1993;50:779-84.
- 82 Schneider J, Weitowitz HJ. Tumors linked to para-occupational exposure to airborne asbestos. *Indoor Built Environment* 1996;5:67-75.
- 83 Botha JL, Irwig LM, Strebel PM. Excess mortality from stomach cancer, lung cancer, and asbestosis and/or mesothelioma in crocidolite mining districts in South Africa. *Am J Epidemiol* 1986;123:30-40.
- 84 Musk AW, de Klerk N, Eccles JL, et al. Wittenoom, Western Australia: a modern industrial disaster. *Am J Ind Med* 1992;21:735-47.
- 85 Harrington JS. Mesothelioma among workers in the Québec chrysotile mining and milling industry. *Am J Ind Med* 1992;22:925-6.
- 86 Churg A. Lung asbestos content in long-term residents of a chrysotile mining town. *Am Rev Respir Dis* 1986;134:125-7.
- 87 Hain E, Dalquen P, Bohlig H, et al. Katamnestiche Untersuchungen zur Genese des Mesothelioms. Bericht über 150 Fälle aus dem Hamburger Raum. *Internationales Archiv für Arbeitsmedizin* 1974;33:15-37.
- 88 Smith RJ. Briefing. *Science* 1979;204:285.
- 89 Longo WE, Rigler MW, Slade J. Crocidolite asbestos fibers in smoke from original Kent cigarettes. *Cancer Res* 1995;55:2232-5.
- 90 Moorcroft JS, Duggan MJ. Rate of decline of asbestos fibre concentration in room air. *Am Occup Hyg* 1984;28:453-7.
- 91 Suta BE, Levine RJ. Non-occupational asbestos emissions and exposures. In: L Michalek, SS Chisick, eds. *Asbestos*. Vol 1. Properties, applications, and hazards. New York: John Wiley, 1979:171-205.
- 92 Cunningham HM, Moodie CA, Lawrence GA, et al. Chronic effects of ingested asbestos in rats. *Arch Environ Contam Toxicol* 1977;6:507-13.
- 93 Sébastien P, Masse R, Bignon J. Recovery of ingested asbestos fibers from the gastrointestinal lymph in rats. *Environ Res* 1980;22:201-16.
- 94 Cook MP, Olson GF. Ingested mineral fibers: elimination in human urine. *Science* 1979;204:195-8.
- 95 Boatman H. Use of quantitative analysis of urine to assess exposure to asbestos fibers in drinking water in the Puget Sound area. *Environ Health Perspect* 1983;53:131-9.
- 96 Webber JS, Syrotynski S, King MV. Asbestos-contaminated drinking water: its impact on household air. *Environ Res* 1988;46:153-67.
- 97 Greenberg M. Malignant mesothelioma in paper mill workers: where might the asbestos have come from? *Am J Ind Med* 1996;30:641.
- 98 Molloy LB. Asbestos in place in metropolitan New York. *Ann N Y Acad Sci* 1991;643:614-21.
- 99 Anderson HA, Hanrahan L, Schirmer J, et al. Mesothelioma among employees with likely contact with in-place asbestos-containing building materials. *Ann N Y Acad Sci* 1991;643:550-72.
- 100 Dodson RF, O'Sullivan M, Com C. Technique dependent variations in asbestos burden as illustrated in a case of non-occupational mesothelioma. *Am J Ind Med* 1993;24:235-40.
- 101 Huncharek M. Occult asbestos exposure. *Am J Ind Med* 1991;20:713-14.
- 102 Roggli VL, Longo WE. Mineral fiber content of lung tissue in patients with environmental exposures: household contacts v building occupants. *Ann N Y Acad Sci* 1991;643:511-18.
- 103 Srebro S, Roggli VL. Asbestos-related disease associated with asbestiform tremolite. *Am J Ind Med* 1994;26:809-19.
- 104 Lilienfeld DE. Asbestos-associated pleural mesothelioma in school teachers: a discussion of four cases. *Ann N Y Acad Sci* 1991;643:454-8.
- 105 Stein RC, Kitajewska JY, Kirkham JB, et al. Pleural mesothelioma resulting from exposure to amosite asbestos in a building. *Respir Med* 1989;83:237-9.
- 106 Dodoli D, Del Nevo M, Fiumalbi C, et al. Environmental household exposures to asbestos and occurrence of pleural mesothelioma. *Am J Ind Med* 1992;21:681-7.
- 107 Hillerdal G. Pleural plaques: incidence and epidemiology, exposed workers and the general population. *Indoor Built Environment* 1997;6:86-95.
- 108 Voisin C, Marin I, Brochard P, et al. Environmental airborne tremolite asbestos pollution and pleural plaques in Afghanistan. *Chest* 1994;106:974-6.
- 109 Neuburger M, Gründorfer W, Haider M, et al. Umweltbedingte endemische Pleuraplaques. *Zentralblatt für Bakteriologie und Hygiene, Abteil Original* 1978;167:391-404.
- 110 Neuburger M, Kundi M, Friedl HP. Environmental asbestos exposure and cancer mortality. *Arch Environ Health* 1984;39:261-5.
- 111 Burilov T, Babadjov L. Ein Beitrag zum endemischen Auftreten doppelseitiger Pleuraverkalkungen. *Praxis für Pneumologie* 1970;24:433-8.
- 112 Zolov C, Bourilov T, Babadjov L. Pleural asbestosis in agricultural workers. *Environ Res* 1967;1:287-92.
- 113 Rey F, Boutin C, Steinbauer J, et al. Environmental pleural plaques in an asbestos exposed population of Northeast Corsica. *Eur Respir J* 1993;6:978-82.
- 114 Rey F, Viallat JR, Boutin C, et al. Les mésotéliomes environnementaux en Corse du nord-est. *Rev Mal Respir* 1993;10:339-45.
- 115 McConnochie K, Simonato L, Mavrides P, et al. Mesothelioma in Cyprus: the role of tremolite. *Thorax* 1987;43:342-7.
- 116 Marsova M. Beitrag zur Ätiologie der Pleuraverkalkungen. *Zeitschrift für Tuberkulose* 1964;121:329-34.
- 117 Kiviluoto R. Pleural calcification as a roentgenologic sign of non-occupational endemic anthophyllite asbestosis. *Acta Radiol* 1960;(suppl 194).
- 118 Rautio V. Occurrence of unusual pleural calcification in Finland. Studies on atmospheric pollution caused by asbestos. *Annales de Médecine Interne Fenniae* 1966;55(suppl 47).
- 119 Constantopoulos SH, Malamou-Mitsi VD, Goudevenos JA, et al. High incidence of malignant pleural mesothelioma in neighbouring villages of Northwestern Greece. *Respiration* 1987;51:266-71.
- 120 Bazas T, Oakes D, Gilson JC, et al. Pleural calcification in northwest Greece. *Environ Res* 1985;38:239-47.
- 121 Langer AM, Nolan RP, Constantopoulos SH, et al. Association of Metsovo lung and pleural mesothelioma with exposure to tremolite-containing whitewash. *Lancet* 1987;i:965-7.
- 122 Sakellariou K, Malamou-Mitsi V, Haritou A, et al. Malignant pleural mesothelioma from non-occupational exposure in Metsovo (north-west Greece): slow end of an epidemic? *Eur Respir J* 1996;9:1206-10.
- 123 Sichelidis L, Daskalopoulou E, Chionos D, et al. Five cases of pleural mesothelioma with endemic pleural calcifications in a rural area in Greece. *Med Lavoro* 1992;83:259-65.
- 124 Goldberg P, Luce D, Billon-Galland MA, et al. Role potentiel de l'exposition environnementale et domestique à la trémolite dans le cancer de la plèvre en Nouvelle Calédonie. *Rev Epidemiol Santé Publ* 1995;43:444-50.
- 125 Luce D, Brochard P, Quénel P, et al. Malignant pleural mesothelioma associated with exposure to tremolite. *Lancet* 1994;ii:1777.
- 126 Baris YI, Sahin AA, Ozesmi M, et al. An outbreak of pleural mesothelioma and chronic fibrosing pleurisy in the village of Karam/Ürgüp in Anatolia. *Thorax* 1978;33:181-92.
- 127 Baris YI, Bilir N, Artvinli M, et al. An epidemiological study in an Anatolian village environmentally exposed to tremolite asbestos. *Br J Ind Med* 1988;45:838-40.
- 128 Selcuk Z, Cöplü L, Emri S, et al. Malignant pleural mesothelioma due to environmental mineral fiber exposure in Turkey. Analysis of 135 cases. *Chest* 1992;102:790-6.
- 129 Artvinli M, Baris YI. Environmental fiber-induced pleuropulmonary diseases in an Anatolian village: an epidemiologic study. *Arch Environ Health* 1982;37:177-81.
- 130 Ginzburg EA, Silova MV, Komejeva MJ, et al. Röntgenologie der nichtberufsbedingten Asbestose der Pleura. *Radiologia Diagnostica* 1973;14:307-12.
- 131 Boman G, Schubert V, Svane B, et al. Malignant mesothelioma in Turkish immigrants to Sweden. *Scand J Work Environ Health* 1982;8:108-12.
- 132 Harries PG. *The effects and control of diseases associated with exposure to asbestos in a naval dockyard* [MD Thesis]. Alverstoke, Gosport, UK: Institute of Naval Medicine, 1970.
- 133 McMillan GHG. The health of welders in naval dockyards. *J Occup Med* 1983;25:727-30.
- 134 Churg A. Analysis of lung asbestos content. *Br J Ind Med* 1991;48:649-52.

- 135 US Environmental Protection Agency. *EPA study on asbestos containing materials in public buildings*. Washington, DC: USEPA, 1986.
- 136 Weitowitz HJ, Hillerdal G, Calavrezos A, *et al*. Risiko-und Einflussfaktoren des diffusen malignen Mesothelioms (DMM). Schriftenreihe der Bundesanstalt für Arbeitsschutz. Bonn: BfA, 1993. (Fb696.)
- 137 Murai Y, Kitagawa M. Asbestos fiber analysis in 27 malignant mesothelioma cases. *Am J Ind Med* 1992;22:193-207.
- 138 Tuomi T, Segerberg-Kontinen M, Tammilehto L, *et al*. Mineral fiber concentration in lung tissue of mesothelioma patients in Finland. *Am J Ind Med* 1989;16:247-54.
- 139 Tuomi T, Huuskonen M, Tammilehto L, *et al*. Relative risk of mesothelioma associated with different levels of exposure to asbestos. *Scand J Work Environ Health* 1991;17:404-8.
- 140 Sakai K, Hisanaga N, Huang J, *et al*. Asbestos and non-asbestos fiber content in lung tissue of Japanese patients with malignant mesothelioma. *Cancer* 1994;73:1825-35.
- 141 Dodson RF, O'Sullivan M, Com CJ. Analysis of asbestos fiber burden in lung tissue from mesothelioma patients. *Ukstrux Pathol* 1997;21:321-36.
- 142 Ferguson D. Low-level asbestos: the priorities are wrong. *Med J Aust* 1990;152:617-18.

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EXHIBIT 42

Asbestos Exposure Causes Mesothelioma, But Not *This* Asbestos Exposure:

An Amicus Brief to the Michigan Supreme Court

LAURA S. WELCH, MD*

Manufacturers of asbestos brakes, supported by many manufacturing and insurance industry *amicus curie*, requested the Michigan Supreme Court to dismiss testimony of an expert regarding the ability of asbestos dust from brakes to cause mesothelioma as “junk science.” Scientists are concerned with the sweeping and unequivocal claims that any conclusion that asbestos from brakes caused a signature asbestos-related disease in a particular person must be “junk science.” The manufacturers’ sweeping pronouncements are what veer from accepted, reliable mainstream scientific methods and conclusions. This article outlines the evidence supporting the conclusion that asbestos from brakes can and does cause mesothelioma, and describes the defendants’ attempts to fabricate doubt about this conclusion. *Key words:* asbestos; brakes; chrysotile; mechanic; occupation; epidemiology; mesothelioma.

INT J OCCUP ENVIRON HEALTH 2007;13:318–327

Companies that made and sold asbestos-containing brakes asked the Supreme Court of Michigan to effectively rule that it is impossible to contract asbestos-related diseases as a result of exposure to asbestos from asbestos brakes.[†] As physicians and scientists, we are concerned about the epidemic of asbestos disease that continues to cause the deaths of thousands of workers each year in the United States. The signers of this paper represent hundreds of years of experience researching, diagnosing, and treating asbestos-related diseases in workers and their families. We have published extensively in this field for more than 30 years and have conducted dozens of epidemiologic and other studies into the issues of asbestos and disease. Many of us have testified before legislative and regulatory bodies regarding asbestos and disease and in court proceedings at the request of individuals suffering from mesothelioma and other asbestos-related diseases.

*Dr. Welch is joined by 51 other signers onto this communication; see end of document.

†*Chapin v. DaimlerChrysler Corporation et al.*, Case No. 133178, Supreme Court of Michigan.

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We make no claim to know the “correct” answer to disease causation in the specific case under review in the court. Our concern is with the sweeping and unequivocal claim that any conclusion that asbestos from brakes has caused a signature asbestos-related disease in a particular person must be “junk science.” We find that sweeping pronouncement itself is what veers from accepted, reliable mainstream scientific methods and conclusions.

Ample Evidence Supports the Conclusion That Asbestos from Brakes Can and Does Cause Mesothelioma

Chrysotile causes cancer, including mesothelioma. “There is general agreement among scientists and health agencies . . . [e]xposure to any asbestos type (i.e., serpentine [chrysotile] or amphibole) can increase the likelihood of lung cancer, mesothelioma, and nonmalignant lung and pleural disorders.”¹

Many other reviews support this conclusion, such as those from the American Conference of Governmental Industrial Hygienists,² the American Thoracic Society,³ the Environmental Protection Agency,⁴ the International Agency for Research on Cancer,⁵ the National Toxicology Program,⁶ the Occupational Safety and Health Administration,⁷ the Consumer Products Safety Commission (CPSC),⁸ the World Health Organization,^{9–11} and the World Trade Organization.¹² This scientific consensus is also reflected in the Consensus Report of the 1997 Helsinki Conference,¹³ and publications from the American Cancer Society¹⁴ and the National Cancer Institute of the National Institutes of Health.¹⁵

Thorough scientific inquiry requires consideration of all available information. Accordingly, in reaching the conclusion that chrysotile asbestos causes mesothelioma, scientists properly consider numerous accepted sources of scientific data, including epidemiologic studies of all varieties, case reports and series of case reports, controlled animal experiments, and toxicologic studies.^{1,16–23}

Asbestos industry arguments to the contrary have not been supported over time. Chrysotile asbestos mining companies and manufacturers have argued for more than 30 years either that their products do not cause disease or that there is insufficient evidence to reach a reliable conclusion. Numerous scientific articles and criticisms have specifically exposed the artificial uncertainty cre-

ated by the proponents of chrysotile asbestos, and their position has been repeatedly and consistently rejected by the mainstream scientific and regulatory communities.^{18-20,24-26}

Like many scientists, we are concerned with the development and expansion of “doubt science.”^{27,28} A centerpiece of the “doubt science” model is the assertion that whatever piece of evidence supports the position of the industry in question (or whatever piece of evidence might be as yet undetermined) is *the* critical piece of evidence, to the exclusion of all others. While we acknowledge that industry-sponsored research can and does often provide valuable scientific insight and developments, the efforts of the tobacco and asbestos industries to deny their products cause cancer have become a paradigm for “doubt science.”

In this regard, we are cognizant of the fact that the primary articles upon which the asbestos brake manufacturers rely in this matter were paid for by Ford, General Motors, Chrysler and other asbestos brake manufacturers. Publications by Hessel,²⁹ Goodman,³⁰ and Paustenbach^{31,32} were all expressly funded by Ford, General Motors, and Chrysler. Furthermore, the paper by Hessel et al. appeared in a journal funded by the Ford Motor Company and a subsidiary of General Motors. Wong³³ has been reported to have undisclosed origins as an expert witness report for a brake manufacturer.³⁴ Laden acknowledges funding by a law firm that is “national asbestos counsel” for another asbestos brake manufacturer.³⁵

The Scientific Community is in Consensus that Even Brief and Low-level Exposure to Asbestos Can Cause Mesothelioma

The mainstream scientific community has long recognized and continues to recognize today that there is no “safe” level of exposure to asbestos.^{12,13} As noted by NIOSH:

Excessive cancer risks have been demonstrated at all fiber concentrations studied to date. Evaluation of all available human data provides no evidence for a threshold or for a “safe” level of asbestos exposure.³⁶

Attempts to postulate thresholds for exposure have been dismissed as “logical nonsense.”³⁷

The lack of a defined “safe” level for exposure to asbestos has been supported by subsequent research. For example, a large French study recently concluded that substantial excess mortality occurs at exposure levels below current regulatory levels.³⁸ A recent study examining the relationship between historical asbestos use and disease rates further supports the conclusion that a linear dose–response relationship exists between exposure to asbestos and disease and that no “safe” level of exposure exists.³⁹

One of the main studies upon which the asbestos brake manufacturers rely⁴⁰ similarly concluded that *all* levels of occupational exposure to asbestos increase the risk of mesothelioma:

Compared to those who never worked or who were never exposed, all levels of probability and intensity [of exposure to asbestos] had an increased significant risk, except subjects with low probability of exposure. For exposure classified as “sure” the OR was 13.2.

Application of this study to the current case under review would result in his placement in the “sure” exposure category, and consequently he would be over 13 times more likely to contract mesothelioma than unexposed individuals. Despite this, the asbestos brake manufacturers assert that the Agudo study proves that no person can ever get mesothelioma from asbestos brakes. That argument is unsound and contrary to the consensus of the scientific community that there is no demonstrable threshold of exposure to asbestos below which adverse health effects do not occur. Accordingly, “an occupational history of brief or low-level exposure should be considered sufficient for mesothelioma to be designated occupationally related” to asbestos exposure.¹³

Mesothelioma Is a Signature Malignancy for Asbestos Exposure

There is no debate that asbestos causes mesothelioma, and that the great majority of mesotheliomas are demonstrably caused by asbestos.⁴¹ Some mesotheliomas are never able to be individually linked to asbestos exposure, and the scientific community has defined these cases as “idiopathic” because information regarding asbestos exposure is unavailable.

However, we know that many individuals do not know that they have been exposed to asbestos.⁴² Many more die before being interviewed regarding potential exposures, forcing researchers to make assumptions about exposure based upon information from next of kin, job titles, or death certificates; these sources often fail to reflect all jobs and exposures.^{43,44} Many epidemiologic studies assess occupational exposure but not para-occupational or environmental exposure, because only occupational information is available from existing records. The fact that a percentage of mesotheliomas are labeled “idiopathic” does not, however, support the conclusion that there are large numbers of spontaneous (i.e., non-asbestos-related) mesotheliomas. To the contrary, a large study of numerous sources of information failed to demonstrate evidence for “spontaneous” mesotheliomas,⁴⁵ and a detailed review of mesothelioma cases in Australia found that over 90% had either a history of exposure or substantial asbestos in lung tissue.⁴²

The asbestos brake manufacturers attempt, without support, to recast the definition of “idiopathic.” First,

in an attempt to undercut the indisputable link between asbestos and mesothelioma, they suggest that “idiopathic” mesotheliomas are not caused by asbestos rather than accepting that these are cases where individual exposure has not been identified. Second, they attempt to place mesotheliomas with demonstrable occupational exposures to asbestos—specifically asbestos from brakes—in the “idiopathic” category. There is no scientific support for either position.

Mesothelioma is a signature tumor for asbestos exposure. Individuals with known occupational exposures to asbestos cannot be recast into the “idiopathic” or “unknown exposure” category. When confronted with an individual who has a demonstrated mesothelioma and demonstrated occupational exposure to asbestos, the mainstream scientific community recognizes that the cause of that mesothelioma is the asbestos exposure of the individual even if that exposure was “brief or low-level.”

Because Mesothelioma Is a Signature Malignancy with Essentially One Cause—Asbestos—the Scientific Community Has Long Considered Individual Cases of Mesothelioma to Be Sentinel Events

It is not necessary to have an epidemiologic study of a specific occupation to be able to conclude that an individual’s exposure to a toxic substance in that occupation can be a cause of disease. To the contrary, as noted by Dr. Lemen,

Specific occupations do not need to be studied nor do epidemiological studies need to be performed to show risk of disease before prevention actions are taken or causal connections concluded. To wait for epidemiology studies of each occupational group is not warranted but has been taken by many in the medico-legal profession as the only way to prove causation by occupation. Such misconceived thinking has been very harmful to the future prevention of asbestos-related diseases.⁴⁶

This is particularly so when examining mesothelioma. Repeated studies have shown that all levels of exposure increase the risk of mesothelioma.^{38,40} Moreover, unlike many other cancers, for which there are multiple, well-documented causal factors, mesothelioma is overwhelmingly caused by asbestos. As noted by one of the studies upon which the asbestos brake manufacturers rely:

Mesothelioma is a rare cancer with one major etiologic exposure, therefore surveillance using each case as a sentinel event might seem more reasonable for this disease than for cancers with multifactorial causation.⁴⁷

In 1983 Rutstein developed a list of sentinel health events (SHE-O) that are occupationally related.⁴⁸

Mesothelioma as a sentinel disease for asbestos exposure was on the initial list of SHE-O, and all subsequent revisions. In fact, the worldwide acceptance of mesothelioma as an asbestos-related cancer began with the case series published by Wagner in 1960.⁴⁹

When examining the question of causation of sentinel diseases such as mesothelioma, the scientific community recognizes that case reports and case series reports are useful and valid tools.

Case series are particularly informative in situations where there are identified occurrences of very rare conditions for which there are few, if any, established causal factors. . . . In fact, recognition of even a small number of cases of the “sentinel” diseases—such as liver angiosarcoma and malignant mesothelioma, which is strongly related to asbestos exposure.⁵⁰

The scientific community has concluded that, for sentinel diseases such as mesothelioma, case series reports can be sufficient by themselves to allow reliable conclusions to be drawn regarding causation. Again, as noted by Checkoway:

Case series reports can be virtually conclusive in their own right when the health outcome is a very rare disease or an uncommon manifestation of a relatively common condition.⁵⁰

We do not suggest that such conclusions are indisputable or inviolate; scientific knowledge rarely is. The relevant question is whether reliable and scientifically justifiable conclusions can be drawn based upon such information, when considered in connection with all other available evidence. They can. In fact, proper application of the scientific method requires consideration of all forms of available evidence.

Accepted Method for Evaluating Disease Causation in an Individual: Generally and as Applied to Asbestos Exposure and Mesothelioma

Examining the question of causation of disease in an individual generally involves four questions: 1) was the individual exposed to a toxic agent 2) does the agent cause the disease present in the individual; 3) was the individual exposed to this substance at a level where disease has occurred in other settings; and 4) have other competing explanations for the disease been excluded?

There is no reasonable dispute regarding Question 2—asbestos causes mesothelioma. Additionally, there are no well-accepted competing explanations regarding mesothelioma that must be excluded, resolving Question 4. As a result, when considering the issue of causation of a mesothelioma, once an occupational or para-occupational exposure to asbestos has been established (Question 1), the sole question remaining for

examination is whether the exposure or set of exposures of that individual is similar to exposures that have been documented to cause mesothelioma in others—Question 3.

The mainstream scientific community is in consensus regarding the resolution of Question 3. As discussed above, there is no safe level of exposure to asbestos. Even exposure at current regulatory levels results in excess mesotheliomas.^{7,38} Accordingly, **the consensus of the scientific community is that any occupational or para-occupational exposure to asbestos—even “brief or low-level exposures”—must be considered causal in an individual with a mesothelioma.**

The Claim of the Asbestos Brake Manufacturers That the Studies upon Which They Rely Trump All Other Scientific Knowledge Is Scientifically Unsupportable.

The asbestos brake manufacturers cite a number of epidemiologic studies as proof that asbestos from brakes cannot cause mesothelioma. The manufacturers claim the fact that these studies did not detect a statistically significant increased risk of mesothelioma in the occupational groups studied is conclusive proof that no person can ever contract disease from working with asbestos brakes.

That claim is simply not scientifically supportable. We need not examine here the individual shortcomings of the studies relied upon by the asbestos brake manufacturers. Others have done so cogently and in detail.^{16,34} While our rejection of the asbestos brake manufacturers’ sweeping claim is supported by these critiques, the fundamental scientific failing of their claim is not based on the obvious limitations of the individual studies. There is a difference between a truly negative result and a non-positive result. A true negative study must be large, sensitive, and contain accurate exposure data. Even then, the study will be negative only with respect to the exposure level studied. Far from proving that no person can ever get sick from asbestos dust released by brakes, the best that can be said for the studies is that they are inconclusive. Instead, such a claim is based on the scientifically unsupportable proposition that one study, or group of studies, trumps all other evidence, no matter how extensive and well-documented that evidence is. Additional discussion of the implication of “negative” epidemiologic studies may be found elsewhere.^{51–54}

As noted above, examination of the question of whether a substance is capable of causing disease requires consideration of all scientific disciplines and all available evidence. This is particularly true when asserting that exposure can *not* cause an effect.

The conclusion that some exposure is devoid of harmful effect (e.g. a certain chemical is not carcinogenic) must be based on a synthesis of the

whole available literature: it can never rely on one single study. Hence, all the scientific evidence (i.e. theoretical experimental, and epidemiologic) that exists must be combined.⁵⁵

Substantial insight into this issue is provided by the industry consultants hired by Ford, General Motors, and Chrysler. When hired to represent the auto industry in asbestos-brake litigation, the industry consultants assert that their cited epidemiologic studies trump all other evidence, and conclusively refute the claim that asbestos from brakes can cause mesothelioma.^{29,30} Conversely, when hired by the power industry to provide testimony regarding epidemiologic studies that were damaging to that industry, Dr. Hessel rejected this same position:

Because of such recognized limitations, epidemiology studies by themselves generally do not provide sufficient basis to support conclusions about causation. That is why the assessment of health risk must rely on data from toxicological studies in animals, studies in human cells and tissues and experimental clinical studies.⁵⁶

The opportunistic rejection of whatever evidence exists contrary to the position of the industry being defended is a hallmark of “doubt science.” We disagree with both extremes. Epidemiologic evidence may, in cases, be sufficient to make reasoned and well-founded judgments regarding causation after consideration of other available evidence, even if evidence from one or more other scientific disciplines is absent. Conversely, consideration of other scientific evidence may allow reasoned conclusions regarding causation in the absence of positive epidemiologic studies regarding a specific population.

It is unscientific for the asbestos brake manufacturers to assert that their chosen epidemiologic studies trump all other evidence, just as it was unscientific for the tobacco industry to claim that lack of understanding of the mechanism by which tobacco causes cancer made it impossible to conclude that cigarettes cause cancer. Proper application of the scientific method requires that all available evidence be considered when examining issues of causation.

Evidence Supporting the Conclusion That Asbestos from Brakes Can and Does Cause Disease, Including Mesothelioma

The danger of asbestos in brakes has been recognized for decades. The hazard from exposure to asbestos in friction products has been known and accepted for over 70 years. In 1948, General Motors’ chief industrial hygienist published regarding the hazards created when manipulating asbestos brake materials in the factory.⁵⁷ By 1958, the danger of exposure to asbestos dust from brakes was sufficiently well documented that it was

included in the American Industrial Hygiene Association's Hygienic Guide series.⁵⁸ Additionally, mesotheliomas have been documented repeatedly in workers at friction-product factories.^{34,59-62}

Today, the asbestos brake manufacturers assert that this danger is confined to the friction-product manufacturing facility. However, there is no scientific justification for asserting that dust from an asbestos brake can cause disease when the brake is ground in a factory but cannot cause disease when that same brake is ground in a garage.

Mechanics who work with asbestos brakes without dust-control measures are exposed to asbestos. Numerous studies have demonstrated that mechanics who worked with asbestos-containing brakes without dust-control measures were exposed to asbestos dust. This is particularly true when the mechanic grinds, files, or sands the new asbestos brake and uses compressed air or dry brushing to clean out wear dust from old asbestos brakes.⁶³⁻⁶⁶ Both the EPA and OSHA have issued guidance to reduce the risk of disease from asbestos exposure during brake work.^{7,67,68} OSHA requires the use of dust controls when employees work with asbestos-containing brakes and clutches (for specific details see appendix F of the standard).⁷ The EPA has adopted these standards for municipal employees in jurisdictions not governed by state asbestos-control plans.⁶⁷ Other regulatory agencies have similarly issued guidance to mechanics to reduce exposures to asbestos from brakes and clutches.⁶⁹⁻⁷²

Equally important, it has been proven that use of effective dust-control measures can lower exposure levels during work with asbestos brakes.^{73,74} Accordingly, to provide a reliable basis for the conclusion that asbestos from brakes can never cause disease, a study of brake mechanics would ascertain whether individuals considered "exposed" to asbestos brakes used dust-control practices. None of the studies relied upon by the asbestos brake manufacturers contains such information.

Studies have shown increased incidences of non-malignant asbestos-related diseases among mechanics known to have performed work with asbestos-containing brakes. Excessive non-malignant disease in mechanics occurs in individuals known to have worked with asbestos-containing brakes.^{65,75} It is universally accepted that the amount of asbestos exposure needed to cause asbestosis is greater than the amount needed to cause mesothelioma. Accordingly, studies demonstrating excess asbestosis in asbestos brake-repair workers demonstrate that these workers were historically exposed to quantities of asbestos far in excess of that needed to cause mesothelioma.

Proper scientific inquiry cannot ignore the hundreds of reported cases of mesothelioma in mechanics. We reject the contention of the asbestos brake manufacturers that the scientist must close his or her eyes and refuse to consider case reports or case series of mesothelioma in mechanics, irrespective of how many cases are reported. This contention flies in the face of sound sci-

entific reasoning, which *requires* thoughtful consideration of *all* available evidence.

As discussed above, the consideration of case reports is even more critical when examining rare, sentinel diseases such as mesothelioma because of the great difficulty in conducting epidemiologic studies with sufficient power to reliably detect increases in disease.^{53,54} Hundreds of cases of mesothelioma in mechanics have been reported in the medical literature, including dozens of cases in the studies relied upon by the asbestos brake manufacturers.¹⁶

The precise number of cases is not important for purposes of our discussion, nor is the possibility that some cases may have involved exposures to asbestos from sources other than brakes. The important point is that proper scientific inquiry not only can consider these reports, but, in fact, must consider them. Contrary to the suggestion of the asbestos brake manufacturers, these cases cannot be cavalierly dismissed as "unscientific" or "insufficient to support conclusions regarding causation." When considering the important question of whether working with asbestos-containing brakes can cause incurable, inevitably terminal diseases, such as mesothelioma, case series must be considered and evaluated, along with all other available evidence.

There is nothing novel regarding the use of Sir Austin Bradford Hill's viewpoints to arrive at the conclusion that asbestos from brakes can cause disease. Application of his viewpoints has been an accepted and valid method for examination of questions of causation for decades and remains so today.⁷⁶ His own wise words are worth repeating:

Here then are nine different viewpoints from all of which we should study association before we cry causation. What I do not believe—and this has been suggested—that we can usefully lay down some hard-and-fast rules of evidence that must be obeyed before we can accept cause and effect. None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*. What they can do, with greater or less strength, is to help us make up our minds on the fundamental question—is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?

Contrary to the all-or-nothing position of the asbestos brake manufacturers, there is no single scientific discipline or type of study that takes precedence over others. Thoughtful scientific inquiry requires consideration of all evidence when making determinations regarding causation.

CONCLUSION

Asbestos causes mesothelioma. Mechanics are exposed to asbestos dust during the servicing and replacement

of brakes. While the asbestos brake manufacturers claim that the average amount of asbestos released from brake repair work is comparatively low, there is no reasonable dispute that exposure levels were higher when mechanics routinely ground, filed, and sanded brakes and used compressed air to blow out brake wear debris, and did this work without dust control. It is those historic higher exposures that caused disease appearing now. The scientific community is in consensus that brief and low-level exposures to asbestos can cause mesothelioma. The scientific literature contains hundreds of cases of mesothelioma among brake mechanics; and epidemiologic studies of mechanics known to have performed repair work on asbestos-containing brakes have demonstrated increased levels of nonmalignant diseases.

This combination of evidence, and the vast amount of additional scientific information regarding asbestos and mesothelioma, provides more than sufficient evidence to allow someone to conclude within a reasonable degree of scientific certainty that a mesothelioma in a mechanic who worked with asbestos-containing brakes was caused by that asbestos exposure.

Since 2000, Ford, General Motors, and Chrysler have paid over \$30,000,000 to hire consultants for the purpose of generating the very papers they rely upon, and for testifying regarding those papers in Courts.[†] One of the main industry experts has acknowledged that the papers were conceived and authored for the purpose of buttressing testimony in court cases involving mechanics suffering from mesothelioma.[‡]

The same expert also acknowledged that this business model is a pattern he has also followed with dioxin, benzene, hexavalent chromium, beryllium, formaldehyde, and glycol ethers. Recent revelations regarding undisclosed involvement of the employer of these experts in connection with publication of a paper favorable to the chromium industry have been well publicized and led to the retraction of that paper.^{77,78} It is in no way surprising that the experts and papers financed by these manufacturers conclude that asbestos in brakes can never cause mesothelioma. To the contrary, the exoneration of the sponsoring industry is the *expected* conclusion of doubt science. Despite the best efforts of the asbestos brake manufacturers and their hired experts to fabricate scientific uncertainty where none exists, the mainstream scientific community and regulatory communities have considered the available evidence and concluded that the danger to mechanics from asbestos in brakes is real.

[†]Ford, General Motors, and Chrysler have admitted in litigation that, since 2000, they have paid over \$30,000,000 to these experts. See, Ford and General Motors, Answers to Interrogatories, *Unden v. General Motors*, Case No. 05-6311, Circuit Court for Hillsborough County, Florida, and Chrysler IRS Form 1099s produced in litigation.

[‡]Deposition of Dennis Paustenbach, July 1, 2005, *Mallia v. Bennett Auto et al.*, Case Number 04-16236 CA 42, Circuit Court in and for Dade County, Florida.

Apparently, the asbestos brake manufacturers hope that these arguments can be used to sway the Supreme Court of Michigan and other courts. As scientists who have devoted substantial portions of our professional lives working to research, prevent, and treat asbestos-related diseases, we reject these attempts to fabricate uncertainty where none exists. Instead, we request that these courts attend to the work of thousands of experts from around the world who have concluded that asbestos, in any form, and through any occupational exposure, can and does cause disease.

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References

1. U.S. Public Health Service, U.S. Department of Health and Human Services. Toxicological profile for asbestos. Atlanta, GA: Agency for Toxic Substances and Disease Registry, 2001.

2. American Conference of Governmental Industrial Hygienists. Asbestos: TLV(r) Chemical Substances 7th Edition Documentation. Publication #7DOC-040. Cincinnati OH: ACGIH, 2001.
3. Diagnosis and initial management of nonmalignant diseases related to asbestos. *Am J Respir Crit Care Med* 2004; 170:691-715.
4. Environmental Protection Agency. Airborne asbestos health assessment update. Washington, DC: U.S. EPA (EPA/600/8-84/003F), 1986.
5. International Agency for Research on Cancer. Asbestos: Monograph on the Evaluation of Carcinogenic Risk to Man. Lyon, France: IARC, 1988.
6. National Toxicology Program. Report on Carcinogens, 11th ed. U.S. Department of Health and Human Services, Public Health Service, 2005.
7. Occupational Safety and Health Administration. Occupational exposure to asbestos; final rule. *Fed Reg*. 1994;59:40964-41162.
8. Consumer Product Safety Commission. CANCER HAZARD! CPSC Warns About Asbestos in Consumer Products: Safety Alert. CPSC Document #5080. 2004.
9. World Health Organization. Elimination of asbestos related diseases. Geneva, Switzerland: WHO, 2006.
10. World Health Organization. Environmental Health Criteria 53: Asbestos and Other Natural Mineral Fibres. Geneva, Switzerland: WHO, 1986.
11. World Health Organization. Environmental Health Criteria 203: Chrysotile Asbestos. Geneva, Switzerland: WHO, 1998.
12. World Trade Organization. European Communities—Measures Affecting Asbestos and Asbestos-containing Products. WT/DS135/R. 2000.
13. Asbestos, asbestosis, and cancer: the Helsinki criteria for diagnosis and attribution. *Scand J Work Environ Health* 1997; 23:311-6.
14. Malignant Mesothelioma. American Cancer Society, 2006. 10-19-2006.
15. National Cancer Institute. Factsheet—Asbestos: Questions and Answers. Bethesda, MD: National Institutes of Health, 2003.
16. Lemen RA. Asbestos in brakes: exposure and risk of disease. *Am J Ind Med*. 2004;45:229-37.
17. Frank AL, Dodson RF, Williams MG. Carcinogenic implications of the lack of tremolite in UICC reference chrysotile. *Am J Ind Med*. 1998;34:314-7.
18. Smith AH, Wright CC. Chrysotile asbestos is the main cause of pleural mesothelioma. *Am J Ind Med*. 1996;30:252-66.
19. Cullen MR. Chrysotile asbestos: enough is enough. *Lancet*. 1998;351(9113):1377-8.
20. Landrigan PJ, Nicholson WJ, Suzuki Y, LaDou J. The hazards of chrysotile asbestos: a critical review. *Ind Health*. 1999; 37:271-80.
21. Landrigan PJ, Soffritti M. Collegium Ramazzini call for an international ban on asbestos. *Am J Ind Med*. 2005;47:471-4.
22. Stayner LT, Dankovic DA, Lemen R. Occupational exposure to chrysotile asbestos and cancer risk: a review of the amphibole hypothesis. *Am J Public Health*. 1996;86:179-86.
23. Li L, Sun TD, Zhang X, et al. Cohort studies on cancer mortality among workers exposed only to chrysotile asbestos: a meta-analysis. *Biomed Environ Sci*. 2004;17:459-68.
24. Suzuki Y, Yuen SR. Asbestos fibers contributing to the induction of human malignant mesothelioma. *Ann NY Acad Sci*. 2002; 982:160-76.
25. Landrigan PJ. Asbestos—still a carcinogen. *N Engl J Med*. 1998; 338:1618-9.
26. Egilman D, Fehnel C, Bohme SR. Exposing the “myth” of ABC, “anything but chrysotile”: a critique of the Canadian asbestos mining industry and McGill University chrysotile studies. *Am J Ind Med*. 2003;44:540-57.
27. Michaels D. Manufactured uncertainty: protecting public health in the age of contested science and product defense. *Ann NY Acad Sci*. 2006;1076:149-62.
28. Michaels D. Doubt is their product. *Sci Am*. 2005;292(6):96-101.
29. Hessel PA, Teta MJ, Goodman M, Lau E. Mesothelioma among brake mechanics: an expanded analysis of a case-control study. *Risk Anal*. 2004;24:547-52.
30. Goodman M, Teta MJ, Hessel PA, et al. Mesothelioma and lung cancer among motor vehicle mechanics: a meta-analysis. *Ann Occup Hyg*. 2004;48:309-26.
31. Paustenbach DJ, Finley BL, Lu ET, Brorby GP, Sheehan PJ. Environmental and occupational health hazards associated with the presence of asbestos in brake linings and pads (1900 to present): a “state-of-the-art” review. *J Toxicol Environ Health B Crit Rev*. 2004;7:25-80.
32. Paustenbach DJ, Richter RO, Finley BL, Sheehan PJ. An evaluation of the historical exposures of mechanics to asbestos in brake dust. *Appl Occup Environ Hyg*. 2003;18:786-804.
33. Wong O. Malignant mesothelioma and asbestos exposure among auto mechanics: appraisal of scientific evidence. *Regul Toxicol Pharmacol*. 2001;34:170-7.
34. Egilman DS, Billings MA. Abuse of epidemiology: automobile manufacturers manufacture a defense to asbestos liability. *Int J Occup Environ Health*. 2005;11:360-71.
35. Laden F, Stampfer MJ, Walker AM. Lung cancer and mesothelioma among male automobile mechanics: a review. *Rev Environ Health*. 2004;19:39-61.
36. National Institute for Occupational Safety and Health. Workplace Exposure to Asbestos: Review and Recommendations. NIOSH/OSHA Asbestos Work Group Recommendations. Department of Health and Human Services, 1980: 81-103.
37. Hodgson JT, Darnton A. The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure. *Ann Occup Hyg*. 2000;44:565-601.
38. Iwatsubo Y, Pairon JC, Boutin C, et al. Pleural mesothelioma: dose-response relation at low levels of asbestos exposure in a French population-based case-control study. *Am J Epidemiol*. 1998;148(2):133-42.
39. Lin RT, Takahashi K, Karjalainen A, et al. Ecological association between asbestos-related diseases and historical asbestos consumption: an international analysis. *Lancet*. 2007;369(9564): 844-9.
40. Agudo A, Gonzalez CA, Bleda MJ, et al. Occupation and risk of malignant pleural mesothelioma: a case-control study in Spain. *Am J Ind Med*. 2000;37:159-68.
41. Checkoway H, Pearce NE, Crawford-Brown DJ. Research Methods in Occupational Epidemiology. New York: Oxford University Press, 1989.
42. Leigh J, Driscoll T. Malignant mesothelioma in Australia 1945–2002. *Int J Occup Environ Health*. 2003;9:206-17.
43. Coggon D, Pippard EC, Acheson ED. Accuracy of occupational histories obtained from wives. *Br J Ind Med*. 1985;42:563-4.
44. Lerchen ML, Samet JM. An assessment of the validity of questionnaire responses provided by a surviving spouse. *Am J Epidemiol*. 1986;123:481.
45. Mark EJ, Yokoi T. Absence of evidence for a significant background incidence of diffuse malignant mesothelioma apart from asbestos exposure. *Ann NY Acad Sci*. 1991;643:196-204.
46. Lemen RA. Asbestos: Risk Assessment, Epidemiology, and Health Effects. Boca Raton, FL: Taylor and Francis, 2006.
47. Teschke K, Morgan MS, Checkoway H, et al. Mesothelioma surveillance to locate sources of exposure to asbestos. *Can J Public Health*. 1997; 88:163-8.
48. Rustein DD, Mullan RJ, Frazier TM, Halperin WE, Melius JM, Sestito JP. Sentinel health events (occupational): a basis for physician recognition and public health surveillance. *Am J Public Health*. 1983;73:1054-61.
49. Wagner JC, Sleggs CA, Marchand P. Diffuse pleural mesothelioma and asbestos exposure in the North Western Cape Province. *Br J Ind Med*. 1960;17:260-71.
50. Checkoway H, Pearce N, Crawford-Brown DJ. Research Methods in Occupational Epidemiology. 2nd ed. London, U.K.: Oxford University Press, 2004.
51. Ahlbom A, Axelson O, Stottrup Hansen ES, Hogstedt C, Jensen UJ, Olsen J. Interpretation of “negative” studies in occupational epidemiology. *Scand J Work Environ Health*. 1990;16:153-7.
52. Altman DG, Bland JM. Absence of evidence is not evidence of absence. *BMJ*. 1995;311(7003):485.
53. Bailar JC. How to distort the scientific record without actually lying: truth, and the arts of science. *Eur J Oncol*. 2006;11:217-24.
54. Hernberg S. “Negative” results in cohort studies—how to recognize fallacies. *Scand J Work Environ Health*. 1981; 7 suppl 4:121-6.
55. Hernberg S. Some guidelines for interpreting epidemiologic studies. In: Introduction to Occupational Epidemiology. Chelsea, MI: Lewis Publishing, 1992: 201-23.

56. Hessel PA. Testimony before Public Service Commission of Wisconsin. Docket 05-CE-130. 2007.
57. Castrop. Fume and dust exposure. National Safety News. 1948;20, 53, 72-80.
58. American Industrial Hygiene Association. Hygienic standards: asbestos. J Am Ind Hyg Assoc. 1958;19:161-2.
59. Godwin MC, Jagatic G. Asbestos and mesothelioma. JAMA. 1968;204:1009.
60. Teta MJ, Lewinsohn HC, Meigs JW, Vidone RA, Mowad LZ, Flannery JT. Mesothelioma in Connecticut, 1955-1977. Occupational and geographic associations. J Occup Med. 1983;25:749-56.
61. Robinson CF, Lemen RA, Wagoner JK. Mortality patterns, 1940-1974 among workers employed in an asbestos textile friction and packing product manufacturing facility. In: Lemen RA, Dement J (eds). Dust and Disease. Park Forest, IL: Pathotox Publishers, 1979: 131-40.
62. McDonald AD, Fry JS, Woolley AJ, McDonald J. Dust exposure and mortality in an American chrysotile textile plant. Br J Ind Med. 1983;40:361-7.
63. Sakai K, Hisanaga N, Shibata E, Ono Y, Takeuchi Y. Asbestos exposures during reprocessing of automobile brakes and clutches. Int J Occup Environ Health. 2006;12:95-105.
64. Rohl AN, Langer AM, Wolff MS, Weisman I. Asbestos exposure during brake lining maintenance and repair. Environ Res. 1976; 12:110-28.
65. Lorimer WV, Rohl AN, Miller A, Nicholson WJ, Selikoff IJ. Asbestos exposure of brake repair workers in the United States. Mt Sinai J Med. 1976;43:207-18.
66. Hickish DE, Knight KL. Exposure to asbestos during brake maintenance. Ann Occup Hyg. 1970;13:17-21.
67. Environmental Protection Agency. Current Best Practices for Preventing Asbestos Exposure Among Brake and Clutch Repair Workers. EPA 747-F-04-004. Environmental Protection Agency, 2007.
68. Occupational Safety and Health Administration. Asbestos—Automotive Brake and Clutch Repair Work. SHIB 07-26-2006. U. S. Department of Labor; Occupational Safety and Health Administration, 2006.
69. Washington State Department of Labor and Industries. Working Safely with Asbestos in Clutch and Brake Linings. F413-049-000. Olympia WA, Washington State Department of Labor and Industries, 2001.
70. New Hampshire Pollution Prevention Program. Pitstops Manual: Best Management Practices for Automobile Service Facilities. New Hampshire Department of Environmental Services, 2001.
71. Worksafe Alberta. Control of asbestos during brake maintenance and repair. Edmonton, AB: Department of Human Resources and Employment, Government of Alberta, 2004.
72. Minnesota Pollution Control Agency. Facts about Controlling Brake Dust to Protect Your Health . . . What Every Mechanic Should Know. St. Paul, MN: Minnesota Pollution Control Agency, 1998.
73. Johnson P, Zumwalde RD, Roberts D. Industrial Hygiene Assessment of Seven Brake Servicing Facilities—Asbestos. Cincinnati, OH: National Institute for Occupational Safety and Health, 1979.
74. Roberts D. Industrial Hygiene Report—Asbestos, Allied Brake Shop. Cincinnati, OH: National Institute for Occupational Safety and Health, 1980.
75. Nicholson WJ. Investigation of Health Hazards in Brake Lining Repair and Maintenance Workers Occupationally Exposed to Asbestos. 210-77-0119. Cincinnati, OH: National Institute for Occupational Safety and Health, 1984.
76. Hill AB. The environment and disease: association or causation? Proc R Soc Med. 1995;58:295-300.
77. Waldman P. Publication to retract an influential water study. Wall Street Journal. June 2, 2006.
78. Waldman P. Study tied pollutant to cancer; then consultants got hold of it. Wall Street Journal. 2005.

EXHIBIT 43

IN THE SUPREME COURT OF PENNSYLVANIA

NO. 56 EAP 2014

JOYCE ROST EXECUTRIX OF THE ESTATE OF RICHARD ROST
& JOYCE ROST,

Plaintiffs-Appellees,

v.

FORD MOTOR COMPANY,

Defendants-Appellants

BRIEF OF MUGE AKPINAR-ELCI, MD, MPH, PROF. DR. MED. XAVER BAUR, CARLOS BEDROSSIAN, MD, PHD(HON), FIAC, EULA BINGHAM, PHD, YV BONNIER-VIGER, MD, MSC, MM, CMSQ, FRCPC, JAMES BROPHY, PHD, MASSIMILIANO BUGIANI, MD, BARRY CASTLEMAN, SCD , RICHARD CLAPP, DSC, MPH, DARIO CONSONNI, MD PHD, EMILIE COUNIL, MOHAMED AQIEL DALVIE, BSC, HONS, MSC, PHD, JOHN M. DEMENT, PH.D., CIH, TONY FLETCHER, PHD, PROFESSOR BICE FUBINI, THOMAS H. GASSERT, MD, MSC, DAVID F. GOLDSMITH, MSPH, PHD, MICHAEL GOCHFELD, MD, PHD, LENNART HADELL, MD, PHD, JAMES HUFF, PHD, PETER F. INFANTE, DDS, DRPH, MOHAMED F. JEEBHAY MBCHB, MPH (OCC MED), PHD, T. K. JOSHI, FRCS, FFOM, MARGARET KEITH, PHD, JOHN R. KEYSERLINGK, MD, MSC, FRCS(C), FACS, KAPIL KHATTER, MD, CCFP, MES, SHIRA KRAMER, MHS, PHD, PHILIP J. LANDRIGAN, MD, MSC, FAAP, BRUCE LANPHEAR, MD, MPH, RICHARD A. LEMEN, PH.D., MSPH, CHARLES LEVENSTEIN, PHD, MS, ABBY LIPPMAN, PHD, GERALD MARKOWITZ, PHD, DARIO MIRABELLI, MD, SIGURD MIKKELSEN, MD, DRMEDSCI, CELESTE MONFORTON, DRPH, MPH, RAMA C. NAIR, BSC, MSTAT, MSC, PHD, FACE, L. CHRISTINE OLIVER, MD, MPH, MS, DAVID OZONOFF, MD, MPH, DOMYUNG PAEK, MD, MSC, SCD, SMITA PAKHALÉ, MD, FRCPC, MSC , ROLF PETERSEN, PHD, BETH ROSENBERG, SCD, MPH, KENNETH ROSENMAN MD, FACE, FACPM, DAVID ROSNER, PHD, CRAIG SLATIN, SC.D., MPH, MICHAEL SILVERSTEIN, MD, MPH, COLIN L. SOSKOLNE, PHD ,LESLIE THOMAS STAYNER, PHD, KEN TAKAHASHI, MD, PHD, MPH, DANIEL THAU TEITELBAUM, MD, BENEDETTO TERRACINI, ANNIE THÉBAUD-MONY, FERNAND TURCOTTE, MD, MPH, FRCPC, ANDREW WATTERSON, PHD, CFIOSH, DAVID H. WEGMAN, MD, MSC, LAURA S. WELCH, MD, PROF. EM. DR. MED. HANS-JOACHIM WOITOWITZ AS *AMICI CURIAE* IN SUPPORT OF APPELLEES

**Appeal From the Judgment of the Superior Court of Pennsylvania Entered on
May 19, 2014, at No. 404 EDA 2012, Affirming the Judgment Entered
December 28, 2011, in the Court of Common Pleas, Civil Division,
Philadelphia County at No. 1978 September Term, 2010**

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IN THE SUPREME COURT OF PENNSYLVANIA

NO. 56 EAP 2014

**JOYCE ROST EXECUTRIX OF THE ESTATE OF RICHARD ROST
& JOYCE ROST,**

Plaintiffs-Appellees,

v.

FORD MOTOR COMPANY,

Defendants-Appellants

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TABLE OF CONTENTS

TABLE OF AUTHORITIES.....	iv
STATEMENT OF SUBJECT MATTER AND JURISDICTION.....	1
STATEMENT OF THE ORDER IN QUESTION	1
STATEMENT OF THE SCOPE AND STANDARD OF REVIEW.....	1
STATEMENT OF THE QUESTIONS INVOLVED.....	1
STATEMENT OF THE CASE AND FACTS.....	1
STATEMENT OF INTEREST.....	1
SUMMARY OF THE ARGUMENT.....	3
ARGUMENT.....	4
I. IT IS A SCIENTIFIC FACT THAT EACH EXPOSURE CONTRIBUTES TO THE TOTAL DOSE.....	4
II. A MULTI-FACETED DIAGNOSTIC ANALYSIS IS THE GENERALLY ACCEPTED METHOD FOR ASSIGNING SUBSTANTIAL FACTOR CAUSATION.	5
1. Occupational history	5
2. Individual Susceptibility.....	10
3. Biological Plausibility.....	11
4. Case Reports and Sentinel Events/Signature Diseases.....	13
5. Epidemiological Studies	16
CONCLUSION.....	21

TABLE OF AUTHORITIES

<u>Other Authorities</u>	<u>Page</u>
A. E. Anderson, et al., Asbestos Emissions from Brake Dynamometer Tests, SAE Technical Paper 730549 (1973).	18
Margaret R. Becklake, <i>Asbestos-Related Diseases of the Lung and Other Organs: Their Epidemiology and Implications for Clinical Practice</i> , 114 Am. Rev. Resp. Disease 187 (1976).	13
Jean Bignon, et al., <i>History and Experience of Mesothelioma in Europe</i> , in <i>Mesothelioma</i> 29-53 (Bruce W.S. Robinson & A. Philippe Chahinian, eds., 2002).	17
David S. Egilman & Marion A. Billings, <i>Abuse of Epidemiology: Automobile Manufacturers Manufacture a Defense to Asbestos Liability</i> , 11 Int. J. Occup. Environ. Health 360 (2005).	20
Philip E. Enterline, <i>Asbestos and Cancer: The First Thirty Years</i> (1978).	14
Bernard D. Goldstein & Mary Sue Henifin, <i>Reference Guide on Toxicology</i> , in Reference Manual on Scientific Evidence, 642 (Federal Judicial Center, 3 rd ed. 2011).	5
Bernard D. Goldstein & Mary Sue Henifin, <i>Reference Guide on Toxicology</i> , in Reference Manual on Scientific Evidence, 639-640 (Federal Judicial Center, 3 rd ed. 2011).	10
Bernard D. Goldstein & Mary Sue Henifin, <i>Reference Guide on Toxicology</i> , in Reference Manual on Scientific Evidence, 669-670 (Federal Judicial Center, 3 rd ed. 2011).	13
Bernard D. Goldstein, <i>Toxic Torts: The Devil is in the Dose</i> , 16(2) J.L. & Pol’y. 551 (2008).	12

Morris Greenberg & T.A. Lloyd Davies, *Mesothelioma Register 1967-68*, 31 Brit. J. Ind. Med. 91 (1974). 15

Samuel P. Hammar, et al., *Neoplasms of the Pleura*, in 2 Dail and Hammar's Pulmonary Pathology Volume II: Neoplastic Lung Disease (Joseph F. Tomashefski, Jr., et al., eds., 3rd ed. 2008). 11, 17

John T. Hodgson & Andrew Darnton, *The Quantitative Risks of Mesothelioma and Lung Cancer in Relation to Asbestos Exposure*, 44(8) Ann. Occup. Hyg. 565 (2000). 15

Sir Austin Bradford Hill, *The Environment and Disease: Association or Causation?* Proceedings of the Royal Society of Medicine 295 (1965). 8, 10

M. Huncharek, et al., *Pleural Mesothelioma in a Brake Mechanic*, 46 Brit. J. Ind. Med. 69 (1989). 18

International Agency for Research on Cancer (IARC), *Special Report: Policy: A review of human carcinogens - Part C: metals, arsenic, dusts, and fibres*, 10 The Lancet, 453 (2009). 12, 16

Y. Iwatsubo, et al., *Pleural Mesothelioma: Dose-Response Relation at Low Levels of Asbestos Exposure in a French Population-based Case-Control Study*, 148(2) Am. J. Epidemiol. 133 (1998). 18

Joint Policy Committee of the Societies of Epidemiology, *Position Statement on Asbestos from the Joint Policy Committee of the Societies of Epidemiology (JPC-SE)* (2012). 16

A. LaCourt, et al., *Occupational and Non-Occupational Attributable Risk of Asbestos Exposure for Malignant Pleural Mesothelioma*, Thorax 1 (2014). 17

Richard A. Lemen, *Asbestos in Brakes: Exposure and Risk of Disease*, 45 Am. J. Ind. Med. 229 (2004). 6, 19, 20

Thomas F. Mancuso, et al., <i>Methodology in Industrial Health Studies: The Cohort Approach, with Special Reference to an Asbestos Company</i> , 6 Arch. Env. Health 210 (1963).	8
D. McDonald, et al., <i>Epidemiology of Primary Malignant Mesothelial Tumors in Canada</i> , 26(4) Cancer 914 (1970).	18
Domenico Franco Merlo, et al., <i>A Historical Mortality Study Among Bus Drivers and Bus Maintenance Workers Exposed to Urban Air Pollutants in the City of Genoa, Italy</i> , 67 Occup. Environ. Med. 611 (2010).	19
D. Mirabelli, et al., <i>Excess of mesotheliomas after exposure to chrysotile in Balangero, Italy</i> , 65 Occup. Environ. Med. 815 (2008).	16
National Cancer Institute, <i>Asbestos Exposure and Cancer Risk</i> (2009), http://www.cancer.gov/cancertopics/causes-prevention/risk-factors/cancer-causing-substances/asbestos/asbestos-fact-sheet (accessed March 11, 2015).	20
Nadine S.M. Offermans, et al., <i>Occupational Asbestos Exposure and Risk of Pleural Mesothelioma, Lung Cancer, and Laryngeal Cancer in the Prospective Netherlands Cohort Study</i> , 56(1) J. Occup. Environ. Med. 6 (2014).	18
Giorgio Piolatto, et al., <i>An Update of Cancer Mortality among Chrysotile Asbestos Miners in Balangero, Northern Italy</i> , 47 Brit. J. Ind. Med. 810 (1990).	16
Bernardino Ramazzini, <i>De Morbis Artificum Diatriba</i> (1713), Trans. by W.C. Wright in A.L. Birmingham, <i>Classics of Medicine Library</i> (1983), in <u>Medicine in Quotations: Views of Health and Disease through the Ages</u> , 276 (Edward J. Huth & T.J. Murray, eds., 2 nd ed. 2006).	7
A. Reid, et al., <i>Mesothelioma Risk after 40 Years Since First Exposure to Asbestos: a Pooled Analysis</i> , 0 Thorax, 1 (2014).	20

J. Ribak, et al., <i>Malignant Mesothelioma in a Cohort of Asbestos Insulation Workers: Clinical Presentation, Diagnosis, and Causes of Death</i> , 45 Brit. J. Ind. Med. 182 (1988).	10
Klaus Rödelberger, et al., <i>Asbestos and Man-Made Vitreous Fibers as Risk Factors for Diffuse Malignant Mesothelioma: Results from a German Hospital-Based Case-Control Study</i> , 39 Am. J. Ind. Med. 262 (2001).	17
Klaus Rödelberger, et al., <i>Asbestos Dust Exposure During Brake Repair</i> , 10 Am. J. Ind. Med. 63 (1986).	18
Cora R. Roelofs, et al., <i>Mesothelioma and Employment in Massachusetts: Analysis of Cancer Registry Data 1988-2003</i> , 56 Am. J. Ind. Med. 985 (2013).	19
David D. Rutstein, et al., <i>Sentinel Health Events (Occupational): A Basis for Physician Recognition and Public Health Surveillance</i> , 73(9) Am. J. Public Health 1054 (1983).	14
Irving J. Selikoff, <i>Opening Remarks</i> , 132 Ann. N.Y. Acad. Sci. 7 (1965).	13
E. Skammeritz, et al., <i>Asbestos Exposure and Survival in Malignant Mesothelioma: A Description of 122 Consecutive Cases at an Occupational Clinic</i> , 2(4) Int. J. Occup. Environ. Med. 224 (2011).	15
Joseph R. Testa, et al., <i>Germline BAP1 Mutations Predispose to Malignant Mesothelioma</i> , 43(10) Nature Genetics (2011).	11
Kay Teschke, et al., <i>Mesothelioma Surveillance to Locate Sources of Exposure to Asbestos</i> , 88(3) Canadian J. Pub. Health 163 (1997).	18
A. Tossavainen, et al., <i>Consensus Report: Asbestos, Asbestosis, and Cancer: The Helsinki Criteria for Diagnosis and Attribution</i> , 23(4) Scand. J. Work Environ. Health 311 (1997).	8

- Francesco Turci, et al., *Role of Associated Mineral Fibres in Chrysotile Asbestos Health Effects: The Case of Balangeroite*, 53(5) Ann. Occup. Hyg. 491 (2009). 15
- United States Department of Labor, Occupational Safety & Health Administration (OSHA), Safety and Health Topics, *Asbestos*, <https://www.osha.gov/SLTC/asbestos/> (accessed March 12, 2015). 15
- J. C. Wagner, et al., *Diffuse Pleural Mesothelioma and Asbestos Exposure in the North Western Cape Province*, 17 Brit. J. Indust. Med. 260 (1960). 7, 13
- Laura S. Welch, *Asbestos Exposure Causes Mesothelioma, But Not This Asbestos Exposure: An Amicus Brief to the Michigan Supreme Court*, 13 Int. J. Occup. Environ. Health 318 (2007). 20
- Henrik Wolff, et al., *Consensus Report: Asbestos, Asbestosis, and cancer, the Helsinki Criteria for Diagnosis and Attribution 2014: Recommendations*, 41(1) Scand. J. Work Environ. Health 5 (2015). 8
- 100C World Health Organization, International Agency for Research on Cancer, *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, A Review of Human Carcinogens, Part C: Arsenic, Metals, Fibres, and Dusts* 1-40, 219-309 (2012). 13, 16
- World Health Organization (WHO), International Agency for Research on Cancer (IARC), *IARC Monographs on the Evaluation of the Carcinogenic Risks for Humans, Chemical and Industrial Processes Associated with Cancer in Humans: IARC Monographs, Volumes 1 to 20, Supp. 1* (1979). 13
- World Health Organization (WHO), International Agency for Research on Cancer (IARC), *IARC Monographs on the Evaluation of the Carcinogenic Risks to Humans, Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42, Supp. 7* (1987). 15

STATEMENT OF SUBJECT MATTER AND JURISDICTION

Amici adopt Appellees Statement of Subject Matter and Jurisdiction.

STATEMENT OF THE ORDER IN QUESTION

Amici adopt Appellees Statement of the Order in Question.

STATEMENT OF THE SCOPE AND STANDARD OF REVIEW

Amici adopt Appellees Statement of the Scope and Standard of Review

STATEMENT OF THE QUESTION INVOLVED

Amici adopt Appellees Statement of the Question Involved.

STATEMENT OF THE CASE AND FACTS

Amici adopt Appellees Statement of the Case and Facts.

STATEMENT OF INTEREST

Our¹ understanding as to the nature of the issue before this Court is whether, based upon a review of all the evidence in the record, there was sufficient data to support the jury's finding that exposure to Ford's asbestos products was a substantial contributing factor in the development of Mr. Rost's mesothelioma. Ford and manufacturers of asbestos brakes contend that because Dr. Frank testified that every exposure contributes to the dose, that there can be no admissible evidence of causation.

¹ A list of the Amici and their affiliations is attached as Exhibit A. Their titles and affiliations are given for identification purposes only.

We, as physicians and scientists, remain concerned about the ongoing epidemic of asbestos disease that causes several thousand preventable deaths each year in the United States alone. The signers of this paper collectively possess hundreds of years of experience researching, diagnosing, and treating asbestos-related diseases in workers and their families. We have published extensively in this field for more than 40 years and have conducted dozens of epidemiological and other studies into the issues of asbestos and disease. Many of us have testified before legislative and regulatory bodies regarding asbestos and disease and in court proceedings at the request of individuals suffering from mesothelioma and other asbestos-related diseases.²

Scientists are concerned because it is indeed an irrefutable scientific fact that each exposure does actually contribute to a person's total dose and to that person's risk or probability of developing mesothelioma and other cancers. This is scientific fact. Each individual fiber itself may not necessarily be a significant cause of the mesothelioma in question, but each does necessarily contribute to a person's total dose. Therefore, if this Court were to state that Dr. Frank's concurrence with this axiomatic scientific principle so infects the record that there

² This paper is being signed by 58 physicians and scientists who reviewed the document, support the contents and asked to have their name listed. The signers have received no compensation for their participation in this paper.

can be no causation, this holding will have the absurd result of allowing any asbestos defendant to escape liability merely by laying the “trap” of posing the question: “Does every exposure contribute to the dose,” a question with which no credible expert could disagree.

Second, scientists are concerned that Ford and the manufacturers of asbestos brakes ask this Court to ignore the fact that Dr. Frank employed the generally accepted scientific methodology of reviewing the diagnosis, medical and occupational history, individual susceptibility, biological plausibility, and relevant case reports, case series, and epidemiological studies in order to testify as to whether Mr. Rost’s exposure to asbestos from Ford’s brakes and clutches were substantial factors contributing to Mr. Rost’s disease. To require more than this would defy long standing generally accepted scientific principles of etiology.

SUMMARY OF ARGUMENT

There is a clear difference between the undeniable scientific fact that each exposure contributes to the total dose, versus stating that “one-fiber” or some infinitesimally small exposure to asbestos is a significant or appreciable contribution to causation. While the “one fiber” or “one hit” scientific concept may indeed be true on some theoretical plane, that is not what happens in the real world of asbestos exposures. Diverting attention from an expert testifying about

real world significant exposures by claiming that the case is based on the theory that any exposure/single fiber is a substantial contributing factor is, at best, a clear misunderstanding of the actual testimony, and at worst, intellectual dishonesty and an attempt to deceive this Court. Cumulative exposure (e.g. every exposure contributes to the dose, cumulatively) is a corner-stone of medicine and science; what makes for a significant exposure is a different topic altogether.

It is axiomatic that every exposure to asbestos, while not necessarily a substantial contributing factor, contributes to the total dose. An expert's concurrence with this scientific fact should not "infect" his testimony such that his causation opinion is negated, especially where, as here, the expert employed the generally accepted method of a multi-faceted review of the diagnosis, medical and occupational history, individual susceptibility, biological plausibility, and relevant case and epidemiological studies.

ARGUMENT

I. IT IS A SCIENTIFIC FACT THAT EACH EXPOSURE CONTRIBUTES TO THE TOTAL DOSE.

It is an irrefutable scientific fact that each exposure, while not necessarily a significant cause of the mesothelioma in question, necessarily contributes to a person's total dose. Specifically, there is a clear difference between the undeniable scientific fact that each exposure contributes to the total dose, versus stating that

“one-fiber” or some infinitesimally small exposure to asbestos is a significant or appreciable contribution to causation.

While the “one fiber” or “one hit” scientific concept may indeed be true on some theoretical plane,³ that is not what happens in the real world of asbestos exposures. Diverting attention from an expert testifying about real world significant exposures by claiming that the case is based on the theory that any exposure/single fiber is a substantial contributing factor is, at best, a clear misunderstanding of the actual testimony, and at worst, intellectual dishonesty and an attempt to deceive this Court. Cumulative exposure (e.g. every exposure contributes to the dose, cumulatively) is a corner-stone of medicine and science; *what makes for a significant exposure is a different topic altogether.*

It is our understanding that the legal test employed in this and some other jurisdictions already requires that the Plaintiff present evidence of the frequency, proximity and regularity of exposure to the defendant’s products. Given this requirement, and given the reality that occupational and para-occupational

³ The “one hit” hypothesis for cancer genesis is that each molecule of a cancer causing substance has a very tiny but not zero chance of inducing via mutation one fully cancerous cell that leads to a cancerous tumor. It is one possible explanation on how cancers might form and would provide some additional biological explanation for how the low dose cancers caused by radiation or asbestos occur. It may or may not ultimately be proven to be true, but it is a separate issue from determining what constitutes a significant exposure. Bernard D. Goldstein & Mary Sue Henifin, *Reference Guide on Toxicology*, in Reference Manual on Scientific Evidence, 642 (Federal Judicial Center, 3rd ed. 2011).

exposures to asbestos involve billions or trillions of fibers⁴, the suggestion that an expert who testifies that frequent, regular, and proximate exposure to an asbestos product is a substantial contributing factor is relying on the “any exposure/single fiber” theory is without basis in fact or logic.

II. A MULTI-FACETED DIAGNOSTIC ANALYSIS IS THE GENERALLY ACCEPTED METHOD FOR ASSIGNING SUBSTANTIAL FACTOR CAUSATION.

Ford’s and the industry advocates’ erroneous position is that the “only” method used by Dr. Frank was that “any exposure/single fiber” is a substantial contributing factor. On the contrary, Dr. Frank used a multi-faceted generally accepted methodology studying exposure history, individual susceptibility, biological plausibility, and relevant case reports and epidemiological studies. As set forth below, this is a widely accepted scientific methodology for ascribing substantial factor causation, and should be viewed as sufficient evidence of causation in this case.

1. Occupational history.

Using work histories to identify significantly harmful exposures is at least as ancient as the field of occupational medicine itself, as evidenced by this advice from the father of occupational medicine, Bernardino Ramazzini, in 1713:

⁴ Richard A. Lemen, *Asbestos in Brakes: Exposure and Risk of Disease*, 45 Am. J. Ind. Med. 229 (2004).

When a doctor arrives to attend some patient of the working class...let him condescend to sit down...if not on a gilded chair...on a three-legged stool... He should question the patient carefully...So says Hippocrates in his work 'Affections.' I may venture to add one more question: *What occupation does he follow?*⁵

Qualitative history of exposure has also been the driving force behind the discovery and development of knowledge regarding the dangers of asbestos. The seminal 1960 Wagner study is a case in point.⁶ Thirty-three (33) individual cases of mesotheliomas were reported from a South African asbestos mining town. Thirty-two (32) of those cases had a known qualitative history of exposure to asbestos. There were no exposure measurements, nor epidemiological/statistical analysis. Almost half of the cases were not from miners or first-hand exposure to asbestos but rather were from environmental and household exposures. Despite limitations that many industry advocates would now proclaim fatal to ascribing causation, many scientists believe that this study established that asbestos causes the very rare disease mesothelioma, and that environmental and household

⁵ Bernardino Ramazzini, *De Morbis Artificum Diatriba* (1713), Trans. by W.C. Wright in A.L. Birmingham, *Classics of Medicine Library* (1983), in Medicine in Quotations: Views of Health and Disease through the Ages, 276 (Edward J. Huth & T.J. Murray, eds., 2nd ed. 2006).

⁶ J.C. Wagner, et al., *Diffuse Pleural Mesothelioma and Asbestos Exposure in the North Western Cape Province*, 17 Brit. J. Indust. Med. 260 (1960).

exposures alone were adequate: again, all based on exposure history alone.⁷ Indeed, in the seminal 1965 paper on causation, *The Environment and Disease: Association or Causation?*, Sir Austin Bradford Hill emphasized the importance of exposure history used in conjunction with existing literature to determine a causal link.⁸

Internationally respected asbestos disease specialists reached a scientific and medical consensus, originally in 1997⁹ and reaffirmed in 2014,¹⁰ on the requirements for experts to attribute a given mesothelioma to asbestos exposure. The original 1997 committee consisted of 19 participants of various disciplines from eight (8) countries not producing asbestos, with over 1000 articles published between them. The resulting “Helsinki Consensus” agreed with the traditional generally accepted approach in occupational medicine that “a history of significant occupational, domestic or environmental exposure will suffice for attribution.”

⁷ The first cohort study on mesothelioma was published in 1963. This landmark study provided to epidemiologists and other public health professionals proof of a statistical association. Thomas F. Mancuso, et al., *Methodology in Industrial Health Studies: The Cohort Approach, with Special Reference to an Asbestos Company*, 6 Arch. Env. Health 210 (1963).

⁸ Sir Austin Bradford Hill, *The Environment and Disease: Association or Causation?* Proceedings of the Royal Society of Medicine 295 (1965).

⁹ A. Tossavainen, et al., *Consensus Report: Asbestos, Asbestosis, and Cancer: The Helsinki Criteria for Diagnosis and Attribution*, 23(4) Scand. J. Work Environ. Health 311 (1997).

¹⁰ Henrik Wolff, et al., *Consensus Report: Asbestos, Asbestosis, and cancer, the Helsinki Criteria for Diagnosis and Attribution 2014: Recommendations*, 41(1) Scand. J. Work Environ. Health 5 (2015).

The Helsinki Consensus also stated that the following points need to be considered in determining attribution of a given mesothelioma to asbestos exposures:

- “The great majority of mesotheliomas are due to asbestos exposure;
- “Mesotheliomas can occur in cases with low asbestos exposure.
- “However, very low background environmental exposures carry only an extremely low risk;
- “About 80% of mesothelioma patients have had some occupational exposure to asbestos, and therefore a careful occupational and environmental history should be taken;
- “Even brief or low-level exposure should be considered sufficient for mesothelioma to be designated as occupationally related.
- “A minimum of 10 years from the first exposure is required to attribute the mesothelioma to asbestos exposure, though in most cases the latency interval is longer (e.g., in the order of 30-40 years)

These generally accepted principles serve as the basic framework for occupational medicine and public health professionals when they are making determinations of both whether the total cumulative exposure was capable of causing mesothelioma, and whether some subset of the total exposure was a significant or appreciable exposure.

From the medical and scientific perspective, no bright-line quantitative tests can ever be applied in such causation evaluations. To require quantification where it is almost always impossible and unnecessary to do so, would be a public health travesty. That is, this would have the effect of creating an impossible burden of proof, and no claim would be able to meet the impossible standard: “only rarely are

humans exposed to environmental chemicals in a manner that permits a quantitative determination of adverse outcomes...Human exposure occurs most frequently in occupational settings where workers are exposed to industrial chemicals such as lead or asbestos; however, even under these circumstances, it is usually difficult, if not impossible, to quantify the amount of exposure.”¹¹

Perfect and complete exposure data is virtually never available. But using professional judgment based on the available evidence is generally accepted in the medical and scientific community.¹²

2. Individual Susceptibility.

One other important factor to consider in what constitutes a significant exposure is the concept of individual susceptibility. The great weight of evidence suggests that there are widely varying levels of susceptibility to asbestos, much as there is with tobacco and lung cancer. For example, even with very high exposures such as those experienced by insulation workers, less than 10% of the insulators developed mesothelioma.¹³ On the other hand, just low level chrysotile exposure via home contamination, in the absence of occupational exposures, has been shown to induce high incidences of mesotheliomas in family groups that also have a

¹¹ Bernard D. Goldstein & Mary Sue Henifin, *Reference Guide on Toxicology*, in *Reference Manual on Scientific Evidence*, 639-640 (Federal Judicial Center, 3rd ed. 2011).

¹² Hill, *supra*.

¹³ J. Ribak, et al., *Malignant Mesothelioma in a Cohort of Asbestos Insulation Workers: Clinical Presentation, Diagnosis, and Causes of Death*, 45 *Brit. J. Ind. Med.* 182 (1988).

germ-line BAP1 mutation.¹⁴ Additionally, a diagnosis of mesothelioma combined with a Helsinki Consensus sufficient exposure history, is certainly proof of the body's defenses being overwhelmed and defeated. The capacity of the body's defense is certainly influenced heavily if not defined by individual susceptibility.

3. Biological Plausibility.

The emerging consensus among physicians and scientists is that most forms of cancer develop in a multistage process. This process typically involves a number of mutations, and these mutations must follow in some particular sequence for the cell(s) in question to become a fully cancerous cell which develops into a tumor:

[It is]...now recognized that asbestos fibers themselves are carcinogenic, mainly by indirect mechanisms, and that malignant transformation is a multi-stage process...Direct effects are related to the physical interaction of fibers with target cells or by the generation of free radicals and reactive oxygen species (ROS) at the surface of fibers. Indirect effects are related to an inflammatory response to fibers, including the generation of factors, such as ROS and cytokines as a consequence of attempted but incomplete phagocytosis of fibers by macrophages ("frustrated phagocytosis"). There is now substantial scientific evidence for the indirect model, as discussed in several reviews.¹⁵

¹⁴Joseph R. Testa, et al., *Germline BAP1 Mutations Predispose to Malignant Mesothelioma*, 43(10) Nature Genetics (2011).

¹⁵ See generally Samuel P. Hammar, et al., *Neoplasms of the Pleura*, in 2 Dail and Hammar's Pulmonary Pathology Volume II: Neoplastic Lung Disease (Joseph F. Tomashefski, Jr., et al., eds., 3rd ed. 2008) and specifically pp. 587-588 and 589-599 generally.

Although, as in most areas of medicine, there is much to be learned, scientists have identified “established mechanistic events” in the development of asbestos-induced mesothelioma. These include: impaired fiber clearance leading to macrophage activation, inflammation, generation of reactive oxygen and nitrogen species, tissue injury, genotoxicity, aneuploidy and polyploidy, epigenetic alteration, activation of signaling pathways, and resistance to apoptosis.¹⁶

Cumulative exposure is merely an extension of the ancient concept of dose-response: “...‘the dose makes the poison’ is the oldest maxim in the field.”¹⁷ “Toxicologists generally posit two main dose-response curves: those that have a “threshold” and those that do not...The second general type of a dose-response curve is one that is considered to have no threshold. The most important example for toxic torts is that of cancer. The underlying cause of many cancers is a persistent genetic mutation allowing the unbridled growth of a cell which then results in a clone of cancer cells”.^{18 19}

¹⁶ International Agency for Research on Cancer (IARC), *Special Report: Policy: A review of human carcinogens - Part C: metals, arsenic, dusts, and fibres*, 10 The Lancet, 453 (2009).

¹⁷ Bernard D. Goldstein, *Toxic Torts: The Devil is in the Dose*, 16(2) J.L. & Pol’y. 551 (2008). Bernard D. Goldstein is Professor of Environmental and Occupational Health and former Dean of the University of Pittsburg Graduate School of Public Health.

¹⁸ *Id.* at 554-555.

Research to date confirms the findings of case reports and epidemiological studies: that total body burden (cumulative exposure) has a significant effect on the carcinogenic process and that all forms of commercial asbestos are genotoxic and mutagenic (a dose-response curve without a threshold).

4. Case Reports and Sentinel Events/Signature Diseases

Case reports, especially when dealing with rare diseases that are considered sentinel events/signature diseases for a given exposure, are a powerful form of evidence and one that researchers take into consideration along with cell and animal studies, autopsy studies, as well as epidemiology studies. Such case reports and series also support the attribution position taken in the Helsinki Consensus.

Mesothelioma is a signature malignancy for asbestos exposure. This has been generally accepted in the scientific community based on studies conducted decades ago.^{20 21 22 23} Mesothelioma was listed as a sentinel health event of

¹⁹ Also see Bernard D. Goldstein & Mary Sue Henifin, *Reference Guide on Toxicology, in Reference Manual on Scientific Evidence*, 669-670 (Federal Judicial Center, 3rd ed. 2011): “For agents that produce effects other than through mutations, it is assumed that there is some level that is incapable of causing harm... If the level of exposure was below this no observable effect, or threshold, level, a relationship between the exposure and disease cannot be established ... *This analysis, however, is not applied to substances that exert toxicity by causing mutations leading to cancer.*” (emphasis added).

²⁰ Wagner, *supra*.

²¹ Irving J. Selikoff, *Opening Remarks*, 132 Ann. N.Y. Acad. Sci. 7 (1965).

²² Margaret R. Becklake, Asbestos-Related Diseases of the Lung and Other Organs: Their Epidemiology and Implications for Clinical Practice, 114 Am. Rev. Resp. Disease 187 (1976).

occupational origin in the U.S. over thirty years ago.²⁴ The agent responsible was identified as asbestos and the industry/occupation of concern was “Asbestos industries and utilizers.”²⁵ In the United States, there are no other proven major causes of malignant mesothelioma.

Regarding the specific usefulness of case reports in looking at asbestos related cancer, Phillip Enterline, M.D., in a report funded by and generated for the industry group Asbestos Information Association, stated:

Among the things I gained from this research was a deep respect for the clinicians and pathologists who contributed to the early literature. They showed remarkable insight into the meaning of the observations, and the logic of their conclusions was far more reasoned than I had expected. I became far less sure that the sharp distinction made by many writers between epidemiological as contrasted with clinical-pathological observations served a useful purpose. Even a single case report is a kind of epidemiological observation, since the basis of such reports is usually a feeling, unexpressed, that the case is somehow aberrant for a human population.²⁶

²³ World Health Organization (WHO), International Agency for Research on Cancer (IARC), *IARC Monographs on the Evaluation of the Carcinogenic Risks for Humans, Chemical and Industrial Processes Associated with Cancer in Humans: IARC Monographs, Volumes 1 to 20*, Supp. 1 (1979); 100C World Health Organization, International Agency for Research on Cancer, *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, A Review of Human Carcinogens, Part C: Arsenic, Metals, Fibres, and Dusts* 1-40, 219-309 (2012).

²⁴ David D. Rutstein, et al., *Sentinel Health Events (Occupational): A Basis for Physician Recognition and Public Health Surveillance*, 73(9) Am. J. Public Health 1054 (1983).

²⁵ *Id.* at 1056

²⁶ Philip E. Enterline, *Asbestos and Cancer: The First Thirty Years* (1978).

Regulatory bodies such as the Department of Labor's Occupational Safety & Health Agency (OSHA), after conducting a comprehensive literature review, have found and reported case reports in scientific literature showing very short exposures being capable of causing mesothelioma: "Asbestos exposures as short in duration as a few days have caused mesothelioma in humans."²⁷

As noted above, almost half of the 32 case reports in the seminal 1960 Wagner paper involved environmental or household contact alone. Similarly, one can find individuals within larger cohorts whose exposures were low or intermittent. For example, there is a chrysotile mine in Italy that is free from amphibole asbestos contamination.²⁸ An early study found two (2) miners with mesothelioma, which the authors conclude is evidence of pure chrysotile causing

²⁷ United States Department of Labor, Occupational Safety & Health Administration (OSHA), Safety and Health Topics, *Asbestos*, <https://www.osha.gov/SLTC/asbestos/> (accessed March 12, 2015)., citing: E. Skammeritz, et al., *Asbestos Exposure and Survival in Malignant Mesothelioma: A Description of 122 Consecutive Cases at an Occupational Clinic*, 2(4) Int. J. Occup. Environ. Med. 224 (2011).; Morris Greenberg & T.A. Lloyd Davies, *Mesothelioma Register 1967-68*, 31 Brit. J. Ind. Med. 91 (1974).; World Health Organization (WHO), International Agency for Research on Cancer (IARC), *IARC Monographs on the Evaluation of the Carcinogenic Risks to Humans, Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42, Supplement 7* 106-116 (1987); and John T. Hodgson & Andrew Darnton, *The Quantitative Risks of Mesothelioma and Lung Cancer in Relation to Asbestos Exposure*, 44(8) Ann. Occup. Hyg. 565 (2000).

²⁸ This chrysotile mine has a mineral called balangeroite present as well. This mineral is not a form of asbestos, is not chemically similar to amphibole asbestos, has poor bio-persistence, and upon testing by the researchers was deemed to not be responsible for the excess of mesotheliomas in the area. See Francesco Turci, et al., *Role of Associated Mineral Fibres in Chrysotile Asbestos Health Effects: The Case of Balangeroite*, 53(5) Ann. Occup. Hyg. 491 (2009).

mesothelioma but with low potency.²⁹ Years later and after additional latency had passed, in an updated study looking at not only the miners, but white collar workers and people who lived in the area surrounding the mine, they found a tremendous increase in mesothelioma. Not only were there now fourteen (14) miners with mesothelioma, there were thirteen (13) non-miners including white collar only workers and five (5) environmental cases.³⁰

5. Epidemiological Studies.

There is overwhelming consensus in the medical and scientific communities that exposure to all forms of commercial asbestos can induce mesotheliomas based on peer-reviewed, published epidemiological studies.³¹ Mesothelioma is caused by asbestos-containing dust, not by a job classification or product type — the issue is simply one of inhalation of respirable asbestos fibers. Just as there is no scientific “rule” that worker exposures be quantified in order for attribution, there is no “rule” that a product specific positive epidemiology study be available for attribution.

²⁹ Giorgio Piolatto, et al., *An Update of Cancer Mortality among Chrysotile Asbestos Miners in Balangero, Northern Italy*, 47 Brit. J. Ind. Med. 810 (1990).

³⁰ D. Mirabelli, et al., *Excess of mesotheliomas after exposure to chrysotile in Balangero, Italy*, 65 Occup. Environ. Med. 815 (2008).

³¹ IARC 2009, *supra.*; IARC 2012, *supra.*; Joint Policy Committee of the Societies of Epidemiology, *Position Statement on Asbestos from the Joint Policy Committee of the Societies of Epidemiology (JPC-SE)* (2012).

Nearly all human asbestos epidemiology that has looked at the question has determined that asbestos-induced mesothelioma follows a dose-response pattern, generally with the greater the total dose, the greater the risk of mesothelioma. “One factor that emerges from the Peto model and its modifications is that when there are multiple asbestos exposures, each contributed to cumulative exposure and hence to the risk and causation of MM, within an appropriate latency interval.”³² Researchers have found some additional factors important in analyzing the asbestos mesothelioma dose-response curve, such as time since first exposure, but total cumulative dose consistently is the best indicator of risk: “In this study...the dose-response seemed to be described best by Cumulative Exposure Index.”³³

Moreover, human dose-response studies show significant increased risk at very low levels of exposure. These studies have found increased risk of 2.69 to 7.9-fold based on low-level exposure. *See e.g.* 2014 LaCourt, et al., ≤ 0.1 f/cc/years, Odds Ratio (OR) 4.0 (99% Confidence interval (CI) 1.9-3.3)³⁴; 2001 Rödelsberger, et al., ≤ 0.15 f/cc/years, OR 7.9 (95% CI 2.1-30.0)³⁵; 2014

³² Hammar, *supra*.

³³ Jean Bignon, et al., *History and Experience of Mesothelioma in Europe*, in Mesothelioma 29-53 (Bruce W.S. Robinson & A. Philippe Chahinan, eds., 2002).

³⁴ A. LaCourt, et al., *Occupational and Non-Occupational Attributable Risk of Asbestos Exposure for Malignant Pleural Mesothelioma*, Thorax 1 (2014).

³⁵ Klaus Rödelsberger, et al., *Asbestos and Man-Made Vitreous Fibers as Risk Factors for Diffuse Malignant Mesothelioma: Results from a German Hospital-Based Case-Control Study*, 39 Am. J. Ind. Med. 262 (2001).

Offermans, et al., ≤ 0.2 f/cc/years, Hazard Ratio (HR) 2.69 (95% CI 1.60 o4.53),³⁶ and the 1998 Iwatsubo, et al., 0.5 - 0.99 f/cc/years, OR 4.0 (95% CI 2.0-8.8).³⁷

And epidemiological studies provide additional support for a weight of the evidence conclusion that asbestos from brakes can and does cause mesothelioma. There are numerous epidemiological studies and case reports of mesothelioma in persons whose primary exposure to asbestos is from asbestos-containing brake materials.^{38 39 40 41 42 43} From an industrial hygiene perspective, it does not take long, at levels known to exist in garage environments without asbestos dust control, for a person to receive appreciable exposures.

³⁶ Nadine S.M. Offermans, et al., *Occupational Asbestos Exposure and Risk of Pleural Mesothelioma, Lung Cancer, and Laryngeal Cancer in the Prospective Netherlands Cohort Study*, 56(1) J. Occup. Environ. Med. 6 (2014).

³⁷ Y. Iwatsubo, et al., *Pleural Mesothelioma: Dose-Response Relation at Low Levels of Asbestos Exposure in a French Population-based Case-Control Study*, 148(2) Am. J. Epidemiol. 133 (1998).

³⁸ D. McDonald, et al., *Epidemiology of Primary Malignant Mesothelial Tumors in Canada*, 26(4) Cancer 914 (1970).

³⁹ A. E. Anderson, et al., *Asbestos Emissions from Brake Dynamometer Tests*, SAE Technical Paper 730549 (1973).

⁴⁰ Klaus Rödelberger, et al., *Asbestos Dust Exposure During Brake Repair*, 10 Am. J. Ind. Med. 63 (1986).

⁴¹ M. Huncharek, et al., *Pleural Mesothelioma in a Brake Mechanic*, 46 Brit. J. Ind. Med. 69 (1989).

⁴² Iwatsubo, *supra*.

⁴³ Kay Teschke, et al., *Mesothelioma Surveillance to Locate Sources of Exposure to Asbestos*, 88(3) Canadian J. Pub. Health 163 (1997).

These and other asbestos exposure and disease studies in brake workers were reviewed by Dr. Richard Lemen, Assistant Surgeon General (Ret.) in 2004; Dr. Lemen concluded that “Even the so called “controlled” use of asbestos containing brakes poses a health risk to workers, users, and their families.”⁴⁴ Recently, a cancer registry-based study in Massachusetts reported a greater than two-fold excess of mesothelioma in auto mechanics.⁴⁵ For another epidemiological example, an analysis of mortality in bus drivers and bus maintenance workers in Genoa, Italy demonstrated significant excess deaths (SMR 3.67) from pleural mesothelioma when compared to Italian males.⁴⁶

Brake manufacturers and their consultants invent their own “scientific rule” demanding that a collection of approximately 18-22 “negative” friction studies and industry-financed meta-analyses thereof trumps all other evidence. But for a study or studies to be truly “negative” in the sense hoped for by industry advocates, the study must be large enough to have sufficient “power” to detect an increase in risk,

⁴⁴ Lemen, *Asbestos in Brakes*, *supra*.

⁴⁵ Cora R. Roelofs, et al., *Mesothelioma and Employment in Massachusetts: Analysis of Cancer Registry Data 1988-2003*, 56 Am. J. Ind. Med. 985 (2013).

⁴⁶ Domenico Franco Merlo, et al., *A Historical Mortality Study Among Bus Drivers and Bus Maintenance Workers Exposed to Urban Air Pollutants in the City of Genoa, Italy*, 67 Occup. Environ. Med. 611 (2010). There was not an increased risk when compared to the surrounding population, because the surrounding region contained several shipyards that historically used asbestos. So the choice of comparison population can influence the findings regarding mesothelioma in an urban or working population. This needs to be taken into account when interpreting study findings or individual exposure histories.

have reliable work histories to establish exposure or lack thereof, and be followed for a sufficiently long time to account for latency.⁴⁷ It is also highly preferable that the study be specifically designed to detect an increase in risk for the disease in question. The studies in questions fail on all of the above counts.⁴⁸ As concluded by the highly respected scientific body the National Cancer Institute: “[s]tudies evaluating the cancer risk experienced by automobile mechanics exposed to asbestos through brake repair are limited, but the overall evidence suggests there is no safe level of asbestos exposure.”⁴⁹

⁴⁷ Median latency since first exposure for mesothelioma is 38.4 years. See A. Reid, et al., *Mesothelioma Risk after 40 Years since First Exposure to Asbestos: a Pooled Analysis*, 0 Thorax, 1 (2014).

⁴⁸ A comprehensive survey of the brake literature is not the intent of this brief. However, Amici incorporate by reference: Lemen, *Asbestos in Brakes*, *supra.*; David S. Egilman & Marion A. Billings, *Abuse of Epidemiology: Automobile Manufacturers Manufacture a Defense to Asbestos Liability*, 11 Int. J. Occup. Environ. Health 360 (2005); and Laura S. Welch, *Asbestos Exposure Causes Mesothelioma, But Not This Asbestos Exposure: An Amicus Brief to the Michigan Supreme Court*, 13 Int. J. Occup. Environ. Health 318 (2007).

⁴⁹ National Cancer Institute, *Asbestos Exposure and Cancer Risk* (2009) <http://www.cancer.gov/cancertopics/causes-prevention/risk-factors/cancer-causing-substances/asbestos/asbestos-fact-sheet> (accessed March 11, 2015).

CONCLUSION

It is axiomatic that every exposure to asbestos, while not necessarily a substantial contributing factor, contributes to the total dose. An expert's concurrence with this scientific fact should not "infect" his testimony such that his causation opinion is negated, especially where, as here, the expert employed the generally accepted method of a multi-faceted review of the diagnosis, medical and occupational history, individual susceptibility, biological plausibility, and relevant case and epidemiological studies.

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EXHIBIT 44



ORIGINAL CONTRIBUTIONS

Pleural Mesothelioma: Dose-Response Relation at Low Levels of Asbestos Exposure in a French Population-based Case-Control Study

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A hospital-based case-control study of the association between past occupational exposure to asbestos and pleural mesothelioma was carried out in five regions of France. Between 1987 and 1993, 405 cases and 387 controls were interviewed. The job histories of these subjects were evaluated by a group of experts for exposure to asbestos fibers according to probability, intensity, and frequency. A cumulative exposure index was calculated as the product of these three parameters and the duration of the exposed job, summed over the entire working life. Among men, the odds ratio increased with the probability of exposure and was 1.2 (95% confidence interval (CI) 0.8–1.9) for possible exposure and 3.6 (95% CI 2.4–5.3) for definite exposure. A dose-response relation was observed with the cumulative exposure index: The odds ratio increased from 1.2 (95% CI 0.8–1.8) for the lowest exposure category to 8.7 (95% CI 4.1–18.5) for the highest. Among women, the odds ratio for possible or definite exposure was 18.8 (95% CI 4.1–86.2). We found a clear dose-response relation between cumulative asbestos exposure and pleural mesothelioma in a population-based case-control study with retrospective assessment of exposure. A significant excess of mesothelioma was observed for levels of cumulative exposure that were probably far below the limits adopted in most industrial countries during the 1980s. *Am J Epidemiol* 1998;148:133–42.

asbestos; case-control studies; mesothelioma; occupational exposure

Mesothelioma is a rare cancer that is mainly due to occupational or nonoccupational asbestos exposure. The background level is assumed to be as low as 1–2 per million inhabitants (1). During recent decades, however, its prevalence has been increasing in the general populations of most industrialized countries (2, 3).

In the cohorts of workers occupationally exposed to asbestos that have been followed since the 1960s, the risk of mesothelioma has increased with the level or duration of exposure or both (4–14). The absence of accurate measurements for low exposure levels limits the reliability of any current quantitative assessments of the risk they carry. Furthermore, since only a few subjects in these cohorts were exposed to low levels of asbestos, there is not enough statistical power to show any significant association with mesothelioma.

Case-control studies among the general population and its variety of occupational categories exposed to different asbestos levels are more likely to include subjects whose exposure was low. Despite recent developments in retrospective assessment of exposure (15, 16), the quantitative assessment of low levels remains difficult, since measurements of dust concentration during the relevant periods are not often available.

Previous studies of mesothelioma (4–14) have examined exposure parameters, including cumulative exposure and such time-related variables as time since or age at first exposure. Other exposure parameters, in particular, the time-related pattern of exposure, might be useful. Although the current asbestos exposure pro-

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Abbreviations: CEI, cumulative exposure index; CI, confidence interval; ISCO, International Standard Classification of Occupations (1968 edition); ISIC, International Standard Industrial Classification of All Economic Activities; OR, odds ratio.

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file involves mostly intermittent exposure, the data now available do not allow any conclusion about whether asbestos inhalation at intermittent peaks contributes to the risk of mesothelioma.

The aims of this study were to examine the dose-response relation by using several types of exposure parameters and to study the role of time-related exposure patterns (intermittent compared with continuous) in a large case-control study conducted in France since 1987.

MATERIALS AND METHODS

This report is based on data collected in a hospital-based case-control study of pleural malignant mesothelioma (hereafter referred to as mesothelioma). This study is ongoing, and the present analysis is limited to data collected between January 1, 1987, and December 31, 1993. Five administrative regions of France are currently participating: The study began in the Paris metropolitan area in 1987 and was extended in 1989 to the region of Provence-Alpes-Côte-d'Azur and to Corsica and, in 1992, to Lorraine and Auvergne. The respiratory disease, chest surgery, and oncology departments of all public hospitals and the main private clinics were informed of the study and invited to participate.

Mesothelioma patients in this study met the following criteria: 1) consultation, at any stage of the disease, in a participating hospital; 2) histologically confirmed diagnosis; 3) resident in a participating region at diagnosis; and 4) alive at the time of interview.

The diagnosis of mesothelioma was confirmed by the French Mesothelioma Panel (17, 18). The panel excluded 46 (10 percent) of the subjects initially considered eligible (for whom, after pathology review, the principal diagnosis was adenocarcinoma). In 125 subjects (31 percent of the remaining 405 cases), however, the panel could not reach a conclusion because the histologic sample was insufficient or because the slides had not been sent to the panel. The likelihood of diagnosis was then determined by reviewing clinical data (clinical history, radiologic data), laboratory test reports, and the histologic conclusions of the local pathologists. Hospital controls were individually matched for sex, age (± 5 years), place of residence (administrative department), and racial or ethnic origin (black, white, North African, Asian, or other) and were selected in the departments of internal medicine, ophthalmology, and surgery. Patients with a medical history of malignant tumors or asbestos-related diseases (i.e., asbestosis and lung cancer) were excluded as controls. To the extent possible, controls were chosen in the same hospital as their matching cases.

Data collection

An experienced interviewer questioned patients during their hospitalization. In a few cases, the subject was interviewed at home. A standardized questionnaire was used to collect information on work history: work periods, including the starting and ending dates of each job that lasted at least 6 months; the company's economic branch of activity; and a description of the tasks performed by the subject. This information allowed us to classify the subject's job according to the International Standard Classification of Occupations (ISCO) code for occupations (19) and the International Standard Industrial Classification of All Economic Activities (ISIC) code (20) for industrial activities. For each job period, the subjects were asked five specific questions about direct (handled) and indirect (working in the immediate vicinity of colleagues who handled) asbestos exposure.

Exposure assessment

A panel of five experts in industrial hygiene evaluated occupational exposure to asbestos, as follows: 1) all job periods of all subjects (cases and controls) were sorted by economic branch of activity (ISIC codes) and occupation (ISCO codes); 2) the job periods were selected for review according to the likelihood of exposure of the job titles, classified by ISIC and ISCO codes; 3) the job periods for which subjects reported exposure were selected; and 4) occupational exposure to asbestos was evaluated for all job periods selected in either step 2 or step 3, in sequential order of both the ISIC and ISCO codes. Each job period for each subject was thus evaluated independently. This procedure was chosen to minimize errors in the exposure assessment due to knowledge of the subjects' lifetime exposure.

The experts were blinded to the case-control status of each job period, and decisions were made by consensus. The experts had access to all information from the questionnaire, such as job history, tasks performed, and self-report of direct or indirect exposure to asbestos.

This evaluation of each job allowed each job period to be classified according to the probability, intensity, and frequency of exposure. Categories of intensity and frequency were established by the experts before the evaluation began by using the following semiquantitative scale: probability of exposure: not exposed, possible, definite; frequency: sporadic (less than 5 percent of work time); irregular (5–50 percent of work time); continuous (more than 50 percent of work time); intensity: low (less than 1 fiber/ml); medium (1–2 fibers/ml); high (2–10 fibers/ml); very high (> 10 fibers/ml).

We attributed weighting factors to each exposure category to calculate an exposure index: probability:

null = 0, possible = 0.5, definite = 1; frequency: sporadic = 0.025, irregular = 0.25, continuous = 0.75; intensity: low = 0.1 fiber/ml, medium = 1 fiber/ml, high = 10 fibers/ml, very high = 100 fibers/ml.

Because the latency period of the disease is so long, we did not analyze asbestos exposure during the 20 years before the mesothelioma diagnosis (1, 21, 22).

We used the following exposure parameters for each subject.

Highest probability, intensity, and frequency. Each subject's highest probability of exposure was determined by the highest probability of any job period during lifetime work history. Highest intensity and frequency were determined in the same way.

Duration of exposed jobs. Duration of exposed jobs (years) is defined as the total duration of job periods involving possible or definite exposure.

Cumulative exposure index (CEI). CEI is the lifetime sum of the products of probability, frequency, intensity, and duration for each job period. Because no measurements of airborne asbestos levels were available, all estimations of exposure parameters were based on the experts' subjectivity, that is, semiquantification, to which we subsequently assigned weighting factors. This index of cumulative exposure was expressed in terms of fibers/ml-years inside quotation marks ("f/ml-years").

Pattern of exposure in time. We examined the relative risks associated with the pattern of exposure by distinguishing subjects who had undergone only intermittent exposure from those whose exposure was considered continuous. Subjects' exposure was classified as intermittent if it was sporadic or irregular and if they had never worked at a job with continuous exposure. The continuous category was reserved for subjects who had been employed in at least one job with continuous exposure.

In addition to these composite variables, age at first exposure and time since first exposure were also examined.

Statistical analysis

We calculated the odds ratio by using logistic regression and the unconditional maximum likelihood method, with the aid of BMDP software (23). This technique allowed us to include the cases who had no controls. The analysis took the matching variables into account. The relation between asbestos exposure and mesothelioma was examined separately for men and women.

Quantitative parameters were categorized by percentile points. To allow us to consider the effect of some previously used cutoff points, we used additional categories for studying cumulative exposure (5 and 10 "f/ml-years").

The effect of the time-related exposure pattern (that is, intermittent vs. continuous) was analyzed after taking into account cumulative exposure.

RESULTS

The study included 405 cases and 387 controls (table 1). The largest group of cases (69.9 percent) came from the Paris metropolitan area. Cases and controls did not differ significantly by sex (82 percent and 81 percent men, respectively) or age at interview (63.5 and 63.9 years, respectively). Since almost the entire sample was white (96.8 percent of cases and 97.7 percent of controls), we did not adjust for race or ethnic origin. The socioeconomic category of the subject was determined by the last occupation held before the interview and coded using the major groups of the ISCO (table 2). Cases and controls differed significantly, with more blue-collar workers among the cases. Thus, for all comparisons, the odds ratios were adjusted for socioeconomic category.

Table 3 presents the main occupations and industries that entailed asbestos exposure among the 3,498 job periods for men. We consider in this table only activities and professions that contained at least 50 job periods and for which at least 25 percent of the job

TABLE 1. Main characteristics of cases and controls by study area, French Mesothelioma Case-Control Study, 1987-1993

Study area and years of study	Cases					Controls				
	No.	% of males	Age (years)			No.	% of males	Age (years)		
			Mean	(SD)*	Range			Mean	(SD)	Range
Paris metropolitan area (1987-1993)	283	78	62.9	(10.8)	25-88	279	78	63.4	(11.2)	29-93
Provence-Alpes-Côte-d'Azur (1989-1993)	82	92	64.5	(8.9)	44-85	73	89	65.2	(9.4)	43-84
Corsica (1989-1993)	8	75	67.5	(7.0)	60-81	7	86	64.7	(4.9)	56-71
Lorraine (1992-1993)	28	89	64.8	(12.2)	32-85	25	89	65.8	(10.7)	47-87
Auvergne (1992-1993)	4	88	68.0	(4.1)	63-73	3	75	66.0	(4.0)	62-70
Total	405	82	63.5	(10.5)	25-88	387	81	63.9	(10.7)	29-93

* SD, standard deviation.

TABLE 2. Distribution of mesothelioma cases and controls according to socioeconomic category,* French Mesothelioma Case-Control Study, 1987-1993

	ISCO code (major groups)	Men				Women			
		Cases		Controls		Cases		Controls	
		No.	%	No.	%	No.	%	No.	%
Professional, technical, and related workers	0/1	47	14.3	45	14.5	7	9.6	15	20.3
Administrative and managerial workers	2	22	6.7	17	5.5	1	1.4	0	0
Clerical and related workers	3	35	10.6	40	12.9	28	38.4	25	33.7
Sales workers	4	30	9.1	24	7.7	5	6.9	3	4.1
Service workers	5	14	4.3	32	10.3	13	17.8	20	27.0
Agricultural, animal husbandry, and forestry workers; fishermen; and hunters	6	2	0.6	8	2.6	0		3	4.1
Production and related workers, transport equipment operators, and laborers	7/8/9	179	54.4	145	46.6	19	26.0	8	10.8
No occupational activity		1		1		2		1	

* Socioeconomic category corresponding to the International Standard Classification of Occupations (ISCO) code of the last job held by the subject before interview.

periods were evaluated as possibly or definitely exposed. In the industries and occupations in which we had anticipated asbestos exposure, the proportions of exposure were high. For example, exposure was likely to have occurred in 264 of the 487 (54 percent) men's job periods in the construction industry and in 55 of the 70 (79 percent) men's job periods in the shipbuilding industry. In some occupations, exposure was frequent, e.g., 82 percent among motor vehicle mechanics and 85 percent among plumbers and pipe fitters. The proportion of exposed job periods in the categories of other industrial activities and occupations was low (16 and 19 percent, respectively).

Table 4 indicates the distribution of job periods of male cases and controls according to starting date and exposure intensity for possibly and definitely exposed job periods. Very few job periods were considered as very highly exposed, and those were found mainly among cases (18 job periods in cases vs. four among controls). These were observed after 1950 when the industrial use of asbestos had developed.

Table 5 reports the distribution of male cases and controls according to various exposure parameters. The exposure measures in this table have not been adjusted for the other exposure parameters. Mesothelioma risk increased with exposure probability, intensity, and frequency. The odds ratio for possible exposure was 1.2 (not significant), and for definite exposure, it was 3.6. Risk increased with frequency of exposure, but subjects with sporadic exposure were not at greater risk of mesothelioma than were controls. Risk also increased with the total duration of exposed jobs: The odds ratio for subjects exposed for at least 20 years was 5.4.

The odds ratio for the relation between pleural mesothelioma and asbestos exposure parameters did not increase with time since first exposure, nor was any consistent trend observed with age at first exposure.

As determined by the experts' evaluations and the weighting factors, the cumulative exposure of our population was rather low. Twenty-three percent of the cases and 35 percent of the controls had been exposed to less than 0.5 "f/ml-years." A gradient was observed with the CEI; the odds ratio rose from 1.2 for the subjects with less than 0.5 "f/ml-years" to 8.7 for the category with more than 10 "f/ml-years."

Among women, a significant risk of mesothelioma was observed among those possibly and definitely exposed to asbestos, considered together (odds ratio (OR) = 18.8, 95 percent confidence interval (CI) 4.1-86.2). Because of the small number of women exposed to asbestos, especially among controls (25 cases and two controls, for 33 and 3 percent of their respective categories), we did not analyze the dose-response relation among women any further.

The results about the time-related pattern of exposure reveal a significantly elevated odds ratio among workers whose exposure to asbestos was intermittent (OR = 1.8, 95 percent CI 1.3-2.6). The odds ratio was much greater, however, for continuous exposure (OR = 5.7, 95 percent CI 3.4-9.7). The median CEI within each category considered, i.e., <0.5, 0.5-0.99, 1-9.99, and ≥10 "f/ml-years," was similar among intermittent and continuous exposure cases, except in the highest class of CEI (≥10 "f/ml-years") (0.1, 0.65, 3.5, and 38.7 "f/ml-years" for the intermittent exposure groups and 0.075, 0.65, 3.1, and 71.3 "f/ml-years" for the continuous groups, respectively). We attempted

TABLE 3. Selected principal industrial activities and occupations entailing asbestos exposure among men, French Mesothelioma Case-Control Study, 1987-1993*

Title	No. of job periods	Proportion of exposed job periods† (%)
Industrial activities (4-digit ISIC‡ code)		
5000 Construction	487	54
3843 Manufacture of motor vehicles	113	27
7111 Railway transport	76	30
3841 Shipbuilding and repairing	70	79
3813 Manufacture of structural metal products	65	49
3511 Manufacture of basic industrial chemicals, except fertilizers	52	54
9513 Repair of motor vehicles and motorcycles	62	71
3823 Manufacture of metal and wood working machinery	58	26
3829 Manufacture of machinery and equipment, except electrical not elsewhere classified	54	30
3845 Manufacture of aircraft	51	31
3710 Iron and steel basic industries	51	61
Other industries and industries not specified (n = 7)	2,359	16
Occupations (3-digit ISCO‡ code)		
9-99 Laborers not elsewhere classified	152	26
8-41 Machinery fitters and machine assemblers	110	38
8-55 Electrical wiremen	107	54
8-49 Machinery fitters, machine assemblers, and precision instrument makers (except electrical) not elsewhere classified	99	57
8-73 Sheet-metal workers	85	49
9-54 Carpenters, joiners, and parquet workers	75	37
8-71 Plumbers and pipe fitters	73	85
9-51 Bricklayers, stonemasons, and tile setters	69	58
8-43 Motor vehicle mechanics	67	82
3-91 Stock clerks	58	28
Other professions	2,603	19
Total job periods	3,498	27

* In these tables, only activities and professions that contained at least 50 job periods and for which at least 25 percent of the job periods were evaluated as possibly or definitely exposed were considered.

† Possible or definite exposure to asbestos without taking into account the 20-year latency period.

‡ ISIC, International Standard Industrial Classification of all Economic Activities; ISCO, International Standard Classification of Occupations.

to separate the possible effect of the exposure delivery pattern from that of cumulative exposure by a stratified analysis. The odds ratios increased with the CEI among subjects with intermittent and with continuous exposures (table 5). The amplitude of the odds ratio differed, however, between these categories. When we examined the odds ratios for subjects within each of our CEI categories, they were almost twice as high for subjects with continuous exposure as for those intermittently exposed, except for the CEI category of 0.5-1 "f/ml-years."

DISCUSSION

This study, one of the larger population-based case-control studies published (24-37) sheds light on several important aspects of mesothelioma and asbestos.

As far as we know, our study is the first conducted in a general population that uses a semiquantitative

assessment of exposure to examine the dose-response relation between asbestos exposure and mesothelioma.

The mesothelioma cases of this study were identified in hospitals that had agreed to participate in the case-control survey. Cases seen in other hospitals and those who were not followed within a hospital structure were not included. There is no reason to suppose, however, that the type of health care facility depended on the level of asbestos exposure. We ought to point out another source of selection bias. Mesothelioma diagnosis remains difficult. The patient who has a known history of asbestos exposure is more likely to be diagnosed with mesothelioma than a patient with similar symptoms but no known history of asbestos exposure. This bias could have heightened the dose-response relation between asbestos exposure and mesothelioma. There are probably few cases erroneously diagnosed as mesothelioma, since the French Me-

TABLE 4. Distribution of job periods among men, according to the intensity of exposure* and decade of beginning, French Mesothelioma Case-Control Study, 1987-1993

Probability of exposure	Distribution job periods													
	Before 1930		1930-1939		1940-1949		1950-1959		1960-1969		1970 and after		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Cases														
Not exposed	83	77.6	172	75.1	332	66.9	280	62.8	202	61.2	215	69.8	1,284	67.0
Low	10	9.4	25	10.9	65	13.1	55	12.3	54	16.4	38	12.3	247	12.9
Medium	12	11.2	26	11.4	74	14.9	64	14.4	50	15.2	29	9.4	255	13.3
High	2	1.9	6	2.6	23	4.6	40	9.0	20	6.1	21	6.8	112	5.9
Very high	0		0		2	0.4	7	1.6	4	1.2	5	1.6	18	0.9
Total	107	100	229	100	496	100	446	100	330	100	308	100	1,916†	100
Controls														
Not exposed	65	82.3	192	84.2	341	80.6	282	80.8	218	79.3	183	83.9	1,281	81.5
Low	2	2.5	21	9.2	46	10.9	33	9.5	29	10.6	17	7.8	148	9.4
Medium	7	8.9	13	5.7	31	7.3	27	7.7	26	9.5	15	6.9	119	7.6
High	4	5.1	2	0.9	4	1.0	6	1.7	1	0.4	3	1.4	20	1.3
Very high	1	1.2	0		1	0.2	1	0.3	1	0.4	0		4	0.3
Total	79	100	228	100	423	100	349	100	275	100	218	100	1,572‡	100

* Intensity for possible or definite exposure to asbestos without taking into account the 20-year latency period.

† Job periods for which the year of beginning is missing = 6.

‡ Job periods for which the year of beginning is missing = 4.

sothelioma Panel excluded, after pathology review, 10 percent of subjects initially considered eligible and confirmed the diagnosis for 62 percent of the cases on the basis of pathology reports. We accepted the remaining 28 percent after reviewing available histologic data and hospital records.

The use of hospital controls could have entailed some bias. In particular, cases and controls differed in socioeconomic status, with the latter group containing fewer blue-collar workers. This difference could have arisen from a selection bias and might reflect the controls' failure to represent adequately the population from which the cases were drawn, or it might be due to a particularly high rate of pleural mesothelioma among blue-collar workers because of their high prevalence of asbestos exposure. In the latter case, taking socioeconomic status into account could have led to overadjustment of the relation between asbestos exposure and pleural mesothelioma. The crude odds ratios, however, were of same order of magnitude as the adjusted values.

The validity of the information about asbestos exposure depends on how well we have avoided three types of errors: difference in the quality of interview data according to disease status (recall bias or interviewer bias), errors by the experts in classifying the subjects into defined categories, and errors related to the accuracy of the weighting factors subsequently assigned to each category. As recently stated in an International Agency for Research on Cancer meeting on retrospective assessment of occupational exposure in epidemiology (38), the validity of expert judgment, which relies on both the knowledge and the experience of industrial hygienists, has rarely been evaluated.

Indeed, when no objective method of measuring exposure is available, their judgment is most often considered the gold standard.

Our study assessed frequency and intensity of exposure by using ordinal categories with specific boundaries. This procedure should have minimized the misclassification of subjects between extreme exposure categories. The experts themselves, however, reported sometimes encountering difficulties in distinguishing between sporadic and irregular exposure and between low and moderate exposure.

Moreover, they suggested that the quality of their assessment for the periods under consideration (20 or more years ago) might not be as good as for more recent years because of the lack of published data for these periods. These errors could have led to the nondifferential misclassification of subjects into exposure categories and the possible underestimation of the odds ratios (39).

To avoid the exposure suspicion bias, the experts were blinded to case-control status when they evaluated exposure. Recall bias could have influenced the quality of the answer to the questionnaire and, subsequently, the expert judgment. To test this potential bias, we compared the experts' assessment with results from an asbestos job exposure matrix (40). We found no difference between cases and controls (data not shown), suggesting that it was unlikely that a substantial recall bias had affected the experts' judgment. The interviewers, however, were aware of case-control status and thus might have conducted the interviews of the case subjects more thoroughly than those of controls. Since the experts considered all of the information available, they might have been able to evaluate

TABLE 5. Odds ratios for relations between pleural mesothelioma and asbestos exposure parameters among men, French Mesothelioma Case-Control Study, 1987-1993, with a latency period of 20 years

Asbestos exposure parameters	No. of cases	No. of controls	OR*	95% CI†
Highest probability of exposure				
Not exposed	95	154	1.0	
Possible	51	71	1.2	0.8-1.9
Definite	184	87	3.6	2.4-5.3
Highest intensity of exposure				
Low	55	74	1.2	0.8-1.9
Medium	106	66	2.8	1.8-4.3
High	74	18	7.1	3.9-12.9
Highest frequency of exposure				
Sporadic	56	86	1.0	0.7-1.6
Irregular	94	46	3.3	2.1-5.1
Continuous	85	26	5.7	3.4-9.7
Duration of exposed job (years)				
1-7	63	64	1.7	1.1-2.6
8-19	74	60	2.0	1.3-3.1
≥20	98	34	5.4	3.2-8.9
Time since first exposure (years)				
20-37	77	53	2.3	1.4-3.6
38-48	83	47	2.8	1.8-4.5
≥49	75	58	2.2	1.4-3.6
Age at first exposure (years)				
<16	66	55	1.9	1.2-3.1
16-22	96	52	3.0	1.9-4.6
≥23	73	51	2.3	1.5-3.7
Cumulative exposure ("f/ml-year"‡)				
0.001-0.49	77	109	1.2	0.8-1.8
0.5-0.99	29	12	4.2	2.0-8.8
1-9.9	80	27	5.2	3.1-8.8
≥10	49	10	8.7	4.1-18.5
Cumulative exposure ("f/ml-year")				
Temporal exposure pattern§				
Intermittent				
<0.5	66	98	1.1	0.8-1.7
0.5-0.99	19	8	4.0	1.7-9.7
1-9.99	48	21	4.0	2.2-7.2
≥10	17	5	5.9	2.1-16.7
Continuous				
<0.5	11	11	1.9	0.8-4.8
0.5-0.99	10	4	4.6	1.4-15.4
1-9.99	32	6	9.2	3.7-23.1
≥10	32	5	11.3	4.1-30.7

* Odds ratios (ORs) adjusted for age and socioeconomic category.

† CI, confidence interval.

‡ Cumulative exposure index was based on subjective assessment, that is, semiquantification of exposure by the experts and selected weighting factors assigned to each category of exposure, with no objective measurement of airborne asbestos levels. Thus, the exposure unit, f/ml-years, is expressed in quotation marks.

§ Subjects' exposure was classified as intermittent if it was sporadic or irregular and if they had never worked at a job with continuous exposure. The continuous category was reserved for subjects who had been employed in at least one job with continuous exposure.

exposure more precisely for the cases than for the controls. The frequency of the exposure category "possible," used when the experts could not reach a definite conclusion, was higher among controls than among cases, so that this type of error cannot be excluded. We thus undertook a supplementary analysis to examine, at least in part, the effect of this bias. First, we considered all of the jobs in the possible category as nonexposed. The pattern of dose-response relation was very similar to that observed: no significant risk for subjects in the category of less than 0.5 "f/ml-years" and an odds ratio of 7.8 (95 percent CI 3.8–16.2) for those in the category of more than 10 "f/ml-years." Classifying all of the possibly exposed subjects as definitely exposed did not change the dose-response relation pattern very much either (OR = 1.0, 95 percent CI 0.7–1.6 for the lowest category and OR = 7.7, 95 percent CI 3.8–15.7 for the highest).

The validity of the dose-specific risks in our study also depends greatly on the values of the weighting factors selected for each exposure category. For this purpose, we attempted to retain the intervals used by the experts. Although this procedure is assumed to provide more precise exposure evaluation than would a relative ranking of subjects by an ordinal scale without specified boundaries, some misclassification of subjects according to dose-specific exposure probably occurred. Indeed, all jobs classified in the same exposure category were assigned the same weighting value without consideration of the variability of exposure within the category. Such nondifferential misclassification of the subjects usually attenuates the relation between exposure and disease and flattens the dose-response curve (39). We should note that the intervals used by the experts for the categories of intensity were rather dissymmetric—narrow for medium exposure and large for very high exposure. There were few job periods with very high exposure, however, so that errors due to the variability in this category should have had little effect on the dose-response relation observed.

We observed a dose-response relation with cumulative exposure. Because, as stated, the exposure assessment for the earliest periods might have been underestimated and because of the imprecision of intensity weighting factors, we tested two models using two other series of coefficients for weighting intensity of exposure: 1) second model: 0.5, 1.5, 6, and 550 fibers/ml, for low, medium, high, and very high exposures, respectively (midpoints of boundaries), and 2) third model: 0.5, 5, 50, and 500 fibers/ml for low, medium, high, and very high exposures, respectively. These models showed a dose-response relation with the CEI similar to that in the first model, but they did not show

as clear a dose-response trend as the first model. In the second model, the odds ratio was 1.0 (95 percent CI 0.7–1.6) for the lowest dose and 6.4 (95 percent CI 3.4–12.2) for the highest. The corresponding odds ratios for the third model are 0.9 (95 percent CI 0.5–1.4) for the lowest and 7.1 (95 percent CI 4.2–11.9) for the highest.

The pattern of the dose-response curve could have depended on the length of latency period selected. We have used a 20-year latency period, as suggested by McDonald and McDonald (1, 21), who concluded that latency is seldom less than 20 years and usually 30–40 years. We also examined the effects of 10- and 30-year latency periods. The results obtained with the former were very similar to those we found with the 20-year latency period. A 30-year latency period resulted in a lower odds ratio and a less clear dose-response relation, suggesting that exposure misclassification occurred using such a long latency period.

Because no objective measurement was available to test the validity of the experts' evaluation, we express the cumulative exposure using units of f/ml-years in quotation marks. Even in cohort studies, however, precise measurement of exposure is difficult (2, 41).

In this study, we used several surrogate parameters for dose to examine dose-response relation, as suggested by Blair and Stewart (42) and Suarez-Almazor et al. (43). We considered separately the intensity, frequency, and duration of exposure, and each was significantly related to mesothelioma. The relative risk increased along with each parameter. In addition, when each of these parameters was adjusted for the others, the relative risk of each, although lower, remained significant. These results suggest that each exposure parameter contributed to some extent to the occurrence of mesothelioma, although the dose-response relation seemed to be described best by the CEI.

The existence of a causal association between asbestos exposure and mesothelioma was first demonstrated in 1960 (44). Both cohort (6–9, 11–14, 45) and case-control (32, 34–37, 46, 47) studies focusing on mesothelioma and examining surrogate parameters for dose have reported a dose-response relation.

However, because of the rarity of mesothelioma, even among asbestos workers, little quantitative information is available from which the dose-response relation can be precisely estimated (1, 41, 48).

Peto et al. (49), using mathematical models, observed that the risk of mesothelioma in one occupationally exposed cohort (North American insulators) was best described by a model in which the risk increases with the third or fourth power of time since first exposure. They also concluded that their data were compatible with a linear dose-response relation

between the level of asbestos exposure and the risk of mesothelioma. Our data for the higher categories of CEI also support this conclusion. The pattern of a dose-response relation is more doubtful at low doses because the uncertainties of exposure evaluation are highest for low doses.

Some indication of the effect of exposure that is low level by the brevity of its duration comes from industrial cohort studies. Very few cases of mesothelioma have been observed among those whose exposure was very brief: There were no cases of mesothelioma among members of the cohort of Australian Blue Asbestos workers who were exposed for less than 3 months (47), none among the North American insulators whose exposure lasted less than 15 months (4), and only one, rather than the 25 expected, among Rochdale textile workers exposed for less than 10 years (8). These cohorts do not, however, provide data that allow us to examine the effect of low-intensity exposure.

Illgren and Browne (50) considered whether a threshold exposure might exist and concluded that mesothelioma was unlikely in persons exposed for less than 5 f/ml-years. Our results indicate, however, that mesothelioma cases occurred below a cumulative exposure of 5 f/ml-years and perhaps below 0.5 f/ml-years.

Very few studies have focused on the time-related pattern of exposure as a factor in mesothelioma. Schenker et al. (51) examined the risk of mesothelioma among railroad workers, distinguishing between "intermittent" and "regular" asbestos exposure on the basis of job categories. No significant risk was observed for those whose exposure was intermittent, but those in the regular exposure category were at high risk.

Our study examined the temporal exposure pattern according to the frequency of exposure and the CEI. We observed a dose-response relation with cumulative exposure for both intermittent and continuous patterns of exposure. Much more attention to the role of these temporal patterns is needed, adjusting for cumulative exposure. Our results suggested that intermittent exposure does not entail as high a risk of mesothelioma as does continuous exposure. Assessment of this apparent excess risk of continuous compared with intermittent exposure, however, should bear in mind the likelihood that more subjects with intermittent exposure are misclassified.

We could not examine mesothelioma risk according to fiber types because our study design (i.e., case-control study in a general population) did not allow us to identify those subjects whose exposure was only to chrysotile fibers.

The odds ratio between exposure to asbestos and mesothelioma was much higher for the women in our study than for the men. No evidence of individual, sex-related susceptibility to mesothelioma has been found (52). One explanation for this might be the different distributions of asbestos-related occupations between men and women. Since asbestos-related occupations were rarely held by women, any exposure that did occur may have been very well characterized, leading, in turn, to fewer misclassification errors than for males, particularly among controls.

We found a clear dose-response relation between cumulative exposure to asbestos and pleural mesothelioma in a population-based case-control study with retrospective assessment of exposure. A significant excess of mesothelioma was observed for levels of cumulative exposure that were probably far below the limits adopted in many industrial countries during the 1980s.

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REFERENCES

1. McDonald JC, McDonald AD. Epidemiology of mesothelioma. In: Liddel D, Miller K, eds. *Mineral fibers and health*. Boca Raton, FL: CRC Press, 1991:147-68.
2. Health Effect Institute Asbestos Research. *Asbestos in public and commercial buildings: a literature review and synthesis of current knowledge*. Report of the literature panel. Cambridge, MA: Health Effect Institute Asbestos Research, 1991.
3. Iwatsubo Y, Pairon JC, Archambault de Beaune C, et al. Pleural mesothelioma: a descriptive analysis based on a case-control study and mortality data in Ile de France, 1987-1990. *Am J Ind Med* 1994;26:77-88.
4. Selikoff IJ, Hammond EC, Seidman H. Mortality experience of insulation workers in the United States and Canada, 1943-1976. *Ann N Y Acad Sci* 1979;330:91-116.
5. Hobbs MST, Woodward SD, Murphy B, et al. The incidence of pneumoconiosis, mesothelioma and other respiratory cancer in men engaged in mining and milling crocidolite in Western Australia. In: Wagner JC, ed. *Biological effects of mineral fibers*. Lyon, France: International Agency for Research on Cancer, 1980:615-27. (IARC publication no. 30).
6. Jones JSP, Smith PG, Pooley FD, et al. The consequences of exposure to asbestos dust in a wartime gas-mask factory. In: Wagner JC, ed. *Biological effects of mineral fibers*. Lyon, France: International Agency for Research on Cancer, 1980: 637-53. (IARC scientific publication no. 30).

7. Finkelstein MM. Mortality among employees of an Ontario asbestos-cement factory. *Am Rev Respir Dis* 1984;129:754-61.
8. Peto J, Doll R, Hermon C, et al. Relationship of mortality to measures of environmental asbestos pollution in an asbestos textile factory. *Ann Occup Hyg* 1985;29:305-55.
9. Newhouse ML, Berry G, Wagner JC. Mortality of factory workers in east London 1933-80. *Br J Ind Med* 1985;42:4-11.
10. Armstrong BK, de Klerk NH, Musk AW, et al. Mortality in miners and millers of crocidolite in western Australia. *Br J Ind Med* 1988;45:5-13.
11. Raffn E, Lynge E, Juel K, et al. Incidence of cancer and mortality among employees in the asbestos cement industry in Denmark. *Br J Ind Med* 1989;46:90-6.
12. Albin M, Jakobsson K, Attewell R, et al. Mortality and cancer morbidity in cohorts of asbestos cement workers and referents. *Br J Ind Med* 1990;47:602-10.
13. McDonald JC, Liddell FDK, Dufresne A, et al. The 1981-1920 birth cohort of Quebec chrysotile miners and millers: mortality 1976-88. *Br J Ind Med* 1993;50:1073-81.
14. De Klerk NH, Musk AW, Armstrong BK, et al. Diseases in miners and millers of crocidolite from Wittenoom, Western Australia: a further follow-up to December 1986. *Ann Occup Hyg* 1994;38:647-55.
15. Bouyer J, Hémon D. Retrospective evaluation of occupational exposures in population-based case-control studies: general overview with special attention to job exposure matrices. *Int J Epidemiol* 1993;22:S57-S64.
16. Goldberg M, Hémon D. Occupational epidemiology and assessment of exposure. *Int J Epidemiol* 1993;22:S5-S9.
17. Bignon J, Sébastien P, Di Menza L, et al. French mesothelioma register. *Ann N Y Acad Sci* 1979;330:455-66.
18. Bignon J. Overview of current issues with respect to mesothelioma. *Eur Respir Rev* 1993;3:12-17.
19. International Labor Office. International standard classification of occupations. Geneva, Switzerland: International Labor Office, 1968.
20. United Nations. International standard industrial classification of all economic activities. New York, NY: United Nations, 1971.
21. McDonald AD, McDonald JC. Epidemiology of malignant mesothelioma. In: Antman K, Aisner J, eds. Chap. 2. Asbestos-related malignancy. Orlando, FL: Harcourt Brace Jovanovich, 1987:31-55.
22. Lanphear BP, Buncher CR. Latent period for malignant mesothelioma of occupational origin. *J Occup Med* 1992;34:718-21.
23. Dixon WE, Brown MB, Engelman L, et al. BMDP statistical software. Berkeley, CA: University of California Press, 1990.
24. Elmes P C, McCaughey WTE, Wade OL. Diffuse mesothelioma of the pleura and asbestos. *Br Med J* 1965;1:350-3.
25. McEwen J, Finlayson A, Mair A, et al. Mesothelioma in Scotland. *Br Med J* 1970;4:575-8.
26. McDonald AD, Harper A, El Attar OA, et al. Epidemiology of primary malignant mesothelial tumors in Canada. *Cancer* 1970;26:914-19.
27. Rubino GF, Scansetti G, Donna A, et al. Epidemiology of pleural mesothelioma in northwestern Italy (Piedmont). *Br J Ind Med* 1972;29:436-42.
28. Ashcroft T. Epidemiological and quantitative relationships between mesothelioma and asbestos on Tyneside. *J Clin Pathol* 1973;26:832-40.
29. Zielhuis RL, Versteeg JPI, Planteydt HT. Pleural mesothelioma and exposure to asbestos. *Int Arch Occup Environ Health* 1975;36:1-18.
30. McDonald JC, McDonald AD. Malignant mesothelioma in North America. *Cancer* 1980;46:1650-6.
31. Teta MJ, Lewinsohn HC, Meigs JW, et al. Mesothelioma in Connecticut, 1955-1977. *J Occup Med* 1983;25:749-56.
32. McDonald JC, Armstrong B, Case B, et al. Mesothelioma and asbestos fiber type. *Cancer* 1989;63:1544-7.
33. Cicioni C, London SJ, Garabrant DH, et al. Occupational asbestos exposure and mesothelioma risk in Los Angeles County: application of an occupational hazard survey job-exposure matrix. *Am J Ind Med* 1991;20:371-9.
34. Muscat JE, Wynder EL. Cigarette smoking, asbestos exposure and malignant mesothelioma. *Cancer Res* 1991;51:2263-7.
35. Rogers A, Leigh J, Berry G, et al. Relationship between lung asbestos fiber type and concentration and relative risk of mesothelioma. *Cancer* 1991;67:1912-20.
36. Tuomi T, Huuskonen MS, Virtamo M, et al. Relative risk of mesothelioma associated with different levels of exposure to asbestos. *Scand J Work Environ Health* 1991;17:404-8.
37. Spirtas R, Heineman EF, Bernstein L, et al. Malignant mesothelioma: attributable risk of asbestos exposure. *Occup Environ Med* 1994;51:804-11.
38. Siemiatycki J. Exposure assessment in community-based studies of occupational cancer. *Occup Hyg* 1996;3:41-58.
39. Copeland KT, Checkoway H, McMichael AJ, et al. Bias due to misclassification in the estimation of relative risk. *Am J Epidemiol* 1977;105:488-95.
40. Orlowski E, Pohlabeln H, Berrino F, et al. Retrospective assessment of asbestos exposure. II. At the job level: complementarity of job specific questionnaire and job-exposure matrices. *Int J Epidemiol* 1993;22 (Suppl.):S96-S105.
41. Doll R, Peto J. Asbestos: effects on health of exposure to asbestos. London, England: Health & Safety Commission, Her Majesty's Stationery Office, 1985.
42. Blair A, Stewart PA. Do quantitative exposure assessments improve risk estimates in occupational studies of cancer? *Am J Ind Med* 1992;21:53-63.
43. Suarez-Almazor ME, Soskolne CL, Fung K, et al. Empirical assessment of the effect of different summary worklife exposure measures on the estimation of risk in case-referent studies of occupational cancer. *Scand J Work Environ Health* 1992;18:233-41.
44. Wagner JC, Sleggs CA, Marchand P. Diffuse pleural malignant mesothelioma and asbestos exposure in the North Western Cape Province. *Br J Ind Med* 1960;17:260-71.
45. Selikoff IJ, Seidman H. Asbestos-associated deaths among insulation workers in the United States and Canada, 1967-1987. *Ann N Y Acad Sci* 1991;643:1-14.
46. Hughes JM, Weill H, Hammad YY. Mortality of workers employed in two asbestos cement manufacturing plants. *Br J Ind Med* 1987;44:161-74.
47. De Klerk NH, Armstrong BK, Musk AW, et al. Cancer mortality in relation to measures of occupational exposure to crocidolite at Wittenoom Gorge in Western Australia. *Br J Ind Med* 1989;46:529-36.
48. Hughes JM, Weill H. Asbestos exposure: quantitative assessment of risk. *Am Rev Respir Dis* 1986;133:5-13.
49. Peto J, Seidman H, Selikoff IJ. Mesothelioma mortality in asbestos workers: implications for models of carcinogenesis and risk assessment. *Br J Cancer* 1982;45:124-35.
50. Illgren EB, Browne K. Asbestos-related mesothelioma: evidence for a threshold in animals and humans. *Regul Toxicol Pharmacol* 1991;18:116-32.
51. Schenker MB, Garshick E, Munoz A, et al. A population-based case-control study of mesothelioma deaths among U.S. railroad workers. *Am Rev Respir Dis* 1986;134:461-5.
52. Luce D, Brochard P, Quénel P, et al. Malignant pleural mesothelioma associated with exposure to tremolite. *Lancet* 1994;344:1777.

EXHIBIT 45

Asbestos and Man-Made Vitreous Fibers as Risk Factors for Diffuse Malignant Mesothelioma: Results From a German Hospital-Based Case-Control Study

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Background This study examines the role of occupational factors in the development of diffuse malignant mesothelioma with special emphasis on the dose-response relationship for asbestos and on the exposure to man-made vitreous fibers (MMVFs).

Methods One hundred and twenty-five male cases, diagnosed by a panel of pathologists, were personally interviewed concerning their occupational and smoking history. The same number of population controls (matched for sex, age and region of residence) underwent similar interviews by trained interviewers. Odds ratios (OR) were calculated for an expert-based exposure index using conditional logistic regression.

Results Exposure to asbestos shows the expected sharp gradient with an OR of about 45 for a cumulative exposure > 1.5 fiber years (arithmetic mean 16 fiber years). A significant OR was calculated even for the lowest exposure category: "> 0-≤ 0.15 fiber years". Although the mean cumulative exposure to MMVF is roughly 10% of the exposure to asbestos, an increased OR is observed in an evernever evaluation. This observation is heavily hampered by methodical problems. A corresponding case-control study was performed using a lung tissue fiber analysis in addition to interviews. Both interviews and the lung tissue analysis yielded similar OR levels between the reference and the maximum exposure intervals.

Conclusions Despite a possible influence as a result of selection and information bias, our results confirm the previously reported observation of a distinct dose-response relationship even at levels of cumulative exposure below 1 fiber year. Moreover, the study confirms that asbestos is a relevant confounder for MMVF. A causal relationship between exposure to MMVF and mesothelioma could neither be detected nor excluded, as in other studies. *Am. J. Ind. Med.* 39:262-275, 2001. © 2001 Wiley-Liss, Inc.

KEY WORDS: mesothelioma; case-control; asbestos; MMVFs; occupational history; lung tissue

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INTRODUCTION

Diffuse malignant mesothelioma (DMM) is predominantly caused by asbestos fibers [HEI-AR, 1991; Mark and Yokoi, 1991; Rösler et al., 1994; Spirtas et al., 1994; Gun, 1995]. In the past, its incidence in the general population was low, but it has been increasing for decades in industrialized countries and it may take another 20 years before its peak is passed [Peto et al., 1999]. In addition to asbestos exposure at the workplace, contact in the household and environmental exposure to asbestos are established causes of DMM [Hain and Dalquen, 1974; Vianna and Polan, 1978; Großgarten and Weitowitz, 1993; Rödel-sperger et al., 1996; Schneider et al., 1996; Magnani et al., 1997; Rees et al., 1999]. It has been demonstrated that the time since initial exposure and the type of asbestos are important for the quantification of the risk [Doll and Peto, 1985]. A risk estimate based on accurate workplace measurements is not yet available. Nevertheless, it has recently been demonstrated that an increase of risk may occur even below a cumulative exposure of a few fiber years (fibers/mL $\times$ years) [Iwatsubo et al., 1998]. However, a reliable dose-response relationship between the concentration of long amphibole fibers and the risk of mesothelioma has been consistently established by several research groups on the basis of lung tissue fiber analysis, while no relationship was observed for chrysotile fibers [Rödel-sperger et al., 1999]. This is true even though the amphibole fibers in the lung tissue do not seem to be a good indicator of the fiber content of the pleura, where chrysotile fibers are predominantly observed [Smith and Wright, 1996].

Animal experiments show that other kinds of fibers, with a minimal length above 5 μ m, may also induce mesothelioma after direct application [Pott, 1991]. They confirm the hypothesis that fibers, which are sufficiently long, thin, and durable, are carcinogenic [DFG, 1997]. Besides asbestos sufficient evidence for this hypothesis in humans has only been obtained for erionite [IARC, 1988; DFG, 1997]. In inhalation experiments in rats only erionite fibers caused mesothelioma whereas asbestos and ceramic fibers, but not other man-made vitreous fibers (MMVF), provoked lung cancer. However, even for asbestos this effect was observed only at very high fiber concentrations, which are not feasible for MMVF, since they are much longer and thicker than asbestos fibers and would, therefore, require a much higher mass concentration. This model is, therefore, considered too insensitive for predicting carcinogenic effects in humans [Pott and Röllner, 1993; Infante et al., 1994, 1996; Rödel-sperger and Weitowitz, 1995]. The question of the carcinogenicity of MMVF is of utmost public health relevance. Epidemiological observations have revealed an increased lung cancer mortality in producers of glass, stone, and slag wool, but the causal relationship to MMVF remained unclear [Infante et al., 1994, 1996; DeVuyst

et al., 1995; DFG, 1997]. The concentration of MMVF is higher for processing than for production [IARC, 1988; WHO, 1988; Corn et al., 1992]. However, epidemiologic investigations in craftsmen processing these fibers are difficult since they also process asbestos.

The original aim of this study was to investigate not only asbestos, but also MMVF and other inorganic fibers as causal factors of the DMM [Weitowitz et al., 1993; Rödel-sperger, 1996; Rödel-sperger et al., 1998, 1999]. Since it was necessary to carry out a lung tissue fiber analysis, in addition to recording occupational histories, patients undergoing surgical resection for a diagnosis other than mesothelioma were selected as controls in the participating hospitals. Most of them suffered from lung cancer. In addition, a suitable group of population controls was recruited for the cases from the area of Hamburg. The results obtained for pairs of cases and population controls from the area of Hamburg are reported in this paper. It was from the first results of this study that there was a strong association between exposure to asbestos and to MMVF. Hence, it was first necessary to make a thorough examination of the influence of asbestos. Meanwhile, in connection with the study of Iwatsubo et al., [1998], a critical commentary on the use and the methodological problems of population-based mesothelioma case-control studies has emphasized the importance of direct risk estimation in a low-dose population [Siemiatycki and Boffetta, 1998]. Accordingly, we have examined the relationship between exposure to asbestos and the risk of mesothelioma and compared this with the relationship which was obtained from lung tissue fiber analysis [Rödel-sperger et al., 1999].

MATERIAL AND METHODS

Subjects

The 415 incident patients with suspected diagnosis of diffuse malignant mesothelioma (DMM), recruited between January 1, 1988 and December 31, 1991 from clinics in Hamburg, Heidelberg, Essen, Munich, and Berlin, included 324 cases (275 male, 49 female) with a definite diagnosis confirmed by a panel of pathologists.

The present study was restricted to cases from Hamburg, which were individually matched to population controls. They had to be of German nationality, willing and able to give a personal interview and to provide written informed consent. Of 137 male and 37 female cases (almost all patients of DMM being treated in two specialized hospitals in Hamburg during the recruitment period) it was possible to include 125 male cases in the final analyses after matching with controls (according to region of residence, sex, year of birth $\pm$ 5 years). Females were not included on account of the small sample available. Population controls

TABLE I. Characteristics of Male Cases and Controls from Hamburg

No.	Cases 125	Controls 125
Age (years)		
Median	62.0	64.0
Mean	62.5	64.2
SD	9.4	10.0
No. of jobs		
Median	6.0	6.0
Mean	6.0	5.6
Ever smoked	99 (79.2%)	107 (85.6%)

were randomly drawn from the mandatory registries of suitable administrative units [Woitowitz et al., 1993]. The response rate was 63%. One case/control pair had a year-of-birth difference >5 years. However, this did not influence the results presented in this paper. Some basic characteristics of cases and controls are shown in Table I.

Data Collection

In the first step, a structured questionnaire was used by trained interviewers to obtain information on job history

and, in a second step, to obtain further specific information on occupational exposure to asbestos, MMVF, and other mineral fibers. Additionally, smoking, residential exposure, medical history, leisure-time activities and basic demographic characteristics were registered. Interviewers participated in several intensive training seminars during the recruitment phase. In a subset of variables from the questionnaire—(e.g., the duration of the interview and the number of job periods) the data were entered immediately in order to monitor and reduce possible interviewer effects.

Quantification of Occupational Exposure to Asbestos and MMVF

The description which in the first step was obtained for every job held (duration of at least 12 months) was supplemented with information from the second step (without limit of duration) and an expert industrial hygienist used these data to assess the cumulative dose of exposure to Asbestos and to man-made vitreous fibers.

Expert judgment was obtained blind with respect to the case-control status. Fiber concentration was quantified by assignment to one, two or even three of five exposure categories (Table II).

The geometric mean of the experts' estimate of the maximal and minimal value of fibers/ml per working shift

TABLE II. Definition of the Categories of the Asbestos Fiber Concentration and the Reproducibility of the Estimates of Two Experts

Categories of fiber concentration: definition by concentration intervals

Category	Fiber concentration fibers/ml				
	None	Low	Middle	High	Very high
Minimal value	0	0.005	0.025	0.25	2.0
Maximal value	0	0.025	0.25	2.0	10.0
Expert 1	none	low	middle	high	total
Expert 2					
Estimation of the minimal concentration value ^a					
None	191	10	4	—	205
Low	10	16	5	3	37
Middle	1	2	7	2	12
High	1	2	8	—	11
Total	203	32	25	8	265
Estimation of the maximal concentration value ^a					
None	191	—	9	5	205
Low	3	1	—	3	7
Middle	5	2	7	4	19
High	3	1	6	24	34
Total	203	4	22	26	265

^aNumber of job periods per exposure category. If the experts were not able to assign the exposure to a certain category, they were allowed to combine two or more of them. In this case the minimal value resulted from the lowest and the maximal value from the highest category. Agreement is 82% for minimal and 84% for maximal concentration value.

was multiplied by the number of the working shifts with exposure. Integrating over the life span of each individual yielded the cumulative exposure to fibers (fiber years). For job periods with exposure to both asbestos fibers and MMVF the duration of exposure was only recorded once for both fiber species together. Because of the large differences between the minimal and maximal value of the concentration estimate and of the category of the frequency of working shifts with exposure, the arithmetic mean concentration, averaged over all job periods and correspondingly the cumulative exposure in fiber years, is taken as five times the geometric mean value (compare Table III and the section "Error of the Expert Estimate of the exposure to asbestos").

The quantitation is based on our own experience in measurement [Woitowitz and Rödelberger, 1983; Arhelger et al., 1984; Rödelberger et al., 1980, 1986, 1991], the international literature for asbestos [Woitowitz et al., 1983] and for man-made fibers [Walton and Coppock, 1987; IARC, 1988; WHO, 1988]. A second industrial hygienist reevaluated 265 job periods of 50 patients in order to check the reproducibility of the concentration estimates. The agreement for both rates is described in Table II.

The experts agreed in assigning the category "none" for 191 job periods (72%). For 48 periods (18%) asbestos exposure was scored by both while 26 times (10%) this was scored by only one of them. In all, the experts scored asbestos exposure for 74 job periods. When these are evaluated separately only 34% of the minimal values and 43% of the maximal values are classified in the same exposure category, while 15% of the minimal and 36% of the maximal values differ for more than one category. The

weighted κ values are 0.61 (95% CI 0.53–0.70) and 0.68 (95% CI 0.59–0.78) for the minimal and maximal concentration values, respectively, (SAS-procedure proc freq). If distinction is only made between exposed and unexposed people, both values increase to 0.72 (95% CI 0.62–0.82). For each expert the number of overestimates was nearly equal to the number of underestimates. Finally, the following parameters were selected for each person:

- Time since first exposure (years) defined as years since the beginning of the first job period with exposure to asbestos.
- Duration of an asbestos exposure (years) defined as duration of all job periods with exposure to asbestos.
- Highest intensity of asbestos exposure (f/ml) estimated during any period of the working life.
- Cumulative exposure to asbestos and MMVFs (f/ml $\times$ years) defined as fiber dose. For asbestos the cumulative exposure was calculated until the date of the interview and to time points 10 and 20 years previously.

Statistical Analysis

Odds ratio (OR) and 95% confidence intervals (95% CI) were calculated by conditional logistic regression using the SAS procedure PHREG [SAS institute, 1992]. Occupational risks were analyzed separately for job categories and industries, and for the parameters of exposure.

Job titles and industries were coded according to standard classifications [Statistisches Bundesamt, 1975, 1979]. The analysis of job histories was based on these

TABLE III. Frequency of the Geometric Mean Fiber Concentrations per Working Shift with an Exposure to Asbestos. Estimated for 454 Single Job Periods with an Exposure to Asbestos. Possible Concentrations are Obtained from Table II by Taking the Geometric Mean Values for Various Combinations of Lower and Upper Limits of the Concentration Ranges

Job periods				Cases		Controls	
				n	%	n	%
All periods				746		697	
Periods with exposure to asbestos							
No.	GM f/ml	Range f/ml		324	100	130	100
1	0.0112	0.005	0.025	108	33.3	51	39.2
2	0.0354	0.005	0.25	99	30.6	47	36.2
3	0.0791	0.025	0.25	25	7.7	8	6.2
4	0.1	0.005	2	12	3.7	4	3.1
5	0.2236	0.025	2	41	12.7	13	10.0
6	0.5	0.025	10	16	4.9	0	0.0
7	0.7071	0.25	2	1	0.3	0	0.0
8	1.581	0.25	10	22	6.8	7	5.4
9	4.472	2	10	0	0.0	0	0.0

codes which were grouped into 32 job categories and 21 branches of industry [Jöckel et al., 1994, 1998]. An ever vs. never exposure concept was used, in addition to information on the longest-held job, which had been commenced at least 20 years before the onset of disease; on evaluation this yielded comparable results.

In order to adjust for the established impact of asbestos on mesothelioma risk, 4–5 categories of the different parameters of exposure were set up and included into the logistic regression as additional dummy variables. Five categories of cumulative exposure were used for MMVFs in a similar manner. An ever/never evaluation was also performed.

RESULTS

Job History

The mean duration of lifetime employment was 42 years for cases and 43 years for controls. Asbestos exposure was registered for 454 of a total of 1,443 single job periods of cases and controls. Table III gives the geometric mean value (GM) and the corresponding range of fiber concentration per shift for the five categories of exposure defined in Table II and their combinations together with the number of job periods assigned to these categories. The percentage of the job periods with asbestos exposure amounts to 43.4% for cases compared to 18.3% for controls. The frequency distribution of job periods with asbestos exposure is similar for cases and for controls.

Table IV gives the percentage of job periods with asbestos exposure, the duration of exposure and the

arithmetic mean fiber concentration calculated as five times the GM value. After 1950 the frequency of exposure and fiber concentration, but not the mean duration of exposure, are higher for the cases than for the controls.

Tables V and VI show the number of cases and controls together with the odds ratios (ORs) for 22 of the 32 predefined occupations and for 20 of the 21 predefined industries, where at least five cases or five controls were exposed. Again the percentages of job periods with asbestos exposure and the estimate of the arithmetic mean fiber concentrations during these periods are also presented.

Significantly increased ORs and the highest numbers of mesothelioma cases were observed for the occupation of mechanics, fitters, and plumbers ($n = 62$), and in the industry of engine and vehicle building ($n = 82$).

Asbestos Exposure

We considered years since first exposure, years of duration of exposure, highest intensity of exposure estimated during any period of the working life, and cumulative asbestos exposure as parameters of an occupational asbestos exposure (Table VII). None of these parameters has been adjusted for the effects of the others. Comparing exposed persons to not-exposed ones yields a significantly increased OR for any of the categories of any of these parameters. For each of the parameters, with the exception of time since first exposure, the OR even increases among exposed persons, when the lower intervals of exposure are compared to the higher ones. A steep risk gradient up to $OR = 47$ is observed for the highest intensity of exposure, for years of exposure, and for the cumulative dose estimate. This result does not alter very much by introducing cut-off points 10 or 20 years before the end of observation for the calculation of the cumulative exposure.

Exposure to MMVFs

Table VIII reveals that elevated risks have been found for three intervals of cumulative exposure to MMVFs, although their concentration range is lower, by a factor of 10, than the corresponding range for asbestos exposure (see Table VII). Adjustment for asbestos exposure, however, causes a distinct reduction of the OR and the results are no longer significant. Instead of analyzing on the basis of a dose estimation, an ever/never evaluation may be performed by comparing the first exposure group (0 fiber years = never) to the three upper groups altogether (= ever). In this case the OR remains significant even after adjustment for asbestos.

Additionally, in Table IX exposure estimates and ORs are compared for four different groups of persons with and without exposure to asbestos or MMVFs. A significantly increased OR is registered for cases and

TABLE IV. Job Periods Starting During Different Periods of Calendar Time

Time period	Cases		Controls	
Number of job periods and % with asbestos exposure				
Before 1950	343	39.7%	340	14.1%
1950-1970	352	50.3%	281	24.6%
1970-	51	21.6%	76	17.1%
Mean duration of exposure (years)				
Before 1950	6.02		6.14	
1950-1970	10.94		10.04	
1970-	5.85		7.29	
Mean fiber concentration (fibers/ml)				
Before 1950	0.75		0.97	
1950-1970	1.08		0.51	
1970-	0.90		0.33	

Characterisation of job periods according to the percentage with an asbestos exposure, the mean duration of exposure and the estimate of the (arithmetic) mean of the fiber concentration which is averaged among all shifts with an exposure.

TABLE V. Number of Cases and Controls and Odds Ratio from an Ever/Never Evaluation of 22 of 32 Occupations Where At Least Five Cases or Five Controls were Exposed. Within Each of the Occupations the Job Periods are Characterized by the Percentage of Jobs with an Asbestos Exposure and by the Arithmetic Mean of the Fiber Concentration

Key ^a	Occupation ^a	Cases No.	Controls No.	OR ^b	Job periods of cases and controls		
					% of all periods	Only periods with an asbestos exposure	
						Fiber concentration OM $\times$ 5 t/m ³	
11,41-43	Farmer	17	25	0.60	92	0	0.00
21-32	Forestry worker, fisherman,						
44,52	Animal husbandry worker	4	6	0.67	15	13.3	0.10
12,51	Gardener, vineyard worker	2	5	0.40	16	0	0.00
71-91	Miner	6	8	0.75	21	0	0.00
141-150	Chemical processor and related worker	13	11	1.18	48	60.4	1.39
181-184, 501-504	Joiner, wood processing worker	9	8	1.12	79	21.5	0.34
191-252	Metal production and processing worker	26	14	2.09*	81	45.7	0.80
261-306	Mechanic, fitter, plumber	62	21	2.82*	359	72.1	0.79
311-315	Electrician	15	5	3.00*	88	37.5	0.41
391-433	Food production and processing worker	3	5	0.60	47	0	0.00
441-453	Carpenter, bricklayer, roofer	8	10	0.78	96	34.4	0.69
461-472	Road construction worker, pipe layer, well digger, Unskilled construction worker	17	17	1.00	96	15.6	0.73
481-492	Tile setter, plasterer, pavilion, upholsterer	11	3	3.67*	30	63.3	2.94
531	Unskilled worker not elsewhere classified	5	8	0.57	19	31.6	0.14
541-549	Stationary engine and heavy equipment operator	19	7	3.40*	41	65.9	0.70
601-635	Technician engineer	19	9	2.25	89	46.1	0.28
681-706	Sales assurance agent	11	26	0.38*	80	3.8	0.06
711-744	Transportation & store worker	48	39	1.32	227	22.9	0.20
751-784	Administrative & organization clerk	34	49	0.57*	201	4.0	0.07
791-805	Protective service worker	59	71	0.56	240	7.5	0.09
861-893	Teacher, scientist, social worker	4	7	0.57	41	14.6	0.10
901-937	Housekeeper, cleaner, hairdresser, bartender	5	7	0.71	28	14.3	0.62

^a A priori defined occupational groups, see [Jöckel et al., 1994, 1998], code according to standard classification of industries [Statistisches Bundesamt, 1975, 1978].

^b Odds ratio matched for age and region of residence.

^c Cases, population controls and control patients.

* $p < 5\%$, two-sided.

controls, which were exclusively exposed to MMVFs, if they are compared to those exposed to neither MMVFs nor asbestos.

DISCUSSION

Retrospective exposure assessment is one of the main problems arising from case-control studies [Finkelstein, 1995; Siemiatycki, 1996, 1997; Benke et al., 1997]. Exposure estimates are often based on job exposure matrices (JEM) where estimates describing probability, frequency, and intensity of exposure are not related to specific persons

but to specific combinations of occupations and industries. Different types of exposures are often estimated side by side [Siemiatycki, 1996; Benke et al., 1997; Cocco, 1999]. The mesothelioma case-control study of Iwatsubo et al., [1998] for example, is based on this concept. In our study, however, the frequency and the upper and lower limits of intensity of exposure to asbestos and MMVFs were estimated semi-quantitatively for the single job periods of individual persons. Other types of fiber-containing materials, such as talc or amipulgit, were considered at least qualitatively. Besides asbestos, MMVF was by far the most frequent cause source of exposure to fibers and it was only for MMVF that

TABLE VI. Number of Cases and Controls and Odds Ratio from an Ever/Never-Evaluation of 20 of 21 Industries Where at least Five Cases or Five Controls were Exposed. Within Each of the Industries the Job Periods are Characterized by the Percentage of Jobs with an Asbestos Exposure and by the Arithmetic Mean of the Fiber Concentration

Key ^a	Industries ^a	Cases No.	Controls No.	OR ^b	Jobs periods of cases and controls		
					All periods	only periods with an asbestos exposure	
					% of all periods	fiber concentration ORE × 5 l/ml	
011-077	Fishing, forestry, farming and horticulture	20	31	0.58	124	1.61	0.10
100-118	Energy and mining	20	11	1.82	61	34.4	1.89
200-205	Chemical and oil industry	13	16	0.79	65	30.8	0.78
210-216	Rubber and plastics	9	7	1.33	36	83.3	1.62
221-227	Stone and glass	15	9	2.00	36	55.6	2.73
230-239	Metal production	20	9	3.20 ^c	72	52.8	0.30
240-249	Engine and vehicle building	82	45	3.18 ^c	351	65.5	1.01
250-259	Electrical and sheet metal	15	10	1.71	61	14.8	0.23
260-269	Paper, wood, and print	11	17	0.57	97	6.2	0.13
270-279	Leather and textile	6	7	0.86	19	10.5	0.65
281-298	Food and tobacco	16	14	1.17	77	2.6	0.06
300-308	Construction	36	36	1.00	232	25.9	0.43
310-316	Installation	27	9	4.00 ^c	92	57.6	0.29
401-439	Trade	11	17	0.63	115	7.0	0.11
511-517	Transportation	36	29	1.33	152	32.9	0.18
551-555	Stock-keeping and shipment	14	12	1.18	74	32.4	0.26
600-657	Financial service and insurance	4	9	0.38	33	3.0	0.18
731-745, 98	Cleaning service, barbershop, house-keeping, waste disposal	4	8	0.50	25	16.0	0.59
751-799	Education, sport, health	11	20	0.53	75	12.0	0.20
94, 96							
811-890	Public service and non-profit organizations	73	80	0.74	352	9.9	0.11

^a A priori defined industries, see [Jockey et al., 1994, 1998], code according to standard classification of industries (Statistisches Bundesamt, 1975, 1979).

^b Odds ratio matched for age and region of residence.

^c Cases, population controls and control patients.

^d $p < 5\%$, two-sided.

an increased risk was estimated (Tables VIII, IX). However, exposure to MMVFs is heavily confounded with exposure to asbestos; therefore this result has to be discussed very carefully. First, a critical examination of the study design has to be performed [Siemiatycki and Boffetta, 1998] and in addition, comparisons may be made with results which have previously been obtained for a second series of hospital controls using the same method, and with results of lung tissue fiber analysis [Woitowitz et al., 1993; Rödelsperger, 1996; Rödelsperger et al., 1999].

Selection Bias

It has been argued that the diagnosis of mesothelioma may be made more probable if asbestos exposure is evident

[Siemiatycki and Boffetta, 1998]. This diagnostic bias would increase the risk estimate for asbestos. In our study a panel of pathologists was installed to exclude diagnostic errors. Each diagnosis obtained by the pathologist of a participating hospital had to be confirmed by a member of this panel. The whole panel was then included in the decision for 24% of the diagnoses, where the decisions were discrepant. A total of 15% of the cases considered was discarded (5% in agreement between the two pathologists and 10% by a panel decision).

Selection bias for the selection of population controls is minimized by the matching procedure. In contrast, many of the hospital controls of our previous study suffered from lung cancer [Woitowitz et al., 1993], which is well known to be caused by asbestos.

TABLE VII. Odds Ratios for the Relationship between Mesothelioma and Asbestos Exposure Together with the Number of Cases and Controls According to Different Parameters of the Asbestos Exposure

	125 Cases	125 Controls	Odds ratio ^a	95%-CI
Time since first exposure (years)				
not exposed	11	67	1	
≤30	12	4	22.5	4.3-119
>30-40	40	22	18.9	5.3-67.3
>40	62	32	19.6	5.7-67.2
Duration of exposure (years)				
not exposed	11	67	1	
>0-10	24	21	10.4	2.9-37.1
>10-20	22	14	16.5	4.1-65.6
>20-30	19	8	27.7	5.8-132
>30	49	15	43.7	10.8-177
Highest intensity of exposure^b				
not exposed	11	67	1	
low	14	12	9.2	2.3-35.9
medium	37	25	17.9	5.0-64.4
high	63	21	46.3	12.1-178
Cumulative exposure up to end of observation (fiber years)				
not exposed	11	67	1	
>0-0.15	14	12	7.9	2.1-30.0
>0.15-1.5	38	25	21.9	5.7-83.8
>1.5-15	46	16	47.1	11.5-193
>15	16	5	45.4	8.1-257
Cumulative exposure up to 10 years before end of observation				
not exposed	11	67	1	
>0-0.15	15	13	7.9	2.1-29.5
>0.15-1.5	39	24	24.8	6.2-93.0
>1.5-15	45	16	51.8	12.4-215
>15	15	5	42.6	7.3-249
Cumulative exposure up to 20 years before end of observation				
not exposed	14	68	1	
>0-0.15	15	13	9.2	2.4-35.0
>0.15-1.5	44	24	20.5	5.8-72.6
>1.5-15	40	16	32.2	8.5-122
>15	12	4	43.8	7.1-269

^aOdds ratio matched for age and region of residence.^b"Low" (<0.1 fibers/ml), "high" (>1 fiber/ml) or "medium" (otherwise) according to five times the geometric mean fiber concentration given in Table II.

Information Bias

Information bias may be caused by the different situation of the interview for mesothelioma patients compared to that for the healthy reference population [Siemiatycki and Boffetta, 1998]. In the total for our population controls it is likely that there will be a great deal of information bias increasing the risk estimate while selection bias ought to be

low. This may lead to an overestimate. In contrast, the interview situation should be comparable both for the cases and for the hospital controls of the previous study, who have been treated by pulmonary resection. Hence, information bias, which may increase the risk estimate, should be low, while selection bias, which is expected to decrease the risk, should be high. The overall result might be to underestimate the risk. In order to reduce this type of bias, biographical

TABLE VIII. Odds Ratios and Number of Cases and Controls in Males and Exposure to MMVF

Geometric mean $\times$ 5 (fiber years)	Cases	Controls	Odds ratio ^a	95%-CI	Odds ratio ^b	95%-CI
never = 0	70	111	1.00	—	1.00	—
>0-0.015	10	6	2.96	0.92-9.57	0.78	0.16-3.77
>0.015-0.15	11	4	4.19*	1.17-15.00	3.11	0.56-17.2
>0.15-1.5	20	1	26.28*	3.39-203.75	7.95	0.88-72.3
>1.5	14	3	6.50*	1.47-28.80	5.43	0.72-41.0
ever >0	55	14	6.12*	2.90-12.83	3.08*	1.17-8.07

^a Odds ratio matched for age and region of residence.^b Odds ratio adjusted for asbestos fiber years by means of four indicator variables, as defined in Table III.* $p < 5\%$, two-sided.

history of all job periods was obtained in a first step, then a check list of asbestos and other fibrous products, including brand names, working processes and photos, was presented in a second step, but only minor additions were obtained.

Exposure Assessment Bias

An underestimate of the higher past exposure levels may be caused by information bias or even by change in the methods of fiber counting [Doll and Peto, 1985; Siemiatycki and Boffetta, 1998]. A magnification of the dose-response relationship may result. On the other hand, random errors as a result of misclassification of exposure usually bias the risk toward null value (no association) [Armstrong, 1998].

In Table IV, where exposure estimates of exposure to asbestos for different time periods are presented, the percentage of jobs with asbestos exposure, the mean duration of exposure, and fiber concentration for cases is higher between 1950 and 1970 than in the time periods before and afterwards. This pattern, apart from the fiber concentra-

tion, is similar for population controls. A similar pattern in time was observed in the French mesothelioma case-control study [Iwatsubo et al., 1998]. In this study the highest rate of job periods with asbestos exposure also was observed between 1950 and 1970, but the percentage of about 38% in cases and 20% in controls lies below the German results. In contrast, the prevalence of exposure is higher in France from 1970. This observation might be explained by the restrictions in the use of asbestos, which were introduced in Germany at the end of the 1970s.

In our study quantitative estimates may be subject to error by using only one common duration of exposure in job periods where asbestos and MMVFs were used side by side. For job periods with exposure to asbestos the percentage for an additional exposure to MMVFs was only 22% in cases and 9% in controls. In periods with an exposure to MMVFs the percentage of an additional asbestos exposure was 85% in cases and 67% in controls. Hence, an overestimate must be expected, particularly for the cumulative exposure to MMVFs.

TABLE IX. Exposure to Asbestos and MMVF in Males. Estimate of MMVF and Asbestos Fiber Dose, Numbers of Cases and Controls and Odds Ratio

Exposure	Mean fiber years	125 Cases	125 Controls	Odds ratio ^a	95%-CI
MMVF -	0	9	65	1.00	—
Asbestos -	0				
MMVF +	0.6	2	2	15.1*	1.05-218
Asbestos -	0				
MMVF -	0	61	46	19.8*	4.7-83
Asbestos +	7.1				
MMVF +	2.4	53	12	61.3*	12.9-292
Asbestos -	16.2				

^a Odds ratio matched for age and region of residence.* $p < 5\%$, two-sided.

Error of the Expert Estimate of the Exposure to Asbestos

According to Table III the factor between the GM value of fiber concentration per shift and the upper and lower limits, respectively, of the exposure category which corresponds to this GM value may vary between 2.2 (No.9), and 20 (No.4) with weighted mean values of 6.4 for cases and 5.5 for controls. This expert estimate of the range of uncertainty largely describes the random error for single job periods. The mean bias for the exposure estimates of all job periods should lie below these factors. A similar but lower uncertainty results from classifying the number of working shifts with exposure to asbestos into only three categories where the highest category, e.g., even everyday exposure which is registered as "more than once per week," only contributes half of the working days of a year.

For a single job period the cumulative exposure to asbestos is obtained by the years of duration of exposure normally multiplied with the arithmetic mean values (AM) of fiber concentration per shift and the rate of working shifts with the exposure. Here AM amounts to half the sum of the lower and the upper limit of the expert estimate and therefore, an upper limit much higher than the lower limit would yield an AM which is roughly half the upper limit. A better description of the range of uncertainty is obtained using the GM, but GM values are systematically lower than AM values. The AM of fiber concentration is estimated five times the GM in order to compensate this bias, which results from the uncertainties of the estimate of the fiber concentration (factor 3) and of the frequency of asbestos exposure (factor 1.5). The weighed average of the AM values for all jobs with exposure to asbestos is 0.93 f/ml for the cases while it is 0.66 f/ml for the controls (Table III).

Consistency Between Exposure and Risk Estimates

OR significantly increases (Table VII) for each of the three parameters of cumulative exposure even within the first exposure interval $> 0 - \leq 0.15$ fiber years. Exceptional behavior is observed for the time after first exposure. Here the OR remains constant, although a steep relationship should exist for this parameter. However, this discrepancy may be explained from study design: Controls were matched to cases with respect to the year of birth. There is a good correlation between cases and controls for the age and the time of first exposure.

In Tables V and VI, the percentage of job periods with asbestos exposure and the concentration estimate as parameters of exposure are compared to the OR. The correlation is better with the percentage of job periods with an asbestos exposure ($R = 0.810$ for occupations and $R = 0.769$ for industries, both $P < 0.001$) than with mean fiber concentra-

tion ($R = 0.765$, $P < 0.001$ and $R = 0.524$, $P = 0.018$). The most distinct discrepancy appears between the installation and the stone and glass industries. For the former, the highest OR of 4 (statistically significant) is associated with a small average concentration of 0.29 f/ml. For the latter, an OR of 2 (not significant) is associated with the highest concentration estimate of 2.7 f/ml.

In the "installation industry" a total of 56 job periods of 27 cases and 21 job periods of nine controls was observed. They worked as tin smith or plumber (12 cases and 2 controls), carried out heating installation (5 cases and 3 controls), air conditioning installation (2 cases and 1 control) or worked as electrician (4 cases and 2 controls) or, interior designer or painter (4 cases and 1 control). In this industry working procedures were distributed homogeneously among cases and controls and, therefore, estimates of asbestos exposure were similar for both of them. The low exposure estimates are reliable since exposure mainly resulted from pipe insulation with asbestos, asbestos cement, welding protection, and sealing.

In the "glass and stone" industries a total of only 27 job periods of 15 cases and nine controls was observed. Nine cases but only one control ($P = 0.02$) worked as insulators and definitely used asbestos in most periods; three times this was spray asbestos. One further case had mined asbestos in the Urals as a prisoner of war and two others had worked in the asbestos industry. The latter is also true for one control but he mainly worked inside the office as a designer. One of the remaining three cases was a boilerman in a glass factory. The other two worked as locksmiths in the cement industry. In contrast, the seven remaining controls worked in quarries ($n = 4$) and in concrete production ($n = 3$). The work periods of cases and controls are very obviously different in the "glass and stone" industry. While the high exposure estimate is convincingly justified by the work place descriptions of the cases, the OR is reduced by a large number of controls with places of work where a much lower degree of asbestos exposure should be expected.

Comparison with Lung Tissue Fiber Analysis

The fiber burden of the pulmonary tissue has been analyzed for a total of 66 cases (60 male and 6 female) and 66 hospital controls (primarily lung cancer cases) of the original study, among them 27 cases and 39 controls are from Hamburg as reported elsewhere [Rödelisberger, 1996; Rödelisberger et al., 1999]. The dose estimates for these cases on the average (AM) are 1.7 times higher, than for the cases from the present study. A subsample of 20 male cases was included in both studies, among them was the one with the highest exposure estimate of 167 fiber years.

For the patients of the lung tissue study, cumulative asbestos exposure, as derived from the interview, correlates with the concentration of asbestos fibers longer than 5 μm in

the lung tissue for amphibole ($R = 0.44$, $P < 0.001$), but not for chrysotile fibers [Rödelberger, 1996]. Regression analysis reveals that a fiber dose of one fiber year roughly corresponds to a concentration of 80,000 amphibole fibers longer than 5 μm per gram dry lung tissue (g dry). This relationship is in good agreement with other estimates [Consensus Report, 1997].

A clear dose-response relationship could be observed between the concentration of these long amphibole fibers and the risk of mesothelioma [Rödelberger and Weitowitz, 1995; Rödelberger et al., 1999]. An OR of almost 100 was obtained from the almost linear relationship, when 10 of 66 cases (15%) in the reference interval $< 50,000$ fibers/g dry were compared to 29 of 66 cases (44%) in the uppermost interval $\geq 500,000$ fibers/g dry.

Correspondingly, from the present study (Table VII) an OR of about 45 is observed, if the 11 cases (9%) of the reference interval (0 fiber years) are compared to the 62 cases (50%) of the two uppermost intervals ≥ 1.5 fiber years.

Within these uppermost exposure intervals the average dose estimate combined for cases and controls amounts to 25 fiber years for the lung burden study and to 16 fiber years for the interview study. Obviously, the results of both studies are very similar. This is true, though the OR of the lung burden study should be reduced in comparison to the present study because of the choice of hospital controls instead of population controls. On the other hand, the diminution of the OR by random error may be much stronger for the interview study.

Comparison With Other Case-Control Studies

In this study some 91% of the cases compared to 54% of the controls were occupationally exposed to asbestos (Table VII). Since only male individuals from Hamburg were included, the results are not representative for the German population as a whole. For example, higher exposure to asbestos can be expected in Hamburg due to shipyards and asbestos-processing industries [Hain and Dalquen, 1974]. The rates correspond to the upper limits of the ranges of 12–95% for mesothelioma cases and 2–48% for controls, which have been reported from international mesothelioma case-control studies [Brochard et al., 1993].

Iwatsubo et al. [1998] observed a pattern very similar to the results of Table VII for the different parameters of exposure, but in the uppermost intervals OR generally only reached 5 to 9 compared to about 45 in the German study. Again the OR remained almost constant for the time since first exposure. Its value is 2.2–2.8 in the French and 18.9–22.5 in the German study. The percentage of cases exposed is much higher for the German study (91% compared to 71%). In contrast, the rate of exposure among the German

population controls is somewhat lower than for the French hospital controls (46% compared to 51%).

The ORs observed in our study fully support the well-established epidemiologic evidence for the carcinogenicity of asbestos with respect to mesothelioma. However, due to the low number of pairs with exposed controls and non-exposed cases, the absolute magnitude of the OR should be regarded with caution: the maximum OR decreased from about 100 in the original study [Weitowitz et al., 1993] to 45 in the present paper when the definition for "not exposed to asbestos" slightly was altered from " < 0.015 fiber years" to "0 fiber years" according to Iwatsubo et al., [1998]. According to Table VII the latter reference category contained 11 cases and 67 controls, among them eight pairs. The three remaining cases formed pairs with exposed controls.

Furthermore, if our results obtained for 125 population controls are compared to the results obtained for 125 additionally available hospital controls consisting primarily of lung cancer patients [Weitowitz et al., 1993], the maximum OR decreases from 100 to about 10. If, however, the matching is broken and a stratified unconditional logistic regression is applied the maximum OR decreases to 17 for the population controls while it remains almost constant for the hospital controls (OR = 9.4 in the maximum). A clear dose-response relationship is obtained even for these hospital controls and even for an exposure " > 0.15 –1.5 fiber years" there is a significantly increased OR of 3.2 (95% CI: 1.7–6.1).

Asbestos Fibers and MMVFs

The estimate of the exposure to MMVFs is only about 10% of the exposure estimated for asbestos (Table IX) and, in addition, the effect of MMVF is greatly affected by this exposure. By adjusting for asbestos, a significantly increased OR only remains in the ever/never evaluation, which does not depend on the dose estimate (Table VIII). Considering the two cases and two controls, who were only exposed to MMVF but not to asbestos yield a significantly increased OR of 15.1 (Table IX). Despite the difference in fiber years the risk estimate is very similar for those exposed to asbestos alone. Therefore, MMVF even might be more hazardous than asbestos. However, this conclusion is severely hampered by the problems of estimation of exposure, which influence both the adjustment for asbestos exposure and the definition of non-exposed. In addition, the type of asbestos—chrysotile or amphibole—is unknown in spite of its well-known importance [Rödelberger et al., 1999]. Further difficulties arise from the small sample size in cells with differing exposure with respect to either agent. Accordingly in the original report [Weitowitz et al. 1993], restriction to cases and controls without exposure to asbestos did not yield an increased OR since—as was discussed in the last section—the definition of the reference category was " < 0.015 fiber years" instead of "0 fiber

years." Therefore, in agreement with other studies, there is insufficient evidence to establish a causal relationship between the exposure to MMVF and mesothelioma. Nevertheless, even those studies, which do not show significantly increased incidence of mesothelioma, cannot exclude the possibility MMVF being carcinogenic with sufficient precision [Doll, 1987; Simonato et al., 1987; Marsh et al., 1990; Marsh et al., 1996; Boffetta et al., 1997].

In agreement with other studies [McDonald et al., 1990], our lung burden study did not reveal increased concentrations of MMVF, even after heavy exposure to glass or rock wool [Rödelsperger, 1996; Rödelsperger et al., 1998]. Yet, as for chrysotile, it cannot be excluded that these fibers may have caused a tumor, even if they are not present in lung tissue, when it is diagnosed [Baker, 1991; Weitowitz et al., 1991].

CONCLUSIONS

For all measures of asbestos exposure the OR increases significantly up to about 45 in the uppermost intervals. Even within the first exposure interval " $> 0 - \leq 0.15$ fiber years" the OR significantly increases. This relationship may be influenced by information bias, exposure assessment bias, and the random error. Nevertheless, a stratified analysis, where matching is broken, and a further series of hospital controls yields a lower but still substantial OR.

The OR estimate shows a plausible relationship to the estimate of fiber concentration and to the percentages of jobs with asbestos exposure for different occupations and industries. The highest numbers of mesothelioma together with a significantly increased OR are found in "mechanics, fitters and plumbers" and for the "engine- and vehicle-building" industry. Discrepancies appear between the "glass and stone", and the "installation" industry since OR is reduced for the latter despite a much higher concentration estimate. This may be explained by a substantial difference in the type of exposure of cases and controls in this industry.

Although exposure to MMVF is much lower than the exposure to asbestos, an increased OR is observed in an ever/never evaluation. It even remains significant, if confounding by asbestos is considered by adjustment or if evaluation is restricted to cases and controls without any exposure to asbestos. However, when considering the problems of dose estimation and the sample size, a causal relationship can neither be proven nor excluded.

A further case-control analysis, based on lung tissue fiber concentrations in addition to the interview, yields similar ORs, if reference intervals and uppermost exposure intervals contain similar percentages of all cases. These results confirm the distinct dose-response relationship of the interview study even at a cumulative exposure below 1 fiber year. They clearly support the outcome of the French mesothelioma case-control study.

REFERENCES

- Arhelger R, Rödelsperger K, Brülkel B, Weitowitz H-J. 1984. Staubgefährdung bei der Entsorgung von Asbestspritzisolierung. (Dangerous dust exposure during the removal of insulation of sprayed asbestos.) *Zbl Arbeitsmed* 34:291-299 (In German).
- Armstrong BG. 1998. Effect of measurement error on epidemiological studies of environmental and occupational exposures. *Occup Environ Med* 55:651-656.
- Baker DE. 1991. Limitations in drawing etiologic inferences based on measurement of asbestos fibers from lung tissue. *Ann NY Acad Sci* 643:61-70.
- Benke G, Malcolm S, Forbes A, Salzberg M. 1997. Retrospective assessment of occupational exposure to chemicals in community-based studies: validity and repeatability of industrial hygiene panel ratings. *Int J Epidemiol* 26(3):633-642.
- Boffetta P, Saracci R, Andersen A, Bertazzi PA, Chang-Claude J, Cherrie J, Ferro G, Frenzel-Beyne R, Hansen J, Olsen J, Plato N, Teppo L, Westerholm P, Winter P, Zocchetti C. 1997. Cancer mortality among man-made vitreous fiber production workers. *Epidemiology* 8:259-268.
- Brochard P, Paire JC, Iwatsubo Y, Bignon J. 1993. Work-related mesothelioma. *Eur Respir Rev* 3:74-78.
- Cocco P, Dosemeci M. 1999. Peritoneal cancer and occupational exposure to asbestos: results from the application of a job-exposure matrix. *Am J Ind Med* 35:9-14.
- Consensus Report. 1997. Asbestos, asbestosis, and cancer: the Helsinki criteria for diagnosis and attribution. *Scand J Work Environ Health* 7: 311-316.
- Corn M, Lees PSJ, Breysse PN. 1992. Characterization of end-user exposures to residential insulation products. Final report for medical and scientific committee. Thermal Insulation Manufacturers Association, Stamford, CT.
- Deutsche Forschungsgemeinschaft (DFG). 1997 (1993 in German). Fibrous dusts. In: Greim H. Commission for the investigation of health hazards of chemical compounds in the work area, editor. Occupational toxicants. Critical data evaluation for MAK values and classification of carcinogens. Vol. 8. Weinheim: Verlag Chemie. p141-338.
- DeVuyt P, Demontier P, Swaen GMH, Paire JC, Brochard P. 1995. Respiratory health effects of man-made vitreous (mineral) fibers. *Eur Respir J* 8:2149-2173.
- Doll R, Peto J. 1985. Asbestos. Effects on health of exposure to asbestos. Health and Safety Commission (ed). Her Majesty's Stationary Office, London.
- Doll R. 1987. Symposium on MMMF. Copenhagen, October 1986: Overview and conclusions. *Ann Occup Hyg* 31:805-819.
- Finkelstein MM. 1995. Potential Pitfall in Using Cumulative Exposure in Exposure-Response Relationships: Demonstration and Discussion. *Amer J Ind Med* 28(1):41-47.
- Großgaren K, Weitowitz H-J. 1993. Erkrankungen der Pleura durch Asbest und Erionitfaserstaub. (Diseases of the pleura caused by asbestos and erionite fibers.) *Dtsch Arzteblatt* 90:706-723 (In German).
- Gun RT. 1995. Mesothelioma: Is asbestos exposure the only cause? *Med J Aust* 162:429-431.
- Hain E, Dalquen P. 1974. Katanestische Untersuchungen zur Genese des Mesothelioms. Bericht über 150 Fälle aus dem Hamburger Raum. (Investigations on the origin and the development of mesothelioma. Report on 150 patients from the region of Hamburg.) *Int Arch Arbeitsmed* 33:15-37 (In German).

- HEI-AR (Health Effects Institute—Asbestos Research): Asbestos in public and commercial buildings. 1991. A literature review and synthesis of current knowledge. Cambridge, Massachusetts: Health Effects Institute—Asbestos Research.
- International Agency for Research on Cancer (IARC). 1988. Monographs on the evaluation of carcinogenic risks of chemicals to humans. Man made mineral fibers and rocks. Lyon: IARC Scientific Publications. 8*43.
- Infante PF, Schuman LD, Dement J, Huff J. 1994. Fibrous glass and cancer. *Am J Ind Med* 26:559–584.
- Infante PF, Schuman LD, Huff J. 1996. Fibrous glass insulation and cancer: Response and rebuttal. *Am J Ind Med* 30:113–120.
- Iwatsubo Y, Pignon JC, Boutin C, Menard O, Massin N, Caillaud D, Orlowski E, Calzavara-Saia F, Bignon J, Brochard P. 1998. Pleural mesothelioma: Dose-response relation at low levels of asbestos exposure in a French population-based case-control study. *Amer J Epidemiol* 148(2):133–142.
- Jäckel K-H, Ahrens W, Böhm-Audorf U. 1994. Lung cancer risk and welding—preliminary results from an ongoing case-control study. *Am J Ind Med* 25:805–812.
- Jäckel K-H, Ahrens W, Jahn I, Pohlabein H, Böhm-Audorf U. 1998. Occupational risk factors for lung cancer: a case-control study in West Germany. *Int J Epidemiol* 27:549–560.
- Magnani C, Ivaldi C, Boua M, Terracini B. 1997. Pleural malignant mesothelioma and environmental asbestos exposure in Casale Monferrato, Piedmont. Preliminary analysis of a case-control study. *Med-Lav* 88(4):302–309.
- Mark EF, Yokoi T. 1991. Absence of evidence of a significant background incidence of diffuse malignant mesothelioma apart from asbestos exposure. *Ann NY Acad Sci* 643:196–204.
- Marsh GM, Enterline PE, Stone RA, Henderson VL. 1990. Mortality among a cohort of U.S. man-made mineral fiber workers: 1985 follow-up. *J Occup Med* 32:594–604.
- Marsh GM, Stone RA, Youk AO, Smith TS, Quinn MM, Henderson VL, Schall LC, Wayne LA, Lee KY. 1996. Mortality among United States rock wool and slag wool workers: 1989 update. *J Occup Health Safety Aust N Z* 12:297–312.
- McDonald JC, Case BW, Enterline PE, Henderson V, McDonald AD, Ploourde M, Sebastian P. 1990. Lung dust analysis in the assessment of past exposure of man-made mineral fiber workers. *Ann Occup Hyg* 34:427–441.
- Peto J, Decarli A, LaVecchia C, Levi F and Negri E. 1999. The European mesothelioma epidemic. *Br J Cancer* 79:666–672.
- Pott F. 1991. Beurteilung der Kanzerogenität von Fasern aufgrund von Tierversuchen. (An evaluation of the carcinogenicity of fibers basing on animal experiments.) In: VDI-Berichte 833. Faserförmige Stäube: Vorschriften, Wirkungen, Messung, Minderung. (Fibrous dusts: Regulations, effects, measurements, prevention). Düsseldorf: VDI-Verlag. p 39–106 (In German).
- Pott F, Roller M. 1993. Die kreberzeugende Wirkung von Fasern unter besonderer Berücksichtigung der Inhalationsversuche. (The carcinogenic effect of fibers with special regard to the inhalation experiment.) In: Gesellschaft zur Förderung der Luftthygiene und Silikoseforschung e.V. Düsseldorf. Editor. *Umweltthygiene* 25:178–247 (In German).
- Rees D, Myers JE, Goodman K, Fourie E, Blignaut C, Chapman R, Buchmann MO. 1999. Case-Control Study of Mesothelioma in South Africa. *Amer J Ind Med* 35:213–222.
- Rödelisperger K. 1996. Anorganische Fasern im menschlichen Lungengewebe. Lungenstabsinzeranalyse zur Epidemiologie der Risikofaktoren des diffusen malignen Mesothelioms (DMM). (Inorganic fibers in human lung tissue. Epidemiology on the risk factors of the diffuse malignant mesothelioma (DMM) basing on lung dust fiber analysis.) Bundesanstalt für Arbeitsmedizin. Bremerhaven: Wirtschaftsverlag NW. p1–366 (In German).
- Rödelisperger K, Weitowitz H-J, Krieger HG. 1980. Estimation of exposure to asbestos-cement dust on building sites. In: Wagner JC, editor. *Biological Effects of Mineral Fibers*. Lyon: International Agency for Research on Cancer. IARC Scientific Publications. Vol. 2: 30:845–853.
- Rödelisperger K, Jahn H, Brückel B, Manke J, Paur R, Weitowitz H-J. 1986. Asbestos Dust Exposure During Brake Repair. *Amer J Ind Med* 10:63–72.
- Rödelisperger K, Weitowitz H-J. 1991. Asbestfaserstaub-Dosimetrie als Grundlage epidemiologischer Dosis-Häufigkeits-Untersuchungen. (The Estimate of the cumulative asbestos exposure as a prerequisite of epidemiological investigations on dose-response relationships.) In: VDI-Berichte 888. Krebszeugende Stoffe in der Umwelt. (Carcinogenic substances in the environment.) Düsseldorf: VDI-Verlag 293–323 (In German).
- Rödelisperger K, Weitowitz H-J. 1995. Airborne fiber concentrations and lung burden compared to the tumour response in rats and humans exposed to asbestos. *Ann Occup Hyg* 39:715–725.
- Rödelisperger K, Schneider J, Weitowitz H-J. 1996. Umwelt- und Innenraumgefährdung durch Asbestfaserstaub außerhalb des Arbeitsplatzes. (Non-occupational outdoor and indoor exposure to asbestos dust.) *Gefahrst Reinh Luft* 56:117–126 (In German).
- Rödelisperger K, Weitowitz H-J, Brückel B, and Artheiger R. 1998. Non asbestos mineral fibers in human lungs. *Eur J Oncol* 3:221–229.
- Rödelisperger K, Weitowitz H-J, Brückel B. 1999. Dose-response relationship between amphibole fiber lung burden and mesothelioma. *Cancer Detect Prev* 23:183–193.
- Rösler JA, Weitowitz H-J, Lange H-I, Weitowitz RH, Ulm K, Rödelisperger K. 1994. Mortality rates in a female cohort following asbestos exposure in Germany. *J. Occup. Med.* 36 (1994) 889–893.
- SAS Institute. 1992. Technical Report P. 229. SAS/STAT Software: Changes and Enhancements, version 6.07. Cary, NC.
- Schneider J, Rödelisperger K, Pohlabein H, Weitowitz H-J. 1996. Innenraumgefährdung durch Asbestfaserstaub als Risiko- und Einflussfaktor des diffusen malignen Pleuramesothelioms (DMM). (Indoor asbestos exposure as a causal factor of diffuse malignant mesothelioma (DMM).) *Zentralblatt Hyg Umweltmed* 199:1–23 (In German).
- Siemiatycki J. 1996. Exposure Assessment in Community-Based Studies of Occupational Cancer. *Occup Hyg* 3: 41–58.
- Siemiatycki J, Fritschl L, Nadon L, and Gérin M. 1997. Reliability of an Expert Rating Procedure for Retrospective Assessment of Occupational Exposures in Community-Based Case-Control Studies. *Amer J Ind Med* 31:280–286.
- Siemiatycki J, Boffetta P. 1998. Invited commentary: Is it possible to investigate the quantitative relation between asbestos and mesothelioma in a community-based study? (comment). *Am J Epidemiol* 148(2):143–147.
- Simonato L, Fletcher AC, Cherric JW, Andersen A, Bertazzi PA, Charney N, Claude J, Dodgson J, Esteve J, Frentzel-Beyme R, Gardner MJ, Jensen O, Olsen J, Teppo L, Winkelmann R, Westerholm P, Winter PD, Zocchetti C, Saracci R. 1987. The International Agency for Research on Cancer historical cohort study of MMMF production workers in seven European countries: Extension of the follow-up. *Ann Occup Hyg* 31:603–623.

- Smith AH, Wright CC. 1996. Chrysotile asbestos is the main cause of pleural mesothelioma. *Am J Ind Med* 30: 252-266.
- Spiras R, Heineman EF, Bernstein L, Beebe GW, Keshn RJ, Stark A, Hariow BL, Benichou J. 1994. Malignant mesothelioma: attributable risk of asbestos exposure. *Occup Environ Med* 51(12): 804-811.
- Statistisches Bundesamt, Editor. 1975. *Klassifizierung der Berufe—Systematisches und alphabetisches Verzeichnis der Berufsnennung*. (Classification of occupations—systematic and alphabetical catalogue of occupations.) Stuttgart/Mainz: Verlag W. Kohlhammer (In German).
- Statistisches Bundesamt, Editor. 1979. *Systematik der Wirtschaftszweige*. (Systematics of branches of industries.) Stuttgart/Mainz: Verlag W. Kohlhammer (In German).
- Vianna NJ, Polan AK. 1978. Non-occupational exposure to asbestos and malignant mesothelioma in females. *Lancet* 20: 1061-1063.
- Walton WH, Coppock SM, editors. 1987. *Man-made mineral fibers in the working environment*. *Ann Occup Hyg* 31:517-602.
- WHO. 1988. *Manmade mineral fibers*. International Programme of Chemical Safety (IPCS), Geneva. *Environmental Health Criteria* 77: 1-165.
- Woitowitz H-J, Rödelberger K. 1983. Gesundheitsrisiko bei der Anwendung asbesthaltiger Produkte. (Health risks from the application of products containing asbestos.) In: VDI-Berichte Nr. 475. *Faserige Stäube—Messung, Wirkung, Abhilfe*. (Fibrous dusts—measurement, effects, prevention -.) Düsseldorf: VDI-Verlag, p 313-324 (In German).
- Woitowitz H-J, Rödelberger K, Arhelger R, Giesen T. 1983. *Asbestanbelastung am Arbeitsplatz, Meßwerte der internationalen Literatur*. (Work place exposure to asbestos, measuring results from the international literature.) Schriftenreihe der Bundesanstalt für Arbeitsschutz: Gefährliche Arbeitsstoffe Nr. 10. Bremerhaven: Wirtschafts-verlag NW, p 1-497 (In German).
- Woitowitz H-J, Hiltendal G, Calavrezos A, Berghäuser KH, Rödelberger K, Jöckel KH, et al. 1993. Risiko- und Einflußfaktoren des diffusen malignen Mesothelioms (DMM). (Causal factors of the diffuse malignant mesothelioma (DMM).) Bundesanstalt für Arbeitsschutz, Forschungsberichtereihe "Arbeit und Technik", Bremerhaven: Wirtschaftsverlag NW, p 1-296 (In German).

EXHIBIT 46

Friday, October 20, 2006

Friday, October 20, 2006

8:00–10:05

ORAL SESSION

Epidemiology I

32 South Africa: The first link between asbestos and mesothelioma, but not the last word?

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The link between asbestos and mesothelioma was established by the South Africans Wagner, Marchand and importantly Sleggs, whose clinical acumen recognised both the association and that the entity was separate from fulminant tuberculosis. All three main commercial types of asbestos were mined in South Africa – white chrysotile, blue crocidolite and brown amosite, the latter two being particularly mesotheliomagenic. Peak production occurred in 1975, with more than 97% of the global crocidolite and all of the amosite (an acronym for Asbestos Mines of South Africa) produced by South Africa. A rapid decline and closure of these mines occurred within 20 years. More than 90% of all 10.2 million tons of asbestos produced in South Africa was exported, and to 70 countries at peak.

The mesotheliomagenicity of the different fibre types is crocidolite > amosite > chrysotile. The rarity of mesothelioma in chrysotile exposed workers may occur because the chrysotile contains little tremolite, a pattern which repeats in neighbouring Swaziland and Zimbabwe. While data on incidence is sparse, our best information indicates that about 75% of mesothelioma cases are occupational, with 25% associated with environmental exposure. The mining/industrial split is 45/55. The measured incidence in Prieska, a crocidolite mining town, is similar to that of Wittenoom in Australia. There is an ongoing under-diagnosis of mesothelioma in black workers, because being largely rural and poor, they have lesser access to diagnostic and therapeutic services, and also because of the masking effect of tuberculosis (worsened by the HIV pandemic), which harks back to the experience of Sleggs.

Recent litigation settlements in South African courts – first with individual claimants and later with two larger class action suits – have established significant compensation funds of ~USD 100 million for asbestos-related diseases. With South Africa being the first link and having exported most of its asbestos, we are still hearing the last words as export destinations are experiencing their own epidemics of mesothelioma.

33 The mesothelioma epidemic: Occupational, environmental and spontaneous cases

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Background: Asbestos use fell abruptly in Britain around 1980, but there are now 1,900 mesothelioma deaths per year, slightly more than melanoma and almost twice the number for cervical cancer. The total number of British mesothelioma deaths is predicted to be about 90,000, most of which are still to occur, with 250,000 throughout Western Europe.

Methods: We have interviewed 624 mesothelioma patients (513 men, 111 women), 425 resected lung cancers (294 men, 131 women), and 1,420 population controls (1,112 men, 308 women) to obtain lifetime occupational and residential histories.

Results: Defining the reference group as <5 years of low-risk industrial work, odds ratios (95% CI) for 5+ years of exposure before age 35 years were 33.8 (17.0-67.2) for carpenters, 12.2 (7.2-20.8) for plumbers, electricians, painters and decorators, 3.9 (2.0-7.8) for other construction workers, and 12.8 (7.2-22.6) for other recognized high-risk occupations. The male mesothelioma rate was much lower in other occupations, corresponding to a lifetime risk of the order of 1 in 600 men in the reference group.

Conclusions: The lifetime mesothelioma risk for men born before about 1950 will thus be about 5% for carpenters, 2% for other high-risk occupations and almost 1% in general construction. Lung samples obtained from the resected

lung cancers and at post-mortem from mesothelioma patients we have interviewed will define the relationship between lung fibre burden and mesothelioma risk. These data, together with lung samples obtained from young construction workers undergoing surgery for pneumothorax, will determine the risks caused by current exposures. Most female mesotheliomas have no known exposure, so the fivefold increase in female rates since the 1960s may be due largely to environmental exposure. The effects of brief and prolonged chrysotile exposure will be discussed in relation to these findings, and to developing countries where uncontrolled asbestos use is still widespread.

34 The global asbestos epidemic and its reflections in the recent Japanese experience

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Background: Japan experienced an "asbestos-panic" this past year, triggered by news that a major company was responsible for scores of asbestos-related disease (ARD) cases among former employees. Social criticism gained momentum as it became apparent that many residential victims (without job exposure) were also involved. Many other companies having used asbestos came forward to disclose their responsible share of ARDs. Administration faced allegations that control measures lagged behind Western countries: e.g., crocidolite and amosite was banned in 1995; chrysotile was banned in 2004 "in principle." The consumption curve of asbestos in Japan trailed that of many Western countries, concurrent with the "economic catch-up period" and lingered into the late 1990s. Consequently, mesothelioma mortality started to show an upsurge fairly recently (953 deaths or 7.6 per million in 2004). The recent Japanese experience is likely to be a reflection of the global asbestos epidemic.

Methods: We explored the global situation by 1) conducting an ecological study of national-level data between historical asbestos consumption and recent mortality rates of ARDs (mesothelioma (m), pleural m, peritoneal m, and asbestosis). There is concern that, as regards ARDs, industrializing countries may be following the paths of industrialized countries. To address this issue, we followed-up on the above global analyses by 2) assessing the time-trend patterns of historical asbestos consumption and their relation to the time-trend patterns of ARDs.

Results: 1) Clear and plausible correlations were found between the two sets (consumption and mortality) of cross-sectional national data, which were marked for mesothelioma in both sexes and male asbestosis (Lancet, in press). 2) Preliminary results suggest that the global asbestos epidemic is indeed unfolding, but in a manner that can be characterized by distinctive historical time-patterns of consumption (to be submitted).

Conclusions: The burden of ARDs, which has been/is becoming apparent among industrialized countries, will likely shift towards the industrializing countries in a sequential manner.

35 Risk of pleural mesothelioma: A French population-based case-control study (1998-2002)

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Background: In industrialised countries, asbestos has been widely used for decades and occupational exposure to asbestos has been identified as the most important risk factor for pleural mesothelioma. The aims of this study are to analyse the risk of mesothelioma according to occupations and industries, to estimate the attributable risk to asbestos exposure, and to research other factors (synthetic fibres, ionizing radiations, SV40 virus, previous diseases). Only results on occupational exposure are presented in this report.

Methods: A population-based case-control study was conducted between 1998 and 2002 in 19 French districts, within the National mesothelioma surveillance program (covering 25% of the French population). This report is based on 467 cases histologically confirmed (80% males, 41-93 years old) and 868 controls matched for sex, age and district. Data were collected by trained interviewers with a standardised questionnaire, and lifetime occupational exposure was as-

essed by experts. Logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CIs).

Results: Among men, the highest risks were observed for the occupations of plumbers, pipe-fitters, sheet-metal workers, and for the industries of ship repair, asbestos products, metal products, and construction. A significant dose-response relationship was found between cumulative occupational asbestos exposure and pleural mesothelioma, even for the lowest exposure category >0.07 fibres/ml-years (OR 2.8, 95% CI 1.7-4.7). The attributable risk for occupational asbestos exposure was 83.5% (95% CI 77.2-89.8%) for men and 41.9% (95% CI 29.8-54.0%) for women.

Conclusions: This report enabled us to classify occupations and industries according to the risk of pleural mesothelioma. It provides guidance for preventive actions among specific groups of workers, and allows a continuous evaluation of their efficiency. The analyses are ongoing with a focus on non-occupational exposed subjects to asbestos (women in particular).

36 Health effects among World Trade Center responders

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Background: Responders to the World Trade Center disaster on 9/11 and in subsequent months were exposed to a wide range of physical and chemical hazards and to psychological stressors. Anecdotal clinical evidence suggested that many developed aerodigestive disorders and psychological sequelae.

Methods: Over 16,000 rescue and recovery workers have undergone clinical evaluation with the use of a standardized assessment protocol that includes pre- and post-bronchodilator spirometry.

Results: High rates of persistent upper and lower airway abnormalities, gastroesophageal reflux, and post-traumatic stress and depression have been identified among the examinees.

Conclusions: WTC-related exposures encountered by WTC responders caused upper and lower respiratory abnormalities, GERDS, and psychological sequelae that are highly prevalent and persistent. Exposure to asbestos in the rubble and settled dust, especially among specific categories of responders, poses a risk of mesothelioma in the future, the magnitude of which is uncertain.

37 Pleural abnormalities and exposure to asbestos-contaminated vermiculite from Libby, Montana: A twenty year follow-up study

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Background: Vermiculite mined in Libby, Montana was shown to be contaminated with asbestosiform fibers, best described as tremolite-actinolite-richertite-winchite transition fiber. This study is a follow up investigation of a 1980 cross-sectional study of 513 workers exposed predominantly to Libby vermiculite ore. The rationale was to determine the long-term pulmonary effects of exposure to Libby vermiculite used in a secondary manufacturing setting.

Methods: Of the original 513 workers, 82 were deceased and eight could not be located. Of the remaining 423, 70.4% (298) participated in the study, 11.6% (49) refused, and 18.0% (76) did not respond. Of the 298 participants, 94% (280) completed both the radiograph and the interview for inclusion in this analysis. Primary outcomes were pleural and interstitial changes as determined from chest radiography. Pleural thickening was defined as unilateral or bilateral thickening, excluding solitary blunting of the costophrenic angle(s). Parenchymal changes were defined as irregular opacities with a profusion category $>1/0$. Chest radiographs were interpreted by three board certified radiologists (B readers). For a radiograph to be classified as abnormal, two of the three B readers must agree. Exposure to vermiculite ore was defined cumulatively (fiber/cc/years).

Results: Initial analysis of the first 194 participants indicated an increase in the number of workers with pleural changes. Pleural plaques were identified in 25% compared to 4% in the original 1980 cohort. Final results will be presented examining the association of pleura and interstitial findings with exposure indices.

Conclusions: Vermiculite contaminated with asbestosiform fibers has the propensity to cause an increase in pleural changes at low exposure levels. The public health implications of these preliminary findings are important in view of the national distribution of the Libby vermiculite ore for home and commercial uses.

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38 Mesothelioma update for Libby, Montana: Occupational and non-occupational

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Background: In 1986, a McGill University study of vermiculite miners/millers in Libby, Montana reported 4 mesothelioma cases in workers hired before 1965. In 2004 mortality was updated to 1999, adding 8 deaths. No study including workers after 1965 or any para-occupational or non-occupational mesothelioma in Libby has been published previously.

Methods: Case data for mesothelioma in Libby was obtained from 3 sources: a) the published McDonald (McGill) (1986, 2004) follow-up studies of W.R. Grace workers at Libby, Montana; b) information from attorneys representing mesothelioma victims and c) Dr. Brad Black on case numbers, occupational/non-occupational origin and basis of diagnosis at the CARD clinic at Libby, which began in 2000. There is no overlap between the latter and the published studies. Information obtained included years of work at the mine or mill (if any); pathology reports and death certificates.

Results: Four occupational cases were found additional to the 12 published who started work before 1965. One worked for only 6 weeks and 3 died later than 1999. Mesothelioma proportional mortality among workers is over 5%; a proportion seen previously only in crocidolite asbestos miners/millers and amosite-exposed insulation workers. Three more cases were diagnosed among those who began work after 1965, for a total of 19 to date. Ten non-occupational cases were identified; for 7 diagnosed after 2000, (6 confirmed pathologically, 1 clinically) there was also no history of living with a worker. Latency averaged 35 years from first exposure in workers. Latency in non-occupational cases, if equated with time of residence in Libby, exceeds this. Non-occupational cases incident earlier than 2000, while likely, have never been fully ascertained.

Conclusions: Mesothelioma in Libby workers and those without occupational exposure has been under-estimated. Caused by "Libby amphibole", it has ominous implications for known continuing amphibole exposure sources throughout the USA, including widely distributed waste products and "naturally-occurring" amphiboles not commercially exploited.

Friday, October 20, 2006

10:30-12:20

ORAL SESSION

Epidemiology II

39 Australia: Wittenoom and beyond

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Background: The epidemic of mesothelioma in Australia was initially driven by the crocidolite mine and mill at Wittenoom in Western Australia where long-established asbestos hygiene principles and regulations were routinely ignored. Australia was also the largest per capita user of asbestos in the 1950s, resulting in the highest rate of mesothelioma in the world in the 1990s and beyond.

Methods: Rates of mesothelioma in different Australian states over time and overall consumption of asbestos were examined, and different sources of exposure to asbestos were described.

Results: Rates of mesothelioma in Australia appear to be leveling off while use of asbestos has declined. Importation of new asbestos into Australia was finally banned at the end of 2003, but the vast quantities of materials from previous use still remain. Australia's chief manufacturer of asbestos products during the last century tried to avoid its future liabilities by transferring its operations to the Netherlands, but was shamed into establishing a more realistic compensation fund. While the mesothelioma surveillance of the National Occupational Health and Safety Commission appears to have lost impetus, the National Health and Medical Research Council of Australia has recently set aside substantial funds for asbestos-related disease research.

Conclusions: Given that the highest future exposures to asbestos are likely to occur among workers in small demolition and removal operations, the dismantling of workers' protection regulations for small business, through Australia's "new" industrial relations legislation, is likely to result in future high rates of mesothelioma lasting well into this new century.

40 Age and sex differences in malignant mesothelioma after residential exposure to blue asbestos (crocidolite)

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Background: Blue asbestos (crocidolite) was mined and milled at Wittenoom,

EXHIBIT 47

ORIGINAL ARTICLE

Occupational and non-occupational attributable risk of asbestos exposure for malignant pleural mesothelioma

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ABSTRACT

Objectives To estimate the proportion of pleural mesothelioma cases that can be attributed to asbestos exposure in France including non-occupational exposure.

Methods A population-based case-control study including 437 incident cases and 874 controls was conducted from 1998 to 2002. Occupational and non-occupational asbestos exposure was assessed retrospectively by two expert hygienists. ORs of pleural mesothelioma for asbestos-exposed subjects compared to non-exposed subjects, and population-attributable risk (ARp) of asbestos exposure were estimated using a conditional logistic regression.

Results A clear dose-response relationship was observed between occupational asbestos exposure and pleural mesothelioma (OR=4.0 (99% CI 1.9 to 8.3) for men exposed at less than 0.1 f/mL-year vs 67.0 (99% CI 25.6 to 175.1) for men exposed at more than 10 f/mL-year). The occupational asbestos ARp was 83.1% (99% CI 74.5% to 91.7%) for men and 41.7% (99% CI 25.3% to 58.0%) for women. A higher risk of pleural mesothelioma was observed in subjects non-occupationally exposed to asbestos compared to those never exposed. The non-occupational asbestos ARp for these subjects was 20.0% (99% CI -33.5% to 73.5%) in men and 38.7% (99% CI 8.4% to 69.0%) in women. When considering all kinds of asbestos exposure, ARp was 87.3% (99% CI 78.9% to 95.7%) for men and 64.8% (99% CI 45.4% to 84.3%) for women.

Conclusions Our study suggests that the overall ARp in women is largely driven by non-occupational asbestos exposure arguing for the strong impact of such exposure in pleural mesothelioma occurrence. Considering the difficulty in assessing domestic or environmental asbestos exposure, this could explain the observed difference in ARp between men and women.

INTRODUCTION

Malignant mesothelioma is a rare tumour mostly located in the pleura and associated with poor survival. To date, asbestos and erionite fibres are the only recognised risk factors for pleural mesothelioma.^{1 2}

Asbestos had been extensively used in many industries all around the world, and was progressively banned in most industrialised countries, with such action taking place first in Europe in the 1980s and

Key messages

What is the key question?

- What is the overall impact of asbestos exposure including non-occupational exposure on pleural mesothelioma?

What is the bottom line?

- Occupational asbestos exposure explains less than half the pleural mesothelioma cases among women, thus, there is a need to quantify the impact of non-occupational asbestos exposure for pleural mesothelioma.

Why read on?

- This study provides insights regarding non-occupational exposure impact in pleural mesothelioma occurrence, especially among women.

specifically in 1997 in France. However, asbestos is still produced and used in many countries, most of them being developing countries. This massive use of asbestos fibres has been correlated with an increase in the incidence of asbestos-related diseases and, in particular, pleural mesothelioma.³

The causal relationship between occupational asbestos exposure and pleural mesothelioma is already well established,⁴⁻¹³ and it is estimated that approximately 80% of male cases may be attributed to occupational asbestos exposure. Although the role of non-occupational asbestos exposure (para-occupational, domestic or environmental) in the occurrence of pleural mesothelioma has already been demonstrated,¹⁴⁻¹⁶ there is a need to quantify the risk attributable to such exposure, especially in women in whom only 40% of cases can be explained by occupational exposure.¹⁰ Knowledge about overall asbestos exposure (occupational and/or non-occupational exposure) attributable risk could provide further information regarding the aetiology of pleural mesothelioma and could be useful to help authorities for prevention in situations where asbestos-containing materials still persist in developed countries, and where asbestos is still in use in developing countries.

In France, the National Mesothelioma Surveillance Program (PNSM) was set up in 1998

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to provide relevant information on the health effects of asbestos exposure on the French population. It relies on the exhaustive recording of all incident primary pleural tumours in specified districts.¹⁷

The present study reports the occupational, non-occupational and overall asbestos exposure-attributable risk for pleural mesothelioma from a population-based case-control study carried out between 1998 and 2002.

MATERIALS AND METHODS

Study design

The study design was previously reported in detail.¹⁸ Cases were identified through the PNSM from 1998 to 2002 and certified by a standardised diagnostic confirmation procedure.¹⁷ Two controls, selected from the general population, were matched with cases for sex, age (± 5 years) and district of residence. Participation rates of cases and controls were 61.1% and 20.8%, respectively.

Trained interviewers administered a standardised questionnaire to each subject. Only subjects alive at the time of the interview were included. Information about lifetime residential, educational and occupational history (including details on job tasks and do-it-yourself activities), demographic characteristics including the socioeconomic category defined by the last occupation held, previous respiratory diseases, occupations of partners and parents, and family cancer history were collected. A more specific part of the questionnaire focused on specific lifetime situations that might have involved asbestos exposure, for example, spraying fibres, asbestos cement disposal and removal, other insulation with asbestos-containing products (sheets, ropes, gaskets, etc), brake and clutch repairs, and washing asbestos-contaminated clothes. Additional questions concerned other suspected risk factors such as ionising radiations, and man-made mineral fibres (glass fibres and mineral wool, refractory ceramic fibres). Each job held for more than 6 months was coded according to international and national classifications for occupations and industries.

The PNSM obtained the appropriate institutional review board authorisations. Written informed consent for participation in the study was obtained from all participants.

Asbestos exposure assessment

Asbestos exposure was assessed by retrospective expertise.^{8 18} Two experts (an industrial hygienist and an occupational physician) analysed each subject's questionnaire blinded to case-control status.¹⁹

For occupational exposure, each job held for at least 6 months by a subject was translated into four semiquantitative occupational asbestos exposure parameters, including the probability of exposure (possible, definite), frequency of exposure (sporadic, intermittent, frequent or continuous), intensity of exposure (low, medium, high, very high), and the route of exposure (direct, indirect). Table 1 describes these exposure parameters. A subject occupationally exposed to asbestos was defined as a subject who had held at least one job with a non-null probability of exposure. For each subject, the maximal probability of exposure, duration of exposure (years), age at first exposure (years), time since first exposure (years), year at first exposure and a cumulative exposure index (CEI, expressed in fiber/mL-years) were defined. The CEI was calculated by summing the products of probability, frequency, intensity and duration of exposure of each job held by a given subject. Since job occupational exposure parameters are semiquantitative, numerical values were assigned to each of them (table 1). These

Table 1 Description of the exposure parameters used to assess asbestos exposure at job level

Asbestos exposure parameters	Definition	Numerical values*
Probability of exposure	Degree of confidence that exposure really occurred, expressed in percent (%)	
Not exposed	0	0
Possible	>0–50	0.5
Definite	>50–100	1
Frequency of exposure	Expressed in percent of work time (%)	
Sporadic	>0–5	0.025
Occasional	>5–30	0.25
Frequent or continuous	>30–100	0.75
Intensity of exposure	Expressed in f/mL	
Low	>0–0.1	0.1
Medium	>0.1–1	1
High	>1–10	10
Very high	>10	100

*Numerical values assigned to each category in order to calculate cumulative exposure index.

assigned values were the same as those defined in a previous mesothelioma French case-control study,⁸ where authors concluded that these values had the best ability to show a clear dose-response relationship.

Lifetime non-occupational asbestos exposure was also assessed by expertise using information reported by subjects on the use of asbestos-containing materials or performed tasks. The probability, frequency and intensity of exposure, and the route of exposure (domestic, para-occupational and environmental) were assigned to each subject. The definitions of probability, frequency and intensity of exposure were the same as for occupational exposure, except for intensity where the 'low' category was split into 'very low' and 'low'. Domestic exposure was defined by do-it-yourself activities that might have involved asbestos-containing products, for example, home improvements, and brake and clutch repairs. Para-occupational exposure was considered with regard to asbestos-contaminated clothes of relatives, partners and parents who had jobs well known to be associated with asbestos exposure, or with a high risk for pleural mesothelioma. For environmental exposure, only self-reported living near an industrial source of asbestos was considered.¹⁸

Statistical analysis

Analyses were performed separately for men and women. ORs and 99% CIs were estimated for the occupational and non-occupational asbestos exposure parameters using conditional logistic regression models for matched sets. All continuous exposure variables were arbitrarily categorised: duration of exposure: 1–10/>10–20/>20 years; age at first exposure: ≤ 15 / >15 –20/>20 years; time since first exposure: >19 –40/>40–50/>50 years; year at first exposure: >1960 / >1960 –1977/>1977; CEI: >0 –0.1/>0.1–1/>1–10/>10 'f/mL-years' (table 4). All population-attributable risks (ARp) and 99% CIs were calculated using the Mantel–Haenszel estimation.²⁰ The non-occupational asbestos exposure ARp was estimated among matched sets where cases and controls were not occupationally exposed to asbestos. Considering all asbestos exposure, the overall ARp was estimated using OR comparing

subjects occupationally and/or non-occupationally exposed to those never exposed at all. Given the long latency period of pleural mesothelioma, exposures occurring less than 20 years before diagnosis were not taken into account.⁸ Although asbestos exposure was retrospectively assessed by two experts in the domain, this expertise was mainly based on subjects' self-reported tasks or asbestos-containing materials used. Thus, we conducted several sensitivity analyses by setting as not exposed: (1) subjects initially assessed as possibly exposed; (2) subjects initially assessed as exposed at a very low intensity; (3) subjects initially assessed as possibly exposed at a very low intensity; (4) subjects initially assessed as possibly exposed or exposed at a very low level intensity. We also performed additional analyses by setting the lag period at 0, 10 and 30 years.

RESULTS

The study sample comprised 437 cases (362 men, 75 women) and 874 controls (724 men, 150 women). Table 2 presents the main subjects' characteristics. Cases were ascertained in average near 12 months after they had been identified, but they were interviewed before the certification of the diagnosis and, on average, 3 months after they had been recorded. The socio-economic category differed between cases and controls: 59.4% of male cases were blue-collar workers versus 32.2% for controls. Among females, 41.1% of cases were clerical and related, workers versus 28.5% of controls.

Table 3 presents the 10 most frequent occupations and industries among males. There was a slight variation in the proportion of occupations held by male cases and controls. For some occupations, the occurrence of asbestos exposure within those occupations differed between cases and controls; that is, 90.7% of cases who ever held an occupation as sheet-metal workers

were exposed to asbestos within this occupation versus 77.8% of controls.

The relationship between pleural mesothelioma and occupational asbestos exposure is reported in table 4. Among men, ORs for pleural mesothelioma were significantly increased for all exposure parameters, and a dose-response relationship was observed for all of them. OR for men exposed at less than 0.1 f/mL-years compared to those never exposed was 4.0 (99% CI 1.9 to 8.3) vs 67.0 (99% CI 25.6 to 175.1) in men exposed at more than 10 f/mL-years. Among women, a significant association between occupational asbestos exposure and pleural mesothelioma was also observed, OR for women ever exposed compared to those never exposed was 12.0 (99% CI 3.5 to 41.7). The estimated occupational asbestos exposure ARp was 83.1% (99% CI 74.5% to 91.7%) in men and 41.7% (95% CI 25.3% to 58.0%) in women.

Table 5 presents the association between non-occupational asbestos exposure and pleural mesothelioma among subjects never occupationally exposed, that is, 9 matched sets among males (9 cases and 18 controls) and 36 matched sets among females (36 cases and 72 controls). OR for men ever non-occupationally exposed to asbestos compared to those never exposed was 2.4 (99% CI 0.2 to 26.7) and increased to 4.3 (99% CI 1.2 to 15.1) for women. The non-occupational asbestos ARp for subjects never occupationally exposed was 20.0% (99% CI -33.5% to 73.5%) in men and 38.7% (99% CI 8.4% to 69.0%) in women.

The ARp related to overall asbestos exposure (occupational and non-occupational) is presented in table 6. The risk of pleural mesothelioma was strongly associated with asbestos exposure with a slight difference between men (OR=13.0 (99% CI 6.2 to 27.5)) and women (OR=8.0 (99% CI 2.9 to 21.8)).

Table 2 Main characteristics of subjects: 437 cases (362 men; 75 women) and 874 controls (724 men; 150 women), French case-control study, 1998–2002

	Men (1 086)				Women (225)			
	Cases (362)		Controls (724)		Cases (75)		Controls (150)	
	n	%	n	%	n	%	n	%
Age (years)								
Mean (SD)	67.6 (9.3)		66.8 (9.1)		66.6 (9.1)		65.8 (8.9)	
Range	41–93		41–89		41–92		41–89	
Education level (years)								
≤14	185	51.1	275	38.0	33	44.0	60	40.0
>14	177	48.9	449	62.0	42	56.0	90	60.0
Diagnostic-ascertainment period (months)								
Mean (SD)	12.7 (18.8)				12.1 (15.2)			
Range	0–97.1				0.2–65.9			
Diagnostic-interview period (months)								
Mean (SD)	3.4 (3.9)				3.4 (4.4)			
Range	0–43.7				0–36.3			
Last held occupation (ISCO 1968 major group)*								
0/1 Professional, technical and related workers	49	13.5	146	20.2	5	6.9	31	21.5
2 Administrative and managerial workers	15	4.1	68	9.4	3	4.1	1	0.7
3 Clerical and related workers	34	9.4	91	12.6	30	41.1	41	28.5
4 Sales workers	23	6.4	69	9.5	7	9.6	13	9.0
5 Service workers	16	4.4	48	6.6	16	21.9	34	23.6
6 Agricultural, animal husbandry and forestry workers; fishermen; hunters	10	2.8	69	9.5	3	4.1	4	2.8
7/8/9 Production and related workers, transport equipment operators and labourers	215	59.4	233	32.2	9	12.3	20	13.9

*Among women, two cases and six controls had never worked.

Environmental exposure

Table 3 Occupational asbestos exposure: proportion of exposed men in the most represented occupations and industries, French case-control study, 1998–2002

	Cases (362)				Controls (724)			
	n	%	Exposed within job		n	%	Exposed within job	
			n	%			n	%
Occupations (ISCO Edition 1968)								
8-73 Sheet-metal workers	54	14.9	49	90.7	27	3.7	21	77.8
8-49 Machinery fitters, machine assemblers n.e.c.*	46	12.7	31	67.4	37	5.1	25	67.6
7-00 Production supervisors and general foremen	44	12.2	31	70.5	56	7.7	40	71.4
8-71 Plumbers and pipe fitters	39	10.8	36	92.3	14	1.9	12	85.7
8-41 Machinery fitters and machine assemblers	37	10.2	21	56.8	30	4.1	13	43.3
9-99 Labourers n.e.c.*	36	9.9	24	66.7	27	3.7	15	55.6
6-21 General farm workers	31	8.6	0	0.0	86	11.9	4	4.7
9-51 Bricklayers, stonemasons and tile setters	29	8.0	25	86.2	31	4.3	26	83.9
8-34 Machine-tool operators	26	7.2	14	53.8	29	4.0	7	24.1
9-54 Carpenters, joiners and parquetry workers	26	7.2	21	80.8	27	3.7	20	74.1
Industries (ISIC Revision 2)								
5000 Construction	129	35.6	109	84.5	140	19.3	105	75.0
3841 Ship building and repairing	65	18.0	58	89.2	20	2.8	19	95.0
3813 Manufacture of structural metal products	52	14.4	43	82.7	30	4.1	20	66.7
1110 Agriculture and livestock production	48	13.3	5	10.4	145	20.0	32	22.1
6200 Retail trade	33	9.1	8	24.2	94	13.0	19	20.2
6100 Wholesale trade	29	8.0	9	31.0	74	10.2	13	17.6
3819 Manufacture of fabricated metal products except machinery and equipment n.e.c.*	24	6.6	13	54.2	24	3.3	6	25.0
9100 Public administration	24	6.6	6	25.0	71	9.8	11	15.5
3845 Manufacture of aircraft	23	6.4	10	43.5	27	3.7	10	37.0
9310 Education services	23	6.4	9	39.1	82	11.3	19	23.2

*n.e.c.: not elsewhere classified.

The overall asbestos exposure ARp was 87.3% (99% CI 78.9% to 95.7%) in men and 64.8% (99% CI 45.4% to 84.3%) in women.

From the sensitivity analysis, in men, the overall ARp was 68.6% (99% CI 58.0 to 79.1), 85.9% (99% CI 77.2 to 94.7), 86.0% (99% CI 77.2 to 94.7) and 68.6% (99% CI 58.0 to 79.1) for analyses 1, 2, 3 and 4, respectively. In women, the overall ARp was 26.7% (99% CI 12.0 to 41.3), 47.4% (99% CI 30.0 to 65.0), 52.0% (99% CI 34.1 to 69.8) and 22.0% (99% CI 8.0 to 36.0) for analyses 1, 2, 3 and 4, respectively (see online supplementary material).

DISCUSSION

This study permits to quantify the role of some aspects of non-occupational asbestos exposure in the occurrence of pleural mesothelioma. When taking into account all kinds of asbestos exposure, 87.3% of male cases and 64.8% of female cases were attributable to asbestos.

In table 3, we observed an intravariability of asbestos exposure within each occupation and industry category. This is due to the exposure assessment method that incorporated experts' knowledge about that occupation or industry, as well as specific tasks performed, and circumstances of asbestos exposure reported by the subject himself.

The relationship between occupational asbestos exposure and occurrence of pleural mesothelioma is now well known. To date, several case-control studies have analysed this relationship, and all confirmed the causal link between occupational asbestos exposure and pleural mesothelioma,^{4 5 7–13 21} but few have estimated the population-attributable risk of asbestos exposure for

pleural mesothelioma.^{4 5 10 13} Results from the present study are consistent with the literature. However, they may not be generalisable to countries, such as developing countries, countries with different pattern of industrialisation, or which used different type of asbestos fibres.

In France, almost all the asbestos used was imported, and chrysotile seems to have been the most common used type. Sources of asbestos exposure came from mainly construction industry, shipbuilding and repairing industry, manufacture of asbestos cement products, metal-working industry and motor vehicles manufacture or repairing.⁸

Our results support the role of non-occupational asbestos exposure in the aetiology of pleural mesothelioma and make it possible to quantify the weight of such exposure in the occurrence of pleural mesothelioma, especially among women. There is now stronger evidence that pleural mesothelioma may be induced by non-occupational exposure. Several population-based case-control studies have established an association between para-occupational exposure and the occurrence of pleural mesothelioma,^{22–24} as well as for household exposure.^{7 25} A meta-analysis of eight studies provided a summary relative risk of 8.1 (95% CI 5.3 to 12.0).²⁶ While there is evidence of an association between asbestos exposure from a geological source and the increased incidence of pleural mesothelioma,²⁷ recent studies have shown an increased risk of pleural mesothelioma associated with environmental exposure related to proximity with an asbestos plant,^{28 29} as well as environmental exposure due to residence near asbestos mines.^{11 30} Bourdes *et al* reported a summary relative risk for environmental exposure due either to asbestos mines or an asbestos

Table 4 Occupational asbestos exposure and risk of pleural mesothelioma, 437 cases (362 men; 75 women) and 874 controls (724 men; 150 women), French case-control study, 1998–2002

		Men (1 086)						Women (225)						
		Cases (362)		Controls (724)		OR	99% CI	Cases (75)		Controls (150)		OR	99% CI	
Occupational asbestos exposure		n	%	n	%			n	%	n	%			
Not exposed		28	7.7	327	45.2	1.0	—	41	54.7	139	92.7	1.0	—	
Exposed		334	92.3	397	54.8	11.4	6.1 to 21.4	34	45.3	11	7.3	12.0	3.5 to 41.7	
Highest probability of exposure	Possible	43	11.9	102	14.1	5.6	2.6 to 12.1	19	25.3	8	5.3	9.6	2.4 to 38.1	
	Definite	291	80.4	295	40.7	13.2	7.0 to 25.0	15	20.0	3	2.0	18.2	2.9 to 112.9	
Duration of exposure (years)	1–10	71	19.6	119	16.4	7.9	3.8 to 16.1	19	25.3	4	2.7	36.2	2.6 to 513.3	
	>10–20	78	21.6	95	13.1	11.2	5.4 to 23.3	>10	15	20.0	7	4.6	6.6	1.6 to 27.8
	>20	185	51.1	183	25.3	13.9	7.2 to 27.0							
Age at first exposure (years)	≤15	77	21.3	63	8.7	15.8	7.4 to 33.8	≤20	14	18.7	2	1.3	38.2	2.4 to 601.3
	>15–20	122	33.7	115	15.9	14.6	7.3 to 29.4	>20	20	26.6	9	6.0	8.3	2.2 to 31.5
	>20	135	37.3	219	30.2	8.5	4.4 to 16.4							
Time since first exposure (years)	>19–40	81	22.4	119	16.4	8.3	4.0 to 17.2	>19–40	15	20.0	5	3.3	10.2	2.0 to 50.5
	>40–50	114	31.5	131	18.1	12.6	6.2 to 25.6	>40	19	25.3	6	4.0	14.2	2.7 to 75.0
	>50	139	38.4	147	20.3	13.4	6.7 to 26.8							
Year at first exposure	≤1960	256	70.7	275	38.0	13.8	7.2 to 26.7	≤1960	19	25.3	6	4.0	14.3	2.7 to 75.8
	>1960–1977	75	20.7	108	14.9	8.4	4.0 to 17.6	>1960–1977	13	17.3	4	2.7	10.6	2.1 to 55.9
	>1977	3	0.9	14	1.9	1.9	0.3 to 11.8	>1977	2	2.7	1	0.6	7.9	0.2 to 258.8
Cumulative exposure (* f/mL-years *)	>0–0.1	54	14.9	181	25.0	4.0	1.9 to 8.3	>0 to 0.1	13	17.3	6	4.0	6.9	1.5 to 30.9
	>0.1–1	68	18.8	121	16.7	8.3	3.8 to 17.7	>0.1	21	28.0	5	3.3	23.7	3.3 to 168.53
	>1–10	115	31.8	68	9.4	22.5	10.4 to 48.7							
	>10	97	26.8	27	3.7	67.0	25.6 to 175.1							
Attributable risk (99% CI) (%)						83.1 (74.5 to 91.7)		41.7 (25.3 to 58.0)						

Table 5 Non occupational asbestos exposure and risk of pleural mesothelioma among subjects non-exposed to occupational asbestos exposure, 45 cases (9 men; 36 women) and 90 controls (18 men; 72 women), French case-control study, 1998–2002

Non-occupational asbestos exposure	Men				Women					
	Cases (9)		Controls (18)		Cases (36)		Controls (72)		OR	99% CI
	n	%	n	%	n	%	n	%		
Not exposed	6	66.7	15	83.3	17	47.2	56	77.8	1.0	–
Exposed	3	33.3	3	16.7	19	52.8	16	22.2	4.3	1.2 to 15.1
Highest probability of exposure										
Possible	0	0.0	1	5.6	11	30.6	13	18.1	3.2	0.8 to 13.2
Definite	3	33.3	2	11.1	8	22.2	3	4.1	7.5	1.2 to 48.0
Attributable risk (99% CI) (%)									20.0 (–33.5 to 73.5)	
									38.7 (8.4 to 69.0)	

processing plant of 7.0 (95%CI 4.7 to 11.0). To date, there is only weak evidence of a possible effect of passive exposure in buildings containing asbestos on the occurrence of pleural mesothelioma.¹⁵

As in most case-control studies, the major limitation of this study is the retrospective assessment of exposure. While we are confident about the reliability of the occupational and para-occupational asbestos exposure assessment, this is not the case for domestic and environmental asbestos exposure. In the questionnaire, there were specific questions about domestic use of asbestos, or the proximity to an asbestos-processing plant. The reliability of such assessment is poor and is highly subject to recall bias.³¹ Besides the proximity to an asbestos-processing plant, we did not consider other potential sources of environmental exposure, such as residence in buildings containing asbestos, or proximity to construction sites involving asbestos. Moreover, since we did not assess environmental exposure through lifetime residential distance from an asbestos-processing plant or other industrial sources but through self-report, we may have underestimated this kind of exposure, thereby leading to an underestimation of non-occupational and overall ARp. This hypothesis could explain the observed difference in ARp between men and women. Indeed, since 92% of male cases and only 45% of female cases were occupationally exposed, the ARp among women should be more affected by the bias induced by the underestimation of environmental exposure than that among men. A recent French study on the spatial

distributions of male and female incidence of mesothelioma cases with and without any identified occupational or non-occupational asbestos exposure suggested the major influence of asbestos in female mesothelioma, likely through unknown environmental exposure.³² However, we cannot exclude a possible overestimation of the non-occupational ARp and, thus, the overall ARp due to recall bias if we hypothesise that controls tended to under-report environmental or domestic exposure compared to cases. This effect might have been more extreme among women, since most cases were not occupationally exposed leading to a possible over-reporting of environmental or domestic exposure. This plausible hypothesis may also explain the observed difference between men and women for the non-occupational ARp. Indeed, from the sensitivity analyses conducted which aimed to assess the extent of this recall bias, the overall ARp varied from 68.6% to 87.3% among men, and from 22.0% to 64.8% among women. Only 11.6% of male cases were assessed as possibly exposed and 0.6% at a very low intensity versus 42.7% and 28.6% of female cases, respectively. Female cases were mainly considered as exposed at a very low intensity through domestic exposure, that is, use of baking trays, cooking gloves, toasters and ironing boards. Results from these sensitivity analyses demonstrate the difficulty of estimating precisely the overall asbestos ARp among women. Indeed, since the ARp among men is mostly driven by occupational exposure, and because the assessment of such exposure relies on the knowledge of experts in industrial hygiene, there is little impact

Table 6 All asbestos exposure and risk of pleural mesothelioma, 437 cases (362 men; 75 women) and 874 controls (724 men; 150 women), French case-control study, 1998–2002

All asbestos exposure	Men (1 086)				Women (225)					
	Cases (362)		Controls (724)		Cases (75)		Controls (150)		OR	99% CI
	n	%	n	%	n	%	n	%		
Not exposed	17	4.7	263	36.3	19	25.3	104	69.3	1.0	–
Exposed	345	95.3	461	63.7	56	74.7	46	30.7	8.0	2.9 to 21.8
Occupational only	264	76.5	317	68.7	26	46.4	9	19.6		
Non occupational only	11	3.2	64	13.9	22	39.3	35	76.1		
Occupational and non-occupational	70	20.3	80	17.4	8	14.3	2	4.3		
Highest probability of exposure										
Possible	42	11.6	104	14.4	32	42.7	38	25.3	5.8	2.0 to 17.0
Probable	303	83.7	357	49.3	24	32.0	8	5.4	14.7	4.0 to 54.2
Attributable risk (99% CI) (%)									87.3 (78.9 to 95.7)	
									64.8 (45.4 to 84.3)	

of the sensitivity of the 'ever exposed' definition on the ARP estimation. However, since only 40% of female cases are attributable to occupational asbestos exposure, the overall ARP in women is driven by occupational and non-occupational asbestos exposure. Thus, among women, the 'ever exposed' definition, and especially, the 'non-occupationally ever exposed' definition, has an important impact on the estimation of ARP.

The PNSM relies on the exhaustive recording of all incident primary pleural tumours in representative districts of France.¹⁷ Only incident cases who were alive at the time of the interview were included in these analyses. From a substudy on non-response bias, it appeared that the sociodemographic characteristics of cases who died before interview or refused to answer questions, did not differ from those of the cases included in this study.¹⁸ Cases who had died before the interview seemed to be less occupationally exposed than those included (among males, 80.3% vs 92.3%, respectively; among women, 18.7% vs 45.3%, respectively). However, occupational asbestos exposure was derived from simplified questionnaires and mainly assessed through job titles. According to controls selection, it appeared that there were more blue-collar workers among refusing controls and more white-collar workers among participating controls, leading to a possible underestimation of occupational asbestos exposure among our control population.³³

As in all previous published population-based mesothelioma case-control studies, the prevalence of blue collar workers was higher among cases than among controls. We did not adjust for this difference in socioeconomic status between cases and controls, since this is a variable that is linked to asbestos exposure but cannot be considered as potential causal factor of pleural mesothelioma.³⁴

The definition of a lag period of 20 years had no impact on results since they were similar when we implemented a lag period strategy of 0, 10 and 30 years (see online supplementary material).

Since we have performed several comparisons, we have decided to present results with 99% CIs instead of the traditional 95% CIs. In order to estimate the 99% CIs for ARP, we used a method proposed by Greenland,²⁰ which is based on the Mantel-Haenszel estimation and is consistent for sparse data as found in individually matched studies. Since it exists several variance formulas in the literature, we also derived 99% CIs using the bootstrap method,³⁵ and results were very similar (see online supplementary material).

CONCLUSION

After quantification of the role of non-occupational asbestos exposure in the occurrence of pleural mesothelioma, approximately 35% of female cases were still not attributable to asbestos exposure. Since domestic and environmental exposures are hardly identifiable, the overall ARP could be underestimated owing to the underestimation of non-occupational asbestos exposure. Explanations, such as other factors involved in the aetiology of pleural mesothelioma, are also possible.

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REFERENCES

- 1 Dikensoy O. Mesothelioma due to environmental exposure to erionite in Turkey. *Curr Opin Pulm Med* 2008;14:322–5.
- 2 Wagner JC, Sleggs CA, Marchand P. Diffuse pleural mesothelioma and asbestos exposure in the North Western Cape Province. *Br J Ind Med* 1960;17:260–71.
- 3 Tossavainen A. Global use of asbestos and the incidence of mesothelioma. *Int J Occup Environ Health* 2004;10:22–5.
- 4 Agudo A, Gonzalez CA, Bleda MJ, et al. Occupation and risk of malignant pleural mesothelioma: A case-control study in Spain. *Am J Ind Med* 2000;37:159–68.
- 5 Aguilar-Madrid G, Robles-Perez E, Juarez-Perez CA, et al. Case-control study of pleural mesothelioma in workers with social security in Mexico. *Am J Ind Med* 2010;53:241–51.
- 6 Hodgson JT, Darnton A. The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure. *Ann Occup Hyg* 2000;44:565–601.
- 7 Howel D, Arblaster L, Swinburne L, et al. Routes of asbestos exposure and the development of mesothelioma in an English region. *Occup Environ Med* 1997;54:403–9.
- 8 Iwatsubo Y, Pairon JC, Boutin C, et al. Pleural mesothelioma: dose-response relation at low levels of asbestos exposure in a French population-based case-control study. *Am J Epidemiol* 1998;148:133–42.
- 9 Pintos J, Parent ME, Case BW, et al. Risk of mesothelioma and occupational exposure to asbestos and man-made vitreous fibers: evidence from two case-control studies in Montreal, Canada. *J Occup Environ Med* 2009;51:1177–84.

Environmental exposure

- 10 Rake C, Gilham C, Hatch J, *et al.* Occupational, domestic and environmental mesothelioma risks in the British population: a case-control study. *Br J Cancer* 2009;100:1175–83.
- 11 Rees D, Goodman K, Fourie E, *et al.* Asbestos exposure and mesothelioma in South Africa. *S Afr Med J* 1999;89:627–34.
- 12 Rodelsperger K, Jockel KH, Pohlabeln H, *et al.* Asbestos and man-made vitreous fibers as risk factors for diffuse malignant mesothelioma: results from a German hospital-based case-control study. *Am J Ind Med* 2001;39:262–75.
- 13 Spirtas R, Heineman EF, Bernstein L, *et al.* Malignant mesothelioma: attributable risk of asbestos exposure. *Occup Environ Med* 1994;51:804–11.
- 14 Ferrante D, Bertolotti M, Todesco A, *et al.* Cancer mortality and incidence of mesothelioma in a cohort of wives of asbestos workers in Casale Monferrato, Italy. *Environ Health Perspect* 2007;115:1401–5.
- 15 Goldberg M, Luce D. The health impact of nonoccupational exposure to asbestos: what do we know? *Eur J Cancer Prev* 2009;18:489–503.
- 16 Magnani C, Dalmaso P, Biggeri A, *et al.* Increased risk of malignant mesothelioma of the pleura after residential or domestic exposure to asbestos: a case-control study in Casale Monferrato, Italy. *Environ Health Perspect* 2001;109:915–19.
- 17 Goldberg M, Imbernon E, Rolland P, *et al.* The French National Mesothelioma Surveillance Program. *Occup Environ Med* 2006;63:390–5.
- 18 Rolland P, Gramond C, Lacourt A, *et al.* Occupations and industries in France at high risk for pleural mesothelioma: A population-based case-control study (1998–2002). *Am J Ind Med* 2010;53:1207–19.
- 19 Gramond C, Rolland P, Lacourt A, *et al.* Choice of rating method for assessing occupational asbestos exposure: study for compensation purposes in France. *Am J Ind Med* 2012;55:440–9.
- 20 Greenland S. Variance estimators for attributable fraction estimates consistent in both large strata and sparse data. *Stat Med* 1987;6:701–8.
- 21 Cicioni C, London SJ, Garabrant DH, *et al.* Occupational asbestos exposure and mesothelioma risk in Los Angeles County: application of an occupational hazard survey job-exposure matrix. *Am J Ind Med* 1991;20:371–9.
- 22 McDonald AD, McDonald JC. Malignant mesothelioma in North America. *Cancer* 1980;46:1650–6.
- 23 Newhouse ML, Thompson H. Mesothelioma of pleura and peritoneum following exposure to asbestos in the London area. *Br J Ind Med* 1965;22:261–9.
- 24 Vianna NJ, Polan AK. Non-occupational exposure to asbestos and malignant mesothelioma in females. *Lancet* 1978;1:1061–3.
- 25 Magnani C, Agudo A, Gonzalez CA, *et al.* Multicentric study on malignant pleural mesothelioma and non-occupational exposure to asbestos. *Br J Cancer* 2000;83:104–11.
- 26 Bourdes V, Boffetta P, Pisani P. Environmental exposure to asbestos and risk of pleural mesothelioma: review and meta-analysis. *Eur J Epidemiol* 2000;16:411–17.
- 27 Constantopoulos SH. Environmental mesothelioma associated with tremolite asbestos: lessons from the experiences of Turkey, Greece, Corsica, New Caledonia and Cyprus. *Regul Toxicol Pharmacol* 2008;52:S110–15.
- 28 Maule MM, Magnani C, Dalmaso P, *et al.* Modeling mesothelioma risk associated with environmental asbestos exposure. *Environ Health Perspect* 2007;115:1066–71.
- 29 Musti M, Pollice A, Cavone D, *et al.* The relationship between malignant mesothelioma and an asbestos cement plant environmental risk: a spatial case-control study in the city of Bari (Italy). *Int Arch Occup Environ Health* 2009;82:489–97.
- 30 Kielkowski D, Nelson G, Rees D. Risk of mesothelioma from exposure to crocidolite asbestos: a 1995 update of a South African mortality study. *Occup Environ Med* 2000;57:563–7.
- 31 Rothman KJ, Greenland S, Lash TL. *Modern epidemiology*. Third edn. Philadelphia: Lippincott Williams & Wilkins, 2008.
- 32 Goldberg S, Rey G, Luce D, *et al.* Possible effect of environmental exposure to asbestos on geographical variation in mesothelioma rates. *Occup Environ Med* 2010;67:417–21.
- 33 Lacourt A, Rolland P, Gramond C, *et al.* Attributable risk in men in two French case-control studies on mesothelioma and asbestos. *Eur J Epidemiol* 2010;25:799–806.
- 34 Richiardi L, Barone-Adesi F, Merletti F, *et al.* Using directed acyclic graphs to consider adjustment for socioeconomic status in occupational cancer studies. *J Epidemiol Community Health* 2008;62:e14.
- 35 Llorca J, Delgado-Rodriguez M. A comparison of several procedures to estimate the confidence interval for attributable risk in case-control studies. *Stat Med* 2000;19:1089–99.



Occupational and non-occupational attributable risk of asbestos exposure for malignant pleural mesothelioma

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EXHIBIT 48

Asbestos-Related Lung Cancer and Malignant Mesothelioma of the Pleura: Selected Current Issues

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Abstract

Asbestos-related diseases persist, because millions of workers have had prior exposure and many industrializing countries continue to use asbestos. Globally, an estimated 107,000 people die annually from lung cancer, malignant mesothelioma, and asbestosis due to occupational asbestos exposure. Malignant mesothelioma and lung cancer are caused by all major types of asbestos. Asbestos causes more lung cancer deaths than malignant mesothelioma of the pleura; most cases of the latter are due to asbestos exposure. The cancer risk increases with cumulative asbestos exposure, with increased risk even at low levels of exposure to asbestos. Based on empirical studies, an estimated cumulative occupational exposure to asbestos of 1 fiber/mL-year substantially raises malignant mesothelioma risk. No safe threshold for asbestos exposure has been established for lung cancer and mesothelioma. The validity of fiber-type risk assessments depends critically on the quality of exposure assessments, which vary considerably, leading to a high degree of uncertainty. Asbestos exposure without asbestosis and smoking increases the risk of lung cancer. The joint effect of asbestos and smoking is supra-additive, which may depend in part on the presence of asbestosis. Asbestos workers who cease smoking experience a dramatic drop in lung cancer risk, which approaches that of nonsmokers after 30 years. Studies to date show that longer, thinner fibers have a stronger association with lung cancer than shorter, less thin fibers, but the latter nonetheless also show an association with lung cancer and mesothelioma. Low-dose chest computed tomographic scanning offers an unprecedented opportunity to detect early-stage lung cancers in asbestos-exposed workers.

Keywords

- ▶ asbestos
- ▶ lung cancer
- ▶ malignant mesothelioma
- ▶ asbestosis
- ▶ chrysotile

Asbestos, the cause of the most important occupational disease epidemic of the 20th century into the 21st century, remains highly relevant to public health even as it has largely disappeared from manufacture and new uses in the United States, Europe, Japan, and Australia. First, despite its ban from use and manufacture in 55 countries, asbestos continues to be mined and formulated into new products in many countries, most notably in China, India, Russia, and Brazil. Indeed, in 2011, China used nearly as much asbestos, 638,000 metric

tons, as the United States used in its peak year of consumption, 1973.¹ World Health Organization (WHO) estimates that there are currently approximately 125 million people in the world who are exposed to asbestos in the workplace.² Second, most asbestos that was ever used in industrialized countries still remains in place and thereby presents and will continue to offer opportunities for exposure for workers in renovation, maintenance, demolition, and waste removal. Third, there is a large reservoir of people in industrialized countries who,

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despite cessation of exposure, had significant exposure to asbestos in the past. In the United States, for example, there are an estimated 10 to 15 million people who have had prior exposure to asbestos, and, therefore, remain at risk for asbestos-related diseases.

Incidence and Prevalence of Asbestos-Related Diseases of the Chest

According to the most recent WHO estimates, more than 107,000 people die each year on a global basis from asbestos-related lung cancer, malignant mesothelioma, and asbestosis resulting from exposure at work.² Approximately one-half of all deaths due to occupational cancer are estimated to be caused by asbestos. In addition, it is estimated that several thousand deaths annually can be attributed to exposure to asbestos in the home.^{2,3}

The most accurate data on the burden of asbestos-related diseases are the estimated counts of cases of malignant mesothelioma due to its highly specific association with prior exposure to asbestos. There are an estimated 28,000 to 43,000 deaths from malignant mesothelioma worldwide per year.^{4,5} In addition, based on asbestos consumption patterns, it is believed that there are many more unrecognized malignant mesothelioma deaths in countries with no or little reporting, including Russia, China, India, and Kazakhstan.⁵ The highest malignant mesothelioma incidence in the world occurs in the United Kingdom and Australia and is approximately 30 cases per million people per year compared with 8 and 10 cases per million people per year in the United States and Japan, respectively.⁶ In the United Kingdom, malignant mesothelioma caused 1,749 deaths in men in 2005, constituting 1 in 40 cancer deaths among men younger than 80 years.⁷ The incidence of malignant mesothelioma is not expected to peak in many industrialized countries until the next one to two decades due to historical patterns of asbestos consumption.

Lung cancer caused by asbestos is generally more frequent than malignant mesothelioma, even if cases of the latter disease are far more likely to be recognized as being caused by asbestos. The under-recognition of lung cancer caused by asbestos is widely reported.⁸ The ratio between the numbers or incidence of these two diseases varies considerably in individual studies,⁸ though a commonly used ratio of excess asbestos-related lung cancers to malignant mesothelioma is 2:1.^{8,9} Because occupational asbestos exposure was reasonably common in industrialized countries between the 1940s and the 1980s, asbestos-related lung cancer constitutes a significant proportion of all lung cancers occurring in those countries. Accumulated studies indicate that approximately 4 to 10% of lung cancer in most developed countries is due, at present or in the recent past, to asbestos exposure.^{9–12} McCormack and colleagues applied two models to estimate asbestos-related lung cancer mortality based on mesothelioma mortality in 20 countries and obtained a broad range of proportions of lung cancer that are ascribed to asbestos, ranging from 3.2 to 5.4% in the United States to 12.2 to 16.2% in the United Kingdom.⁹

Malignant Mesothelioma

Diffuse malignant mesothelioma, a primary cancer of mesothelial serosa, occurs in four anatomic locations: the pleura, the peritoneum, the pericardium, and the tunica vaginalis (the serous covering of the testis). Approximately 90% of malignant mesotheliomas occur in the pleura, and most of the remaining cases occur in the peritoneum.^{13–15} Regardless of location, asbestos is the common etiology for the majority of malignant mesotheliomas.

Malignant mesothelioma is caused by all types of asbestos, including chrysotile, crocidolite, amosite, anthophyllite, tremolite, and actinolite.¹⁶ This conclusion is based on epidemiological, experimental, and mechanistic studies and reflects a broad consensus of views in the scientific, public health, and regulatory communities.^{3,16–22}

Asbestos is the dominant cause of human malignant mesothelioma and is responsible for at least 85 to 90% of pleural malignant mesothelioma among men. Indeed, over time, as the methods of identifying historical asbestos exposure have improved, the proportion of cases of malignant mesothelioma that were preceded by an identified exposure to asbestos has increased. Leigh and Driscoll reported from the Australian Mesothelioma Registry that 90% of male cases and 61% of female cases reported a history of asbestos exposure.¹³ As importantly, of cases without an identified history of asbestos exposure, most (81%) had lung fiber counts > 200,000 asbestos fibers/g dry lung, indicating prior exposure to asbestos. Thus, the vast majority of the malignant mesothelioma cases in their registry had a prior history of exposure to asbestos. In a national Italian study using detailed mesothelioma registry data, Marinaccio et al found that 87 and 80% of male cases of pleural and peritoneal mesotheliomas, respectively, reported a history of asbestos exposure, usually occupational in origin.¹⁴ Comparable data for women in Italy showed that 63 and 53% of cases of pleural and peritoneal mesotheliomas, respectively, reported a history of asbestos exposure, though in many instances it was nonoccupational in origin.¹⁴ In a national population case-control study of pleural malignant mesothelioma in France, Lacourt et al found that 95 and 75% of male and female cases of pleural malignant mesothelioma, respectively, reported asbestos exposure or were judged to have been exposed to asbestos.²³ From the same study, the population-attributable risk of pleural malignant mesothelioma due to asbestos exposure was 87% among men and 65% among women.²³ Rake and British colleagues conducted a large mesothelioma case-control study in the United Kingdom, based on direct interviews with study participants, and found that 85% of male cases and 38% of female cases were associated with a prior exposure to asbestos.²⁴ They noted that many additional female cases of malignant mesothelioma may be associated with exposure to asbestos in settings that the authors had considered to be low risk.²⁴ In Mexico, Aguilar-Madrid et al studied 177 cases of pleural malignant mesothelioma and found that 81% had had occupational exposure to asbestos.²⁵

Other established causes of malignant mesothelioma are the mineral fibers, erionite and fluoro-edenite, that have

caused malignant mesothelioma in specific geographic regions in Turkey and Sicily, respectively.^{26,27} Radiation for Hodgkin lymphoma and non-Hodgkin lymphoma has been associated with an increased risk of malignant mesothelioma.^{28–30} The DNA virus, SV40, has been studied in relation to mesothelioma induction with conflicting results. A recent review by the International Agency for Research on Cancer determined that there is inadequate evidence to consider SV40 a human carcinogen.³¹

Exposure–Response: Asbestos Exposure and Malignant Mesothelioma

The risk of malignant mesothelioma due to asbestos is dose dependent, as amply demonstrated in many occupational cohort studies across a range of industries. Malignant mesothelioma is known to occur at lower levels of exposure to asbestos, and no dose has been established below which there is no risk of malignant mesothelioma; that is, no “safe” threshold of cancer risk has been demonstrated.

► **Table 1** summarizes findings from several large case-control studies of malignant mesothelioma undertaken in numerous countries that evaluated the risk of mesothelioma

by estimated occupational asbestos exposure. Case-control studies of malignant mesothelioma have selected advantages, because they concentrate large numbers of cases of malignant mesothelioma, which usually occur in relatively small numbers (i.e., < 20 cases) in individual studies of asbestos-exposed cohorts. They also usually capture a set of cases of malignant mesothelioma with diverse histories of asbestos exposure, permitting evaluation of risk associated with differing levels of exposure. All studies in ► **Table 1** show a sharp rise in mesothelioma risk with increasing asbestos exposure. This pattern signifies that at any level of occupational asbestos exposure, adding additional occupational exposure to asbestos increases the likelihood of developing malignant mesothelioma.

There are three consequences of this observed exposure–response pattern. First, for the individual who has had some occupational asbestos exposure, it is essential to avoid additional exposure to asbestos, because it adds, often dramatically, to their risk of developing malignant mesothelioma. Second, in terms of attribution of malignant mesothelioma to prior asbestos exposure, it is clear that each increment in occupational asbestos exposure contributes significantly to

Table 1 Risk of malignant mesothelioma according to levels of occupational asbestos exposure: results of case-control studies

Cumulative exposure (fiber/mL-year)	Cases/controls	Odds ratio	95% CI
French study ³² no. 1			
Not exposed	95/154	1.0	–
0.001–0.49	77/109	1.2	0.8–1.8
0.5–0.99	29/12	4.2	2.0–8.8
1–9.9	80/27	5.2	3.1–8.8
≥ 10	49/10	8.7	4.1–18.5
German study ³³			
Not exposed	11/67	1.0	–
> 0–0.15	14/12	7.9	2.1–30.0
> 0.15–1.5	38/25	21.9	5.7–83.8
> 1.5–15	46/16	47.1	11.5–193
> 15	16/5	45.4	8.1–257
French study ²³ no. 2 (males only)			99% CI
Not exposed	28/327	1.0	–
> 0–0.1	54/181	4.0	1.9–8.3
> 0.1–1	68/121	8.3	3.8–17.7
> 1–10	115/68	22.5	10.4–48.7
> 10	97/27	67.0	25.6–175.1
Intensity of exposure	Cases/Controls	Odds ratio	95% CI
Spanish study ⁴²			
Not exposed	30/127	1.0	–
Low	35/70	3.35	1.72–6.52
Medium	25/18	9.96	4.38–22.7
High	22/6	27.1	9.28–79.3

Abbreviation: CI, confidence interval.

the development of mesothelioma in the group. For example, as shown in ►Table 1, in the two French and the German case-control studies, adding up to 1 fiber/mL-year of exposure to the lowest category of asbestos exposure elevates the exposed persons to the next higher category of asbestos exposure and doubles or triples the risk of malignant mesothelioma.^{23,32,33} Third, finding excess cancer risk at low levels of occupational exposure to asbestos supports the notion that there is no safe level of exposure to asbestos.

Low Level of Asbestos Exposure and Mesothelioma

It has long been known that relatively low doses of asbestos can cause malignant mesothelioma. Malignant mesotheliomas have been documented among neighborhood residents of asbestos-using factories^{34–36}; community residents of asbestos mining areas^{37,38} and household residents of asbestos workers, including peritoneal mesothelioma.^{34,39,40} Given the rarity of malignant mesothelioma in the population in the absence of asbestos exposure, these documented exposure-disease links demonstrated that asbestos exposure outside of the occupational environment causes malignant mesothelioma.

Magnani et al examined nonoccupational asbestos exposure in a case-control study of pleural mesothelioma in Italy, Spain, and Switzerland.⁴¹ They found an odds ratio (OR) of 4.8 (95% confidence interval [CI]: 1.8–13.1) for domestic exposure to asbestos and an OR of 11.5 (95% CI: 3.5–38.2) for neighborhood exposure to asbestos, that is, living within 2,000 m from an asbestos-using facility.⁴¹ There also was a clear dose-response relationship between environmental and domestic exposure to asbestos and mesothelioma.

Recent studies have provided a more quantitative evaluation of the risk of malignant mesothelioma at lower levels of exposures in occupational settings (►Table 1).^{23,32,33,42,43} These studies employed job histories and industrial hygiene expert assessments of the level, timing, and likelihood of asbestos exposures by occupation and industry. Iwatsubo and colleagues queried 405 cases of malignant mesothelioma in a French case-control study between 1987 and 1993 and found that cumulative asbestos exposure of 0.5 to 0.99 fiber/mL-year, even if the exposure was intermittent, was associated with an OR of 4.2 (95% CI: 2.0–8.8). Higher doses led to higher risks.³² Rödelberger et al performed a case-control study in Germany with 125 male cases of malignant mesothelioma and found an OR of 7.9 (95% CI: 2.1–30.0) and 21.9 (95% CI: 5.7–83.8) among the groups with up to 0.15 fiber/mL-year and between >0.15 and 1.5 fiber/mL-year, respectively.³³ In a second French national population case-control study of pleural malignant mesothelioma, Lacourt et al found that cumulative exposure to asbestos among men below 0.1 fiber/mL-year was associated with an OR of 4.0 (99% CI: 1.9–8.3), which doubled to an OR of 8.3 (99% CI: 3.8–17.7) for cumulative exposure >0.1 to 1.0 fiber/mL-year.²³ They also found a clear dose-response relationship between exposure to asbestos and malignant mesothelioma. Offermans et al (not shown in ►Table 1), using an established Finnish job-exposure matrix in a large Netherland cohort study, found a relative risk (hazards ratio) of 2.7 (95% CI: 1.6–4.5) for the group with

the lowest level of asbestos exposure (median cumulative exposure = 0.2 fiber/mL-year).⁴³ Agudo et al studied 132 cases of pleural mesothelioma in Spain in a case-control study and found that “low-intensity” occupational exposure was associated with an OR of 3.4 (95% CI: 1.7–6.5).⁴²

To place these levels of asbestos exposure in perspective, the current legal 8-hour permissible exposure level to asbestos in the United States and the United Kingdom is 0.1 fiber/mL air.^{18,44,45} A 45-year working career at this level yields a cumulative exposure to asbestos of 4.5 fiber/mL-year. Both Occupational Safety and Health Administration (OSHA) and the Health and Safety Executive of the United Kingdom assert that the regulated level is not safe. Indeed, OSHA estimates that 2 to 3 excess chest cancers per 1,000 workers exposed at 0.1 fiber/mL for 45 years will occur.⁴⁵ Both agencies mandate work practices and engineering controls that effectively lower the exposure to asbestos for workers.

Chrysotile as a Cause of Malignant Mesothelioma

There is a broad consensus that chrysotile asbestos causes human malignant mesothelioma.^{16–18,46–48} This causal relation is important not only for the scientific understanding of fiber toxicology but also for its relevance to prevention, public health, public policy, and compensation for people who have developed malignant mesothelioma. First, banning all use of asbestos, including chrysotile, has been adopted by 55 countries and is widely supported.^{47,49} However, chrysotile asbestos remains in use and is the only type of asbestos that is still mined and formulated into new products, almost exclusively in industrializing countries. Until a global ban is achieved, countries, enterprises, and workers who continue to use chrysotile asbestos must have an unqualified understanding that they use a known human carcinogen and must be protected from exposure. Second, 95% of asbestos that has been used in the United States, and much of the asbestos that was used in other countries, has been chrysotile asbestos, and much of this asbestos remains in buildings and equipment, thereby posing a current and future hazard to a broad range of occupations that repair, maintain, renovate, and demolish those buildings and equipment. Third, to the extent that compensation proceedings attempt to attribute mesothelioma risk to different products or asbestos fiber types, the recognition that chrysotile asbestos causes malignant mesothelioma is an essential element in decision making.

The scientific basis for the mesothelial carcinogenicity of chrysotile is an established body of published epidemiological studies, animal carcinogen assays, and pleural fiber burden studies. These have been reviewed elsewhere.^{16,17,19,21,47,50}

Epidemiological studies have shown that malignant mesothelioma has developed among a variety of workers whose exclusive or near-exclusive exposure to asbestos was to chrysotile asbestos. Examples include the Quebec chrysotile miners and millers (33 cases of malignant mesothelioma)⁵¹; workers who were active at the chrysotile mines in Balangero, Italy, or used the mine products (17 cases of malignant mesothelioma)³⁸; textile workers at North Carolina textile plants (8 cases of mesothelioma and pleural cancer)⁵²; textile workers at a South Carolina plant (3 malignant

mesothelioma)⁵³; railroad machinists (14 malignant mesotheliomas)⁵⁴; and workers in a friction products plant (6 cases of malignant mesothelioma).^{55,56} In addition, malignant mesothelioma has been associated in neighborhood or household settings with levels of exposure to chrysotile that are generally less than those seen in companion occupational environments, including seven cases of malignant mesothelioma among Quebec residents in mining areas³⁷ and five cases following household or environmental exposure to chrysotile in relation to the Balangero mine.³⁸

The availability of airborne asbestos measurements and mesothelioma mortality data in a limited number of asbestos cohorts has permitted the estimation of mesothelioma risk per unit dose, usually measured in fiber/mL-year. Aggregation of these studies^{19,20} and meta-analyses⁵⁷ have been performed to identify sources and levels of variation in risk by industry type and by fiber type. Per unit dose, crocidolite exposure is associated with a higher risk of mesothelioma than chrysotile. Amosite also appears to be associated with a somewhat higher risk of mesothelioma than chrysotile though less so than crocidolite. Nicholson estimates that crocidolite is 4 to 10 times more potent than chrysotile and that chrysotile and amosite are roughly equipotent.²⁰ In an analysis published in 2000, Hodgson and Darnton⁵⁷ used a different measure of risk and found a potency ratio for crocidolite:amosite:chrysotile of 500:100:1. However, recent studies^{52,58} have raised doubts and led to revisions in the estimates developed by Hodgson and Darnton. A new study of mortality at three North Carolina textile plants⁵² caused Hodgson and Darnton to revise their fiber potency ratios for malignant mesothelioma downwards sevenfold to 70:14:1 for crocidolite:amosite:chrysotile.⁵⁸ Additional studies^{38,56} have updated the mortality experience of two of the chrysotile asbestos cohorts originally studied by Hodgson and Darnton but have not yet been addressed in a revised meta-analysis. Both of these studies have described additional mesothelioma deaths in their respective cohorts. These include (1) an update of the chrysotile miner cohort in Balangero, Italy, where 14 workers active in mine operations and an additional 13 other exposed individuals have developed malignant mesothelioma,³⁸ and (2) an update of mesothelioma cases in the Connecticut friction product plant, where additional cases of malignant mesothelioma have been documented.⁵⁶

Two outstanding considerations—one scientific and the other practical—color the reliability and significance of putative differences in fiber-specific potency in causing malignant mesothelioma. First, the difficulties in ascertaining mesothelioma deaths over the relevant decades and the highly variable quality in exposure assessments in different study settings temper the validity of study results to form the basis of risk estimates. Many of the relevant individual study exposure assessments have been found to be lacking for numerous reasons: (1) restriction of fibers counted by phase contrast microscopy to fibers $\geq 5 \mu\text{m}$ in length and $>0.25 \mu\text{m}$ in width, thereby failing to count the majority of chrysotile fibers; (2) variation in counts by different phase contrast microscopes; (3) variation in counting methods between

laboratories and over time; (4) use of area samples to characterize personal exposures; (5) absence of, or a limited number of, measurements from selected periods in the history of the study site; (6) incomplete work histories; and (7) uncertain and variable conversion of fiber counts from one method (e.g., midjet impinger-based dust particle counts in millions of particles per cubic foot) to another (fiber counts by phase contrast microscopy).^{8,59,60} Such limitations formed an important basis for the U.S. Environmental Protection Agency (EPA) to reject a proposed update of asbestos risk assessment in 2008.⁶¹ The International Agency for Research on Cancer recently reviewed this issue and concluded that “there is a high degree of uncertainty concerning the accuracy of the relative potency estimates ... because of the severe potential for exposure misclassification in these studies” (p. 239).¹⁶

The other relevant consideration to the relative importance of fiber type for public health is the quantity of different fiber types used. In the United States, 95% of asbestos used in the 20th century was chrysotile, so that for the majority of workers who worked with or near asbestos, chrysotile was, and still remains, the dominant fiber type to which they were exposed. At present, chrysotile is the exclusive or near exclusive fiber mined and used in new products throughout the world, so its potency in causing mesothelioma relative to other asbestos fiber types becomes less relevant.

Rat inhalation and intrapleural injection studies have compared mesothelioma tumor production in response to exposure to the different types of asbestos.¹⁶ Rat inhalation studies show relatively low percentages of animals developing mesotheliomas, but the highest percentage of mesotheliomas was found in animals exposed to chrysotile. Wagner found 2.9% of chrysotile-exposed animals developed mesotheliomas versus 0.7 to 2.8% among the animals exposed to various amphiboles.⁶² Davis et al also found mesotheliomas among rats exposed to chrysotile in inhalation studies, though fiber length confounded the findings.⁶³ Intrapleural and intraperitoneal injection studies in different strains of rats show high proportions of tested animals developing mesotheliomas in response to various types of asbestos, including chrysotile.¹⁶

Fiber burden studies characterize the concentrations of fibers in tissues. Because they are performed on tissues obtained at the time of biopsy, surgery, or autopsy, they characterize fiber concentrations after the tumor has been clinically detected. This presents a challenge for causal inference, as the critical events that caused neoplastic transformation are believed to have occurred many years previously, when the profile of fiber concentration in relevant tissues may have been quite different. Additional constraints of this approach include (1) the absence of a widely used and accepted standard method for conducting tissue fiber counts; (2) the restriction of fiber burden studies to a limited number of individuals who may not be representative of defined asbestos-exposed populations; (3) the use of different microscopes (phase contrast microscopy, scanning electron microscopy, and transmission electron microscopy [TEM]) at varying magnifications that can detect and count different populations of fibers; (4) ranges of “normal” fiber counts in

populations without known occupational exposure to asbestos that vary from one laboratory to the next; and (5) the difficulty of inferring from an organ or tissue where a fiber burden study is performed to the organ or tissue where the disease occurs.^{64–66} This last issue applies to the relevance of lung fiber burden counts to the occurrence of malignant mesothelioma.

Multiple studies have found a dominance of chrysotile fibers, and sometimes exclusively chrysotile fibers, in pleural tissue and in pleural mesothelioma tissue.^{67–69} Sebastien et al reported finding mostly short chrysotile fibers ($84\% \leq 4 \mu\text{m}$ in length) in parietal pleura from a mixture of cases with nonmalignant and malignant asbestos-related diseases.⁶⁷ Suzuki and Yuen⁶⁹ used TEM to measure lung fiber burden in lung, plaque, and mesothelioma tissue in 168 cases of malignant mesothelioma and found that chrysotile was the sole asbestos type found in the mesothelioma tumor tissue in 73% (90/123) of mesothelioma cases and in the lung in 26% (31/119) of mesothelioma cases. Only 1% of chrysotile fibers were $\geq 5 \mu\text{m}$ in length.⁶⁹

Lung Cancer

Asbestos is universally recognized as a human lung carcinogen.^{2,16,17} Like malignant mesothelioma, all of the major asbestos fiber types—chrysotile, crocidolite, amosite, tremolite, actinolite, and anthophyllite—are established as causing lung cancer, based on the cumulative scientific evidence provided by animal experiments, epidemiologic and pathologic studies, and mechanism-based research.^{16,17}

The International Agency for Research on Cancer and others have recently reviewed over 60 epidemiologic studies that examined the relation between occupational exposure to asbestos and lung cancer.^{9,16,70} Most studies showed excess risk of lung cancer from asbestos exposure. The considerable differences in the level of excess risk of lung cancer among different epidemiological studies vary according to a large number factors, including study methods, data quality, reference populations, age structure of study population, country, occupation, industry, industrial process, job tasks, calendar years, exposure intensity and duration, fiber type, fiber dimensions, smoking information, the presence of other lung carcinogens, and others. The best studied contrast in lung cancer risk in different exposure settings is between the Quebec mines and mills,⁷¹ where excess lung cancer risk is modest, and the textile factory in South Carolina,⁵³ where the risk of lung cancer is much higher. Notably, in both settings, Canadian chrysotile asbestos was used.

Dose–Response: Asbestos Exposure and Lung Cancer

Lung cancer risk increases with cumulative exposure to asbestos.^{8,48,60,70,72} Studies of sufficient size and with quantitative exposure assessments have permitted estimation of lung cancer risk at different levels of exposure to asbestos. The slope of the resultant line that characterizes the relationship between exposure and lung cancer represents the potency of asbestos to cause lung cancer for a particular study (K_L in the published literature). These studies have principally been of

cohorts in asbestos textile, cement and friction products manufacturing, insulation, and mining and milling. In general, the increase in lung cancer relative risk has been found to be from 1 to 4% for each year of exposure to 1 fiber/mL (i.e., fiber/mL-year).⁷⁰ The exposure–response relationship is considered to be approximately linear.^{8,70} Indeed, available meta-analyses generally assume a linear dose–response relationship between asbestos exposure and lung cancer.^{57,60,70,72} Most individual studies to date have involved relatively heavy exposure to asbestos, and the lung cancer risk at lower levels is then extrapolated from these studies, or is based on the relatively few studies of lower level exposure to asbestos.⁷² A recent meta-analysis that was based on a nonlinear metaregression model (i.e., a natural spline model) used all available published data on exposure–response relationships at lower levels of asbestos exposure, thereby obviating the need to depend solely on extrapolating from high level exposure results.⁷² The results demonstrated a higher level of lung cancer risk increment per fiber/mL-year for relatively low levels of asbestos exposure compared with previous meta-analyses.⁷²

As noted in the previous section on malignant mesothelioma, a critical source of variation and error in evaluating exposure–response relationships in asbestos is the validity of exposure estimates of the relevant studies. These limitations introduce measurement error, which often leads to the underestimation of relative risk. Importantly, Lenters et al found higher estimates of lung cancer risk due to asbestos in studies that had higher quality exposure assessments, which is likely to explain some of the variability in results among studies.⁶⁰

Role of Asbestosis in Lung Cancer Risk

The relationship between asbestos exposure, asbestosis, and lung cancer risk has long been studied and is complicated, mainly because the risk and intensity of asbestosis increases with increasing asbestos exposure and because study information on the three key lung cancer risk factors—asbestos exposure, asbestosis, and smoking—is incomplete or imprecise in many studies. Nonetheless, it is clear that asbestos exposure in the absence of evidence of asbestosis raises the risk of lung cancer, and the added presence of asbestosis further raises the lung cancer risk.

Asbestos exposure in the absence of asbestosis increases the risk of lung cancer among a variety of different asbestos workers, as supported by a substantial published literature.^{73–81} The range of elevation in lung cancer risk in these studies is approximately 1.5 to 5.5. In a recent update of the mortality of a large North American insulator cohort, Markowitz et al compared long-term insulators to a blue collar control group without asbestos exposure that was part of the Cancer Prevention Study II of the American Cancer Society.⁸¹ They found a lung cancer mortality rate ratio of 3.6 (95% CI: 1.7–7.6) among long-term insulators who had never smoked and had no radiographic evidence of asbestosis compared with the blue collar controls.⁸¹

Asbestosis, usually documented by chest imaging studies, increases the risk of lung cancer, as seen in cohort studies of

asbestos cement workers,⁷⁴ asbestos textile workers,⁷⁶ and asbestos miners.^{77,82} The range of elevations in the standardized mortality ratios for lung cancer was 194 to 996; these elevations were statistically significant. Control for cigarette smoking was rare in these studies, but the magnitude of elevation in lung cancer risk is highly unlikely to have been caused by cigarette smoking alone.⁸³ In the study noted earlier, Markowitz et al found a doubling of risk of lung cancer among long-term insulators with asbestosis compared with insulators without asbestosis, both among never smokers and smokers. The duration and extent of asbestos exposure was similar among the insulators with and without asbestosis; therefore, the difference in lung cancer risk between the two groups was not likely to be due to differences in asbestos exposure.⁸¹

Lung Cancer among Asbestos-Exposed Nonsmokers

Asbestos exposure alone, in the absence of cigarette smoking, causes lung cancer. Hammond et al identified a fivefold increase in lung cancer mortality rate ratio among nonsmoking long-term insulators in their study of 17,800 insulators.⁸⁴ Soon thereafter, McDonald and colleagues reported a dose-related increase in lung cancer deaths among nonsmoker Quebec miners and millers.⁸⁵ Berry et al identified mortality among 1,670 asbestos factory workers between 1971 and 1980 and found a relative risk of lung cancer of 7.3, based on 4 lung cancers, among never smokers.⁸⁶ Wang et al followed 577 chrysotile asbestos manufacturing workers and 435 blue collar controls from 1972 to 2008 and found an overall age-adjusted lung cancer hazard ratio of 7.5 (95% CI: 0.9–62.8) among nonsmoker workers.⁸⁷ In one of the largest relevant studies, Markowitz followed 2,377 insulators from 1981 to 2008 and found a lung cancer mortality rate ratio of 5.2 (95% CI: 3.2–8.5) among nonsmokers, based on 18 lung cancer deaths among nonsmokers.⁸¹

Joint Effect of Asbestos Exposure and Cigarette Smoking in Lung Cancer

The joint effect of asbestos and cigarette smoking in causing lung cancer is widely cited in epidemiology and public health as a classic example of interaction between causes. The best known study of this topic is that published by Hammond et al, who found a multiplicative effect between the asbestos exposure and smoking in elevating lung cancer mortality among 17,800 insulators whose deaths occurred in 1967 to 1976, compared with a blue collar cohort from the Cancer Prevention Study I of the American Cancer Society followed over the same time period. Insulators who had never smoked had a lung cancer death rate ratio of 5.2, compared with the never-smoking control group. The lung cancer mortality ratio in the smoking control group without asbestos exposure was 10.9, and the lung cancer mortality ratio among smoking insulators was 53. The joint effect of asbestos and smoking was multiplicative.⁸⁴

At least two dozen published studies have addressed the issue of the relation between smoking and asbestos exposure in elevating lung cancer risk.^{88–90} Viewed in aggregate, the existing literature favors a joint effect of asbestos and smok-

ing that is synergistic, and, more specifically, greater than additive but probably less than multiplicative.^{70,88,90} Some studies, however, have found a joint multiplicative effect. Central to the difficulty in studying this issue is the dearth of lung cancers among never smokers, including among asbestos-exposed workers, especially among smaller studies.

Recent studies tend to confirm that the joint effect of asbestos and smoking is more than additive but less than multiplicative. Wang et al followed 577 chrysotile asbestos manufacturing workers and 435 blue collar controls in China from 1972 to 2008. Among nonsmoking workers exposed to asbestos, the hazard ratio for lung cancer was 7.5 (95% CI: 0.9–62.8).⁸⁷ Smokers from a non-asbestos-exposed control group had a lung cancer hazard ratio of 6.0. The asbestos workers who smoked had a lung cancer hazard ratio of 17.4, indicating a supra-additive effect of asbestos and smoking, though the effect did not reach statistical significance.⁸⁷ Offermans and colleagues studied >120,000 people in the Netherlands Cohort Study and found a lung cancer hazard ratio of 1.79 (95% CI: 1.04–3.08) among never smokers who had a history of asbestos exposure. The corresponding hazard ratio among current smokers never exposed to asbestos was 7.48 (95% CI: 5.55–10.08). The joint hazard ratio was 10.21 (95% CI: 7.26–14.35), suggesting a joint effect that was midway between additive and multiplicative.⁴³ Reid et al also found a supra-additive effect among Wittenoom miners and millers in Australia.⁹¹

The source of some of the variation in the empirical studies of the joint effect of asbestos and smoking in causing lung cancer has recently been clarified. Markowitz et al described mortality patterns from 1981 through 2008 for 2,377 North American insulators for whom information on smoking, asbestos exposure, and radiographic findings of asbestosis were available.⁸¹ The study had a relatively high number of lung cancer deaths among asbestos-exposed workers who had never smoked ($n = 18$). They found that the lung cancer rate ratio was 3.6 (95% CI: 1.7–7.6) for nonsmoking insulators without asbestosis; 10.3 (95% CI: 8.8–12.2) among the smoking control group; and 14.4 (95% CI: 10.7–19.4) among insulators who had smoked but had no asbestosis. Among nonsmoking insulators with asbestosis, the lung cancer mortality rate ratio was 7.4 (95% CI: 4.0–13.7); 10.3 (95% CI: 8.8–12.2) among the smoking control group; and 36.8 (95% CI: 30.1–45.0) among insulators who had smoked but also had asbestosis.⁸¹

Smoking Cessation and Lung Cancer Risk

The issue of what happens to lung cancer risk when asbestos-exposed workers stop smoking is not only of obvious public health importance but also of scientific interest, given the facts that lung cancer risk increases with time following asbestos exposure but decreases with time following smoking cessation. Reid et al followed 2,935 Australian miners and millers from 1979 to 2002 and found that lung cancer risk generally diminished following smoking cessation but may remain elevated with an OR of 1.9 (95% CI: 0.50–7.2) in subjects ≥ 20 years since quitting smoking.⁹¹ Frost et al examined lung cancer mortality among 98,912 asbestos

workers in Great Britain between 1971 and 2005 and found that lung cancer mortality reduced following smoking cessation but remained possibly elevated ≥ 40 years following smoking cessation (relative risk = 1.5, 95% CI: 0.8–2.8).⁹² Markowitz and colleagues traced mortality among 2,377 insulators from 1981 to 2008, including the nearly 60% of smoking insulators who had quit smoking. They found that lung cancer rate ratios dropped by one-half during the first 10 years following smoking cessation and continued to decrease thereafter. Former smoking insulators with ≥ 30 years following cessation had the same lung cancer risk as insulators who had never smoked cigarettes.⁸¹

Fiber Type and Lung Cancer Risk

Chrysotile asbestos causes lung cancer, as supported by a large body of published epidemiological studies, animal carcinogen assays, and mechanistic studies. These studies have been reviewed.^{16,17,19,21,50,70}

Recent examples of excess lung cancer mortality among workers exposed to chrysotile asbestos are multiple. Wang et al followed 577 chrysotile asbestos manufacturing workers and 435 blue collar controls from 1972 to 2008 in China and found an age- and smoking-adjusted overall hazard ratio of 3.31 (95% CI: 1.60–6.87) for lung cancer among asbestos-exposed workers.⁸⁷ Loomis and colleagues identified mortality patterns among workers at four North Carolina textile plants that used almost exclusively chrysotile asbestos and found a standardized mortality ratio (SMR) of 1.96 (95% CI: 1.73–2.20); 277 workers had died from cancer of the lung or trachea.⁵² Hein et al updated the mortality of the South Carolina textile factory cohort where $> 99.9\%$ of the asbestos used was chrysotile and found a lung cancer standardized mortality ratio of 1.95 (95% CI: 1.68–2.24).⁵³

As in the case of malignant mesothelioma, the relative potency of different types of asbestos in causing lung cancer has been evaluated. Some meta-analyses of asbestos exposure and lung cancer studies have shown an increased potency for amphiboles relative to chrysotile in causing lung cancer by approximately 5- to 10-fold.^{57,93} A more recent meta-analysis that used a different meta-regression modeling method found a nonsignificant three- to fourfold difference in potencies between chrysotile and amphiboles.⁷² A recent meta-analysis that factored in quality of exposure assessments of included studies concluded that potency differences among fiber types narrowed after taking into account quality of exposure assessment and that potency differences were inconclusive when analysis was restricted to studies with higher quality exposure assessments.⁶⁰

In a recent systematic review, Nielsen et al (2014) evaluated existing studies and concluded that “all types of asbestos fibers are associated with lung cancer (and) there is not sufficient evidence to derive different risk estimates for different fiber types (p. 199).”⁷⁰

Fiber Dimension and Lung Cancer Risk

For several decades, animal studies have supported the assertion that longer and thinner fibers ($> 8 \mu\text{m}$ in length and $\leq 0.25 \mu\text{m}$ in width), including asbestos fibers, are more

carcinogenic to lung and mesothelial tissues than shorter fibers. This has been called the “Stanton hypothesis.”⁹⁴ In studies that involved pleural implants in rats, Stanton and colleagues found that longer and thinner fibers (i.e., $> 8 \mu\text{m}$ in length and $\leq 0.25 \mu\text{m}$ in width) of a variety of different materials produced the highest correlation (correlation coefficient = 0.80) with probability of pleural tumors. However, shorter (5–8 μm) or wider (> 0.25 –1.5 μm) fibers were also reasonably correlated with tumor response (correlation coefficient = 0.63 and 0.68, respectively).^{94–96} A series of studies by Davis et al in the 1970s and 1980s addressed fiber length and types and concluded that fibers $> 10 \mu\text{m}$ in length were the more important ones in causing neoplastic responses in the lungs of rats.^{97,98} Lippmann recently reviewed these and other studies and concluded that, since fibers between 0.3 and 0.8 μm in width have peak retention in the lung, and, given that the human alveolar macrophage is larger than the rat macrophage, asbestos fibers > 15 or 20 μm in length and $> 0.15 \mu\text{m}$ in width are most closely associated with lung cancer.⁹⁹

Very few epidemiological studies of asbestos and lung cancer have addressed the full range of fiber lengths, because they have principally relied on asbestos measurements that only counted fibers $> 5 \mu\text{m}$ in length and $> 0.25 \mu\text{m}$ in width (so-called regulated fibers), as required by regulations and dictated by feasibility. Indeed, there are only two epidemiological studies of asbestos-exposed workers with sufficient measurements to allow insight on the issue of fiber length. These studies addressed fiber dimensions in textile mills in South and North Carolina, based on retrospective measurements of archived dust samples using TEM. Stayner et al and Dement et al reported that more than 90% of the asbestos fibers in these archived samples were short and/or narrow ($\leq 5 \mu\text{m}$ in length and/or $< 0.25 \mu\text{m}$ in width) and had not been counted by phase contrast microscopy in earlier studies.^{100,101} They reevaluated the relationship between TEM-based fiber measurements and lung cancer risk and concluded that the strongest association was found between lung cancer and fibers $> 10 \mu\text{m}$ and narrower than 0.25 μm .^{100,102} However, they also found that very short and thin fibers (e.g., $< 1.5 \mu\text{m}$ in length and $< 0.25 \mu\text{m}$ in width) were associated with lung cancer risk. Fiber size categories were highly correlated in the dust samples from the South Carolina and North Carolina chrysotile textile factories, making it difficult to separate out the effect of fiber sizes.^{100,102,103} Hamra et al applied a hierarchical model to the data from the North Carolina textile factory and found that the lung cancer risk associated with different fiber length-width groups was similar.¹⁰³

Lung fiber burden studies add limited insights on this issue. Dodson and colleagues used TEM at 16,000 or 20,000 times magnification to examine the lung asbestos fiber burdens of 20 cases of lung cancer with known exposure to asbestos. They showed that 39 to 69% of detected asbestos fibers were $\leq 5 \mu\text{m}$, and that the majority of both chrysotile and amphibole fibers would not have been counted by phase contrast microscopy (i.e., $> 5 \mu\text{m}$ in length and $\geq 0.25 \mu\text{m}$ in width). Most counted fibers did not meet the dimensions

supported by the Stanton hypothesis ($\geq 8 \mu\text{m}$ in length and $< 25 \mu\text{m}$ in width) with chrysotile having the highest proportion of such fibers.¹⁰⁴ More recently, Adib and colleagues in Quebec used TEM to evaluate lung fiber burdens in cases of lung cancer, asbestosis, and mesothelioma among 123 workers from mining, maintenance, construction, and other industries.¹⁰⁵ Among lung cancer cases, chrysotile and tremolite, especially fibers $< 5 \mu\text{m}$, were the dominant fibers seen in the lungs. Among the subset of 13 lung cancer cases whose last exposure to asbestos was 30 or more years previously, chrysotile fibers were found in all cases, with short ($< 5 \mu\text{m}$) fibers outnumbering longer ($\geq 5 \mu\text{m}$) by at least two- to threefold. Clearly, chrysotile fibers, especially short fibers, are capable of remaining in the lungs for long periods following exposure.

In summary, available data support the hypothesis that longer, thinner fibers have a stronger association with lung cancer than shorter, less thin fibers. However, there are empirical data in animals and epidemiological studies that support an association between shorter fibers and cancer.^{94,102} Fiber burden studies show that short fibers, especially chrysotile, are very frequently present and often outnumber longer fibers in lung tissues of patients with a history of asbestos-related lung cancer, even many years after asbestos exposure ceased. Current evidence does not support the point of view that there is no cancer risk associated with exposure to short asbestos fibers.^{66,96,106}

“Low Level” or Short Duration of Asbestos Exposure and Lung Cancer Risk

Studies completed in the past 10 years or so have confirmed and extended knowledge that lower levels of occupational exposure to all types of asbestos, including chrysotile, cause lung cancer. Loomis and colleagues⁵² identified mortality patterns among workers at four North Carolina textile plants that used almost exclusively chrysotile asbestos and found an overall SMR of 1.96 (95% CI: 1.73–2.20); 277 workers had died from cancer of the lung or trachea. Among workers who worked for < 1 year and 1 to 5 years, the SMR was 1.82 (95% CI: 1.50–2.19) and 1.86 (95% CI: 1.45–2.34), respectively. Hein and others evaluated mortality among 3,072 workers at a South Carolina textile factory that used chrysotile asbestos and found an elevated SMR (1.54, 95% CI: 1.07–2.15) for workers with < 1.5 fiber/mL-year cumulative exposure; there was a clear trend of increasing lung cancer risk with increasing exposure.⁵³ Pira et al followed up 1,973 Italian textile workers exposed to mixed fiber types from 1946 to 1996 and found an overall SMR of 282 (95% CI: 222–354) for lung cancer. Lung cancer risk rose with duration of employment from SMR = 139 (based on 12 lung cancer deaths) among workers who worked < 1 year at the plant to a SMR = 250.8 among workers who worked 1 to < 5 years at the plant, to a SMR = 530.9 among workers of > 10 years work at the plant.¹⁰⁷ Wang and colleagues evaluated nearly four decades of mortality among 1,012 chrysotile asbestos manufacturing workers in China and found that the group with “low level” exposure to asbestos had a hazard ratio of 1.94 (95% CI: 0.84–4.46) with a statistically significant trend

of lung cancer risk with increasing exposure.⁸⁷ De Matteis et al studied 1,537 lung cancer cases from the general population in a Northern Italian case-control study and found a lung cancer OR of 1.76 (95% CI: 1.42–2.18) among those deemed to have low exposure to asbestos.¹⁰⁸ Gustavsson et al performed a population-based case-control study of 1,038 lung cancer cases in Stockholm, controlling for cigarette smoking, and found an OR of 1.90 (95% CI: 1.32–2.74) for cumulative exposure to asbestos of 4 fiber/mL-year of exposure to asbestos, and the risk on the lower end of the range of exposure was greater than that predicted by a linear dose-response relationship.¹⁰⁹ In an earlier study, Seidman et al studied amosite asbestos manufacturing workers in New Jersey and found a 3-fold increase in lung cancer deaths among workers who worked less than 1 year in the plant, which rose to 5.6-fold for workers who worked between 1 and 2 years, and 6.5-fold for workers who worked over 2 years.¹¹⁰

Threshold and Risk of Lung Cancer and Mesothelioma

The current consensus is that there is no known safe level of exposure to asbestos.^{3,18,70,72} Stated otherwise, no threshold has been demonstrated below which there is no identified risk of cancer related to asbestos. This view is based on several lines of evidence, specific and nonspecific to asbestos. Current risk assessment guidelines in the United States support linear extrapolation from the known dose-response curve to lower levels of exposure for DNA-reactive agents.¹¹¹ Although the exact mechanisms of asbestos carcinogenesis are not known at present, asbestos fibers, including chrysotile, are genotoxic and are, therefore, “DNA reactive.”^{16,112,113}

Studies of asbestos-exposed cohorts provide evidence that a threshold for cancer risk has not been established for asbestos. Stayner et al evaluated alternative exposure-response models using data from a South Carolina textile factory.¹¹⁴ The study of asbestos-related diseases at this South Carolina textile factory was judged to employ one of the highest quality exposure assessments available in the published literature on asbestos-related disease.⁶⁰ They found that the best model for lung cancer was linear on a multiplicative scale with the best data fit obtained when the threshold was set at zero. Referring to asbestos exposure, the authors concluded that “there was absolutely no significant evidence for a threshold in ...lung cancer.” In a recent meta-analysis, van der Bij et al used a variety of statistical models to examine the issue of lung cancer risk associated with relatively low exposure to asbestos and found that a natural spline model best fit the data.⁷² They note that no threshold for lung cancer risk due to asbestos exposure has been identified.⁷² In a recent systematic review of asbestos and lung cancer, Nielsen and colleagues report that most relevant meta-analyses have been predicated on linear dose-response relationship models, suggesting no exposure threshold for lung cancer risk.^{57,60,70,72} Nielsen et al concluded that there “is no evidence for a no observed effect level concerning asbestos-related lung cancer.”

Studies detailing the occurrence of malignant mesothelioma and lung cancer at low levels of asbestos exposure were described in previous sections.

Some have hypothesized that asbestos-related lung cancer occurs only in people with asbestosis, and, since the latter appears to have a threshold, a threshold also exists for asbestos-related lung cancer. However, epidemiological studies show that asbestos-related lung cancer occurs in the absence of asbestosis (see above section), undermining this hypothesis.

Mechanisms of Asbestos-Related Lung Cancer

Multiple mechanisms are likely to be involved in asbestos-related carcinogenesis. Excellent recent reviews are available.^{112,115,116} Asbestos causes a wide variety of cellular responses, and it is likely that several these responses relate to pathways that lead to cell transformation and cancer. Asbestos is mutagenic and genotoxic.^{113,115} Asbestos fibers provoke the formation of reactive oxygen species that lead to oxidation of DNA bases and DNA strand breaks^{16,112}; this is considered an indirect form of genotoxicity. In addition to causing oxidative stress, asbestos also alters several antioxidant pathways that restrain the cells' ability to limit damage caused by the reactive free radicals that produce oxidative stress.¹¹² Some of these cellular responses are also likely to underlie fibrogenesis. Asbestos may additionally interfere with DNA repair processes.

Asbestos directly interferes with mitosis during cell division, causing genetic damage in daughter cells.¹¹⁶ A variety of chromosomal abnormalities caused by asbestos fibers have been described.¹¹² An additional carcinogenic mechanism of asbestos is the absorption of other carcinogens on the fiber surface (e.g., polycyclic aromatic hydrocarbons), which may also help explain the joint interactive effect of asbestos and other exposures (e.g., smoking). Cell death (apoptosis), a mechanism to limit proliferation of transformed cells, is also altered by asbestos.

Screening for Asbestos-Related Lung Cancer

Japanese and American investigators demonstrated in the late 1990s that low-dose CT scanning could detect early-stage lung cancers in high-risk smokers.^{117,118} Henschke et al subsequently reported a 92% projected 10-year survival among 302 individuals with screen-detected Stage 1 lung cancer who underwent surgery.¹¹⁹ In 2011, the National Lung Screening Trial, a randomized controlled trial of more than 53,000 people conducted by the U.S. National Cancer Institute, was halted when data review indicated that the CT-screened arm had experienced a significant 20% lung cancer mortality reduction and a 6.7% overall mortality reduction compared with reference group who had received a chest radiograph.¹²⁰ Occupational risk of lung cancer was not a risk factor included in the studies.¹²⁰

In 2013, United States Preventive Services Task Force endorsed the use of this test for people who are at high

risk of lung cancer, though they used only smoking and age to define high risk.¹²¹ More recently, the National Comprehensive Cancer Network, a collaboration of many of the most prestigious cancer centers in the United States, recommended low-dose CT for people 50 years and older who had a 20- or more pack-year history of cigarette smoking and one additional risk for lung cancer, including occupational exposure to asbestos or selected other occupational lung carcinogens.¹²² The American Association of Thoracic Surgery has similar guidelines.¹²³

Use of low-dose CT scanning for early lung cancer detection offers an unprecedented opportunity to detect lung cancer at an early stage in asbestos-exposed workers and to prevent much of the excess lung cancer mortality that has been so well documented during the past 70 years. Occupational medicine physicians, pulmonary physicians, and other occupational health professionals have an essential role in educating, organizing, and promoting lung cancer screening for asbestos-exposed workers.

Disclosure

Dr. Markowitz has provided expert witnesses services in tort lawsuits involving issues of asbestos-related diseases.

References

- 1 Virta R. Asbestos: geology, mineralogy, mining, and uses: US geological survey. In: 2012 Minerals Yearbook; 2013
- 2 Asbestos: elimination of asbestos-related diseases fact sheet No. 343. World Health Organization Media Centre: 2014. World Health Organization. Available at: <http://www.who.int/media-centre/factsheets/fs343/en/>. (Accessed November 13, 2014)
- 3 World Health Organization Elimination of asbestos-related diseases: World Health Organization; 2006
- 4 Driscoll T, Nelson DI, Steenland K, et al. The global burden of disease due to occupational carcinogens. *Am J Ind Med* 2005; 48(6):419–431
- 5 Park EK, Takahashi K, Hoshuyama T, et al. Global magnitude of reported and unreported mesothelioma. *Environ Health Perspect* 2011;119(4):514–518
- 6 Robinson BM. Malignant pleural mesothelioma: an epidemiological perspective. *Ann Cardiothorac Surg* 2012;1(4):491–496
- 7 Rake C, Gilham C, Hatch J, Darnton A, Hodgson J, Peto J. Occupational, domestic and environmental mesothelioma risks in the British population: a case-control study. *Br J Cancer* 2009;100(7): 1175–1183
- 8 Henderson DW, Rödelsperger K, Woitowitz HJ, Leigh J. After Helsinki: a multidisciplinary review of the relationship between asbestos exposure and lung cancer, with emphasis on studies published during 1997–2004. *Pathology* 2004;36(6): 517–550
- 9 McCormack V, Peto J, Byrnes G, Straif K, Boffetta P. Estimating the asbestos-related lung cancer burden from mesothelioma mortality. *Br J Cancer* 2012;106(3):575–584
- 10 Brown T, Darnton A, Fortunato L, Rushton L; British Occupational Cancer Burden Study Group. Occupational cancer in Britain. Respiratory cancer sites: larynx, lung and mesothelioma. *Br J Cancer* 2012;107(Suppl 1):S56–S70
- 11 Boffetta P, Autier P, Boniol M, et al. An estimate of cancers attributable to occupational exposures in France. *J Occup Environ Med* 2010;52(4):399–406

- 12 Marinaccio A, Scarselli A, Binazzi A, Mastrantonio M, Ferrante P, Iavicoli S. Magnitude of asbestos-related lung cancer mortality in Italy. *Br J Cancer* 2008;99(1):173–175
- 13 Leigh J, Driscoll T. Malignant mesothelioma in Australia, 1945–2002. *Int J Occup Environ Health* 2003;9(3):206–217
- 14 Marinaccio A, Binazzi A, Di Marzio D, et al. Incidence of extrapleural malignant mesothelioma and asbestos exposure, from the Italian national register. *Occup Environ Med* 2010;67(11):760–765
- 15 Gemba K, Fujimoto N, Kato K, et al. National survey of malignant mesothelioma and asbestos exposure in Japan. *Cancer Sci* 2012;103(3):483–490
- 16 International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Volume 100C: Arsenic, Metals, Fibres and Dusts. WHO Press; 2012
- 17 National Toxicology Program. 13th Report on Carcinogens. 13: United States Department of Health and Human Services; 2014
- 18 National Institute of Occupational Safety and Health-Occupational Safety and Health Administration Work Group. Workplace Exposure to Asbestos: Review and Recommendations. 81–103: DHHS (NIOSH); 1980
- 19 Stayner LT, Dankovic DA, Lemen RA. Occupational exposure to chrysotile asbestos and cancer risk: a review of the amphibole hypothesis. *Am J Public Health* 1996;86(2):179–186
- 20 Nicholson WJ. The carcinogenicity of chrysotile asbestos—a review. *Ind Health* 2001;39(2):57–64
- 21 Lemen RA. Chrysotile asbestos as a cause of mesothelioma: application of the Hill causation model. *Int J Occup Environ Health* 2004;10(2):233–239
- 22 Kanarek MS. Mesothelioma from chrysotile asbestos: update. *Ann Epidemiol* 2011;21(9):688–697
- 23 Lacourt A, Gramond C, Audignon S, et al. Pleural mesothelioma and occupational coexposure to asbestos, mineral wool, and silica. *Am J Respir Crit Care Med* 2013;187(9):977–982
- 24 Rake C, Gilham C, Hatch J, Darnton A, Hodgson J, Peto J. Occupational, domestic and environmental mesothelioma risks in the British population: a case-control study. *Br J Cancer* 2009;100(7):1175–1183
- 25 Aguilar-Madrid G, Robles-Pérez E, Juárez-Pérez CA, Alvarado-Cabrero I, Rico-Méndez FG, Javier KG. Case-control study of pleural mesothelioma in workers with social security in Mexico. *Am J Ind Med* 2010;53(3):241–251
- 26 Baris I, Simonato L, Artvinli M, et al. Epidemiological and environmental evidence of the health effects of exposure to erionite fibres: a four-year study in the Cappadocian region of Turkey. *Int J Cancer* 1987;39(1):10–17
- 27 Paoletti L, Batisti D, Bruno C, et al. Unusually high incidence of malignant pleural mesothelioma in a town of eastern Sicily: an epidemiological and environmental study. *Arch Environ Health* 2000;55(6):392–398
- 28 Tward JD, Wendland MM, Shrieve DC, Szabo A, Gaffney DK. The risk of secondary malignancies over 30 years after the treatment of non-Hodgkin lymphoma. *Cancer* 2006;107(1):108–115
- 29 De Bruin ML, Burgers JA, Baas P, et al. Malignant mesothelioma after radiation treatment for Hodgkin lymphoma. *Blood* 2009;113(16):3679–3681
- 30 Hodgson DC, Gilbert ES, Dores GM, et al. Long-term solid cancer risk among 5-year survivors of Hodgkin's lymphoma. *J Clin Oncol* 2007;25(12):1489–1497
- 31 International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Malaria and Some Polyomaviruses (SV40, BK, JC, and Merkel Cell Viruses). 104: World Health Organization Press; 2013 (Monograph)
- 32 Iwatsubo Y, Pairon JC, Boutin C, et al. Pleural mesothelioma: dose-response relation at low levels of asbestos exposure in a French population-based case-control study. *Am J Epidemiol* 1998;148(2):133–142
- 33 Rödelisperger K, Jöckel KH, Pohlabeln H, Römer W, Weitowitz HJ. Asbestos and man-made vitreous fibers as risk factors for diffuse malignant mesothelioma: results from a German hospital-based case-control study. *Am J Ind Med* 2001;39(3):262–275
- 34 Newhouse ML, Thompson H. Mesothelioma of pleura and peritoneum following exposure to asbestos in the London area. *Br J Ind Med* 1965;22(4):261–269
- 35 Magnani C, Terracini B, Ivaldi C, Botta M, Mancini A, Andron A. Pleural malignant mesothelioma and non-occupational exposure to asbestos in Casale Monferrato, Italy. *Occup Environ Med* 1995;52(6):362–367
- 36 Greenberg M, Davies TA. Mesothelioma register 1967–68. *Br J Ind Med* 1974;31(2):91–104
- 37 Camus M, Siemiatycki J, Meek B. Nonoccupational exposure to chrysotile asbestos and the risk of lung cancer. *N Engl J Med* 1998;338(22):1565–1571
- 38 Mirabelli D, Calisti R, Barone-Adesi F, Fornero E, Merletti F, Magnani C. Excess of mesotheliomas after exposure to chrysotile in Balangero, Italy. *Occup Environ Med* 2008;65(12):815–819
- 39 Anderson HA, Lilis R, Daum SM, Fischbein AS, Selikoff IJ. Household-contact asbestos neoplastic risk. *Ann N Y Acad Sci* 1976;271:311–323
- 40 Vianna NJ, Polan AK. Non-occupational exposure to asbestos and malignant mesothelioma in females. *Lancet* 1978;1(8073):1061–1063
- 41 Magnani C, Agudo A, González CA, et al. Multicentric study on malignant pleural mesothelioma and non-occupational exposure to asbestos. *Br J Cancer* 2000;83(1):104–111
- 42 Agudo A, González CA, Bleda MJ, et al. Occupation and risk of malignant pleural mesothelioma: a case-control study in Spain. *Am J Ind Med* 2000;37(2):159–168
- 43 Offermans NS, Vermeulen R, Burdorf A, et al. Occupational asbestos exposure and risk of pleural mesothelioma, lung cancer, and laryngeal cancer in the prospective Netherlands cohort study. *J Occup Environ Med* 2014;56(1):6–19
- 44 United Kingdom Statutory Instruments. Control of Asbestos Regulations 2012. 2012:632
- 45 US Department of Labor Occupational Safety and Health Administration. Occupational Exposure to Asbestos; Final Rule. *Federal Register* 1994;59(153):40963–41162
- 46 Gibbs G, Pigg BJ, Nicholson WJ, et al. Chrysotile Asbestos. Environmental Health Criteria 203. Geneva: World Health Organization Press; 1998
- 47 Ramazzini C. Asbestos is still with us: repeat call for a universal ban. *Am J Ind Med* 2011;54(2):168–173
- 48 Helsinki Consensus. Asbestos, asbestosis, and cancer: the Helsinki criteria for diagnosis and attribution. *Scand J Work Environ Health* 1997;23(4):311–316
- 49 International Conference on Monitoring and Surveillance of Asbestos-Related Diseases. The Helsinki Declaration on Management and Elimination of Asbestos-Related Diseases. Espoo, Finland: Finnish Institute of Occupational Health; 2014
- 50 Smith AH, Wright CC. Chrysotile asbestos is the main cause of pleural mesothelioma. *Am J Ind Med* 1996;30(3):252–266
- 51 McDonald AD, Case BW, Churg A, et al. Mesothelioma in Quebec chrysotile miners and millers: epidemiology and aetiology. *Ann Occup Hyg* 1997;41(6):707–719
- 52 Loomis D, Dement JM, Wolf SH, Richardson DB. Lung cancer mortality and fibre exposures among North Carolina asbestos textile workers. *Occup Environ Med* 2009;66(8):535–542
- 53 Hein MJ, Stayner LT, Lehman E, Dement JM. Follow-up study of chrysotile textile workers: cohort mortality and exposure-response. *Occup Environ Med* 2007;64(9):616–625
- 54 Mancuso TF. Relative risk of mesothelioma among railroad machinists exposed to chrysotile. *Am J Ind Med* 1988;13(6):639–657
- 55 Teta MJ, Lewinsohn HC, Meigs JW, Vidone RA, Mowad LZ, Flannery JT. Mesothelioma in Connecticut, 1955–1977.

- Occupational and geographic associations. *J Occup Med* 1983; 25(10):749–756
- 56 Finkelstein MM, Meisenkothen C. Malignant mesothelioma among employees of a Connecticut factory that manufactured friction materials using chrysotile asbestos. *Ann Occup Hyg* 2010; 54(6):692–696
 - 57 Hodgson JT, Darnton A. The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure. *Ann Occup Hyg* 2000;44(8):565–601
 - 58 Hodgson JT, Darnton A. Mesothelioma risk from chrysotile. *Occup Environ Med* 2010;67(6):432
 - 59 Silverstein MA, Welch LS, Lemen R. Developments in asbestos cancer risk assessment. *Am J Ind Med* 2009;52(11):850–858
 - 60 Lenters V, Vermeulen R, Dogger S, et al. A meta-analysis of asbestos and lung cancer: is better quality exposure assessment associated with steeper slopes of the exposure-response relationships? *Environ Health Perspect* 2011;119(11):1547–1555
 - 61 Johnson S. Letter from Stephen L. Johnson, EPA Administrator to Dr. Agnes Kane, Chair of Science Advisory Board Asbestos Committee; 2008
 - 62 Wagner JC, Berry G, Skidmore JW, Timbrell V. The effects of the inhalation of asbestos in rats. *Br J Cancer* 1974;29(3):252–269
 - 63 Davis JM, Jones AD. Comparisons of the pathogenicity of long and short fibres of chrysotile asbestos in rats. *Br J Exp Pathol* 1988; 69(5):717–737
 - 64 Baker DB. Limitations in drawing etiologic inferences based on measurement of asbestos fibers from lung tissue. *Ann N Y Acad Sci* 1991;643:61–70
 - 65 Dodson RF, Atkinson MA. Measurements of asbestos burden in tissues. *Ann N Y Acad Sci* 2006;1076:281–291
 - 66 Dodson RF. Analysis and relevance of asbestos burden in tissue. In: Dodson R, Hammar S, eds. *Asbestos: Risk assessment, Epidemiology, and Health Effects*. 2nd ed. CRC Press; 2011:647
 - 67 Sebastien P, Janson X, Gaudichet A, Hirsch A, Bignon J. Asbestos retention in human respiratory tissues: comparative measurements in lung parenchyma and in parietal pleura. *IARC Sci Publ* 1980;(30):237–246
 - 68 Kohyama N, Suzuki Y. Analysis of asbestos fibers in lung parenchyma, pleural plaques, and mesothelioma tissues of North American insulation workers. *Ann N Y Acad Sci* 1991;643:27–52
 - 69 Suzuki Y, Yuen SR. Asbestos fibers contributing to the induction of human malignant mesothelioma. *Ann N Y Acad Sci* 2002; 982:160–176
 - 70 Nielsen LS, Bælum J, Rasmussen J, et al. Occupational asbestos exposure and lung cancer—a systematic review of the literature. *Arch Environ Occup Health* 2014;69(4):191–206
 - 71 Liddell FD, McDonald AD, McDonald JC. The 1891–1920 birth cohort of Quebec chrysotile miners and millers: development from 1904 and mortality to 1992. *Ann Occup Hyg* 1997;41(1): 13–36
 - 72 van der Bij S, Koffijberg H, Lenters V, et al. Lung cancer risk at low cumulative asbestos exposure: meta-regression of the exposure-response relationship. *Cancer Causes Control* 2013;24(1):1–12
 - 73 Liddell FD, McDonald JC. Radiological findings as predictors of mortality in Quebec asbestos workers. *Br J Ind Med* 1980;37(3): 257–267
 - 74 Finkelstein MM. Radiographic asbestosis is not a prerequisite for asbestos-associated lung cancer in Ontario asbestos-cement workers. *Am J Ind Med* 1997;32(4):341–348
 - 75 Fletcher DE. A mortality study of shipyard workers with pleural plaques. *Br J Ind Med* 1972;29(2):142–145
 - 76 Cheng WN, Kong J. A retrospective mortality cohort study of chrysotile asbestos products workers in Tianjin 1972–1987. *Environ Res* 1992;59(1):271–278
 - 77 Reid A, de Klerk N, Ambrosini GL, et al. The effect of asbestosis on lung cancer risk beyond the dose related effect of asbestos alone. *Occup Environ Med* 2005;62(12):885–889
 - 78 Martischinig KM, Newell DJ, Barnsley WC, Cowan WK, Feinmann EL, Oliver E. Unsuspected exposure to asbestos and bronchogenic carcinoma. *BMJ* 1977;1(6063):746–749
 - 79 Wilkinson P, Hansell DM, Janssens J, et al. Is lung cancer associated with asbestos exposure when there are no small opacities on the chest radiograph? *Lancet* 1995;345(8957):1074–1078
 - 80 Karjalainen A, Anttila S, Vanhala E, Vainio H. Asbestos exposure and the risk of lung cancer in a general urban population. *Scand J Work Environ Health* 1994;20(4):243–250
 - 81 Markowitz SB, Levin SM, Miller A, Morabia A. Asbestos, asbestosis, smoking, and lung cancer. New findings from the North American insulator cohort. *Am J Respir Crit Care Med* 2013; 188(1):90–96
 - 82 Sluis-Cremer GK, Hessel PA, Hnizdo E. Factors influencing the reading of small irregular opacities in a radiological survey of asbestos miners in South Africa. *Arch Environ Health* 1989;44(4): 237–243
 - 83 Axelsson O, Steenland K. Indirect methods of assessing the effects of tobacco use in occupational studies. *Am J Ind Med* 1988;13(1): 105–118
 - 84 Hammond EC, Selikoff IJ, Seidman H. Asbestos exposure, cigarette smoking and death rates. *Ann N Y Acad Sci* 1979;330:473–490
 - 85 McDonald JC, Liddell FD, Gibbs GW, Eysen GE, McDonald AD. Dust exposure and mortality in chrysotile mining, 1910–75. *Br J Ind Med* 1980;37(1):11–24
 - 86 Berry G, Newhouse ML, Antonis P. Combined effect of asbestos and smoking on mortality from lung cancer and mesothelioma in factory workers. *Br J Ind Med* 1985;42(1):12–18
 - 87 Wang X, Yano E, Qiu H, et al. A 37-year observation of mortality in Chinese chrysotile asbestos workers. *Thorax* 2012;67(2):106–110
 - 88 Erren TC, Jacobsen M, Piekarski C. Synergy between asbestos and smoking on lung cancer risks. *Epidemiology* 1999;10(4): 405–411
 - 89 Lee PN. Relation between exposure to asbestos and smoking jointly and the risk of lung cancer. *Occup Environ Med* 2001; 58(3):145–153
 - 90 Liddell FD. The interaction of asbestos and smoking in lung cancer. *Ann Occup Hyg* 2001;45(5):341–356
 - 91 Reid A, de Klerk NH, Ambrosini GL, Berry G, Musk AW. The risk of lung cancer with increasing time since ceasing exposure to asbestos and quitting smoking. *Occup Environ Med* 2006; 63(8):509–512
 - 92 Frost G, Darnton A, Harding AH. The effect of smoking on the risk of lung cancer mortality for asbestos workers in Great Britain (1971–2005). *Ann Occup Hyg* 2011;55:239–247
 - 93 Berman DW, Crump KS. Update of potency factors for asbestos-related lung cancers and mesothelioma. *Crit Rev Toxicol* 2008;38 (Suppl 1):1–47
 - 94 Stanton MF, Layard M, Tegeris A, et al. Relation of particle dimension to carcinogenicity in amphibole asbestos and other fibrous minerals. *J Natl Cancer Inst* 1981;67(5):965–975
 - 95 National Institute of Occupational Safety and Health. Current Intelligence Bulletin 62: Asbestos fibers and other elongate mineral particles: state of the science and roadmap for research. Cincinnati (OH): Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health; 2011 Apr. DHHS (NIOSH) Publication No. 2011-159
 - 96 Boulanger G, Andujar P, Pairon JC, et al. Quantification of short and long asbestos fibers to assess asbestos exposure: a review of fiber size toxicity. *Environ Health* 2014;13:59
 - 97 Davis JM, Beckett ST, Bolton RE, Collings P, Middleton AP. Mass and number of fibres in the pathogenesis of asbestos-related lung disease in rats. *Br J Cancer* 1978;37:673–688
 - 98 Davis JM, Jones AD. Comparisons of the pathogenicity of long and short fibres of chrysotile asbestos in rats. *Br J Exp Pathol* 1988; 69(5):717–737

- 99 Lippmann M. Toxicological and epidemiological studies on effects of airborne fibers: coherence and public health implications. *Crit Rev Toxicol* 2014;44(8):643–695
- 100 Stayner L, Kuempel E, Gilbert S, Hein M, Dement J. An epidemiological study of the role of chrysotile asbestos fibre dimensions in determining respiratory disease risk in exposed workers. *Occup Environ Med* 2008;65(9):613–619
- 101 Dement JM, Loomis D, Richardson D, Wolf SH, Kuempel ED. Estimates of historical exposures by phase contrast and transmission electron microscopy for pooled exposure–response analyses of North Carolina and South Carolina, USA asbestos textile cohorts. *Occup Environ Med* 2011;68(8):593–598
- 102 Loomis D, Dement J, Richardson D, Wolf S. Asbestos fibre dimensions and lung cancer mortality among workers exposed to chrysotile. *Occup Environ Med* 2010;67(9):580–584
- 103 Hamra GB, Loomis D, Dement J. Examining the association of lung cancer and highly correlated fibre size-specific asbestos exposures with a hierarchical Bayesian model. *Occup Environ Med* 2014;71(5):353–357
- 104 Dodson RF, Brooks DR, O'Sullivan M, Hammar SP. Quantitative analysis of asbestos burden in a series of individuals with lung cancer and a history of exposure to asbestos. *Inhal Toxicol* 2004;16(9):637–647
- 105 Adib G, Labreche F, De Guire L, Dion C, Dufresne A. Short, fine and WHO asbestos fibers in the lungs of quebec workers with an asbestos-related disease. *Am J Ind Med* 2013;56:1001–114
- 106 Dodson RF, Atkinson MA, Levin JL. Asbestos fiber length as related to potential pathogenicity: a critical review. *Am J Ind Med* 2003;44(3):291–297
- 107 Pira E, Pelucchi C, Buffoni L, et al. Cancer mortality in a cohort of asbestos textile workers. *Br J Cancer* 2005;92(3):580–586
- 108 De Matteis S, Consonni D, Lubin JH, et al. Impact of occupational carcinogens on lung cancer risk in a general population. *Int J Epidemiol* 2012;41(3):711–721
- 109 Gustavsson P, Nyberg F, Pershagen G, Sch  ele P, Jakobsson R, Plato N. Low-dose exposure to asbestos and lung cancer: dose-response relations and interaction with smoking in a population-based case-referent study in Stockholm, Sweden. *Am J Epidemiol* 2002;155(11):1016–1022
- 110 Seidman H, Selikoff IJ, Hammond EC. Short-term asbestos work exposure and long-term observation. *Ann N Y Acad Sci* 1979;330:61–89
- 111 U.S. Environmental Protection Agency Risk Assessment Forum. Guidelines for Carcinogen Risk Assessment. 630/P-03/001F. Washington, DC, 2005
- 112 Nymark P, Wikman H, Hienonen-Kempas T, Anttila S. Molecular and genetic changes in asbestos-related lung cancer. *Cancer Lett* 2008;265(1):1–15
- 113 Jaurand MC, Renier A, Daubriac J. Mesothelioma: Do asbestos and carbon nanotubes pose the same health risk? *Part Fibre Toxicol* 2009;6:16
- 114 Stayner L, Smith R, Bailer J, et al. Exposure-response analysis of risk of respiratory disease associated with occupational exposure to chrysotile asbestos. *Occup Environ Med* 1997;54:646–52
- 115 Huang SX, Jaurand MC, Kamp DW, Whysner J, Hei TK. Role of mutagenicity in asbestos fiber-induced carcinogenicity and other diseases. *J Toxicol Environ Health B Crit Rev* 2011;14(1–4):179–245
- 116 Toyokuni S. Mechanisms of asbestos-induced carcinogenesis. *Nagoya J Med Sci* 2009;71(1–2):1–10
- 117 Sone S, Takashima S, Li F, et al. Mass screening for lung cancer with mobile spiral computed tomography scanner. *Lancet* 1998;351(9111):1242–1245
- 118 Henschke CI, McCauley DI, Yankelevitz DF, et al. Early Lung Cancer Action Project: overall design and findings from baseline screening. *Lancet* 1999;354(9173):99–105
- 119 Henschke CI, Yankelevitz DF, Libby DM, Pasmantier MW, Smith JP, Miettinen OS; International Early Lung Cancer Action Program Investigators. Survival of patients with stage I lung cancer detected on CT screening. *N Engl J Med* 2006;355(17):1763–1771
- 120 Aberle DR, Adams AM, Berg CD, et al; National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011;365(5):395–409
- 121 Moyer VA; U.S. Preventive Services Task Force. Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2014;160(5):330–338
- 122 National Comprehensive Care Network Clinical Practice Guidelines. Lung Cancer Screening Version 1; 2012. Available at: http://www.rrmginc.com/docs/NCCN_GuidelinesLungCancerScreening.pdf
- 123 Jaklitsch MT, Jacobson FL, Austin JH, et al. The American Association for Thoracic Surgery guidelines for lung cancer screening using low-dose computed tomography scans for lung cancer survivors and other high-risk groups. *J Thorac Cardiovasc Surg* 2012;144(1):33–38

EXHIBIT 49

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Chrysotile Asbestos is the Main Cause of Pleural Mesothelioma

Allan H. Smith, MD, PhD, and Catherine C. Wright, MPH

In contrast to amphibole forms of asbestos, chrysotile asbestos is often claimed to be only a minor cause of malignant pleural mesothelioma, a highly fatal cancer of the lining of the thoracic cavity. In this article we examine the evidence from animal and human studies that relates to this issue. Reported data do not support widely quoted views regarding the relative inertness of chrysotile fibers in mesothelioma causation. In fact, examination of all pertinent studies makes it clear that chrysotile asbestos is similar in potency to amphibole asbestos. Since asbestos is the major cause of mesothelioma, and chrysotile constitutes 95% of all asbestos use world wide, it can be concluded that chrysotile asbestos is the main cause of pleural mesothelioma in humans. © 1996 Wiley-Liss, Inc.

KEY WORDS: chrysotile, asbestos, mesothelioma, epidemiological studies, animal studies, amphibole hypothesis, Stanton hypothesis

INTRODUCTION

Asbestos inhalation is an established cause of cancer in humans, particularly malignant mesothelioma and lung cancer. It is the main cause of cancer resulting from workplace exposure to carcinogens.

Despite extensive cancer studies in humans, certain controversies remain about asbestos exposure and human cancer. The primary controversy is the question of fiber type in causation of mesothelioma. Commercial use of asbestos mainly involves the two amphibole fiber types, crocidolite and amosite, and one serpentine fiber type, chrysotile. However, chrysotile asbestos is often contaminated with small amounts of tremolite, an amphibole fiber. The key questions concern whether or not, and to what extent, exposure to chrysotile asbestos (including its natural contaminant tremolite) causes mesothelioma in humans. While there is evidence that chrysotile asbestos is not a potent cause of malignant peritoneal mesothelioma [EPA, 1986; Doll and Peto, 1985], the role of chrysotile in the causation of pleural mesothelioma is still disputed.

Chrysotile asbestos is established to be a cause of asbestosis and lung cancer. In fact, one of the highest risks of asbestos-related lung cancer was observed in textile manufacturing where 100% chrysotile was used [Dement et al., 1994]. However, the opinion is held by some that chrysotile asbestos is much less hazardous than crocidolite, amosite, and tremolite, particularly where malignant mesothelioma is concerned. McDonald et al. [1989] state: "Amphibole asbestos fibers could explain most mesothelioma cases in Canada and other inorganic fibers, including chrysotile, very few." Wagner [1991] states: "There is overwhelming evidence that crocidolite is the main fibre associated with mesotheliomas. There is no clear evidence that exposure to uncontaminated chrysotile or anthophyllite is associated with these tumors." Two recent articles, however, have concluded that chrysotile is, in fact, an important cause of malignant mesothelioma [Huncharek, 1994; Nicholson and Landrigan, 1994]. Nicholson and Landrigan conducted a thorough review of the evidence concerning the carcinogenicity of chrysotile asbestos. In particular, they utilized the strong time dependence of mesothelioma risk to apportion the contribution of the different exposure periods, and thus of different fiber types, to the observed risk. Huncharek addresses some current controversial issues surrounding asbestos health effects and their relationship to cancer risk assessment and risk management. As these articles point out, the question of the carcinogenic potential of chrysotile

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asbestos is not only of scientific interest, but also has legal, public policy, and public health importance.

The purpose of this paper is to further examine both human and animal evidence concerning the importance of chrysotile asbestos in causing malignant pleural mesothelioma. Specifically, we have identified the 25 epidemiologic cohort studies having the highest ratio of pleural mesotheliomas per 1,000 deaths, and have assessed the type(s) of asbestos fiber exposure in the highest risk cohorts. We have also reviewed those lines of evidence often cited in support of the theory that amphibole asbestos, not chrysotile, is the primary, if not sole, cause of malignant mesothelioma. Such lines of evidence include: results of certain epidemiological studies (such as the gas mask studies), and the "Stanton" and "amphibole" hypotheses.

A REVIEW OF THE EPIDEMIOLOGICAL DATA

A review of the literature was undertaken to identify available asbestos epidemiological studies. Cohort studies (most recent follow-up available as of October 1994) were reviewed for the following data: industry, primary asbestos exposure (the fiber type to which the cohort or subcohort had the greatest exposure), secondary asbestos exposure (fiber types to which the cohort or subcohort had lesser exposure), number of workers in the cohort, number of deaths, number of lung cancer deaths, excess lung cancer deaths, and numbers of mesotheliomas. Pleural mesothelioma incidence within the cohort was determined in terms of the number of pleural mesothelioma deaths per 1,000 deaths as well as the ratio of pleural mesotheliomas to excess lung cancer deaths. When possible, the mortality data for subcohorts with greater than or equal to 20 years since start of employment were used in determining mesothelioma incidence. Cohorts were rank ordered from the highest to lowest ratio of pleural mesotheliomas per 1,000 deaths.

Table I summarizes the data for the 25 top-ranking asbestos cohorts. Other studies which were considered but which ranked below the top 25 cohorts are listed in Table II. Chrysotile was the primary exposure for at least two of the 10 top-ranking cohorts [Mancuso, 1988; Peto et al., 1985] and was the secondary exposure or identified as part of a mixed exposure in six of the 10 top-ranking cohorts. Crocidolite was the primary exposure for three of the top 10 cohorts [Jones et al., 1980; Talcott et al., 1989; McDonald and McDonald, 1978] and was the secondary exposure or identified as part of a mixed exposure in another five cohorts. Amosite was identified as part of a mixed exposure in three of the top 10 cohorts, but was not the primary exposure in any of them. These findings suggest that chrysotile is a major cause of pleural mesothelioma. They are inconsistent with the claim that amphibole fibers are much more potent than chrysotile. If that were the case, one would

expect all the top 10 risk cohorts to be predominantly amphibole exposure cohorts.

The highest ratio of 88.1 pleural mesotheliomas per 1,000 deaths was for railroad machinists exposed to chrysotile [Mancuso, 1988]. This study has been criticized for attributing the mesothelioma incidence to chrysotile exposure rather than possible amphibole exposure [Ohlson, 1989; McDonald and McDonald, 1989; Churg and Green, 1990]. Mancuso's responses to such criticism demonstrate that the principal exposure of the railroad machinists was to lagging or removal of lagging, which was chrysotile. While other jobs may have used amphiboles, leading to the possibility of secondary exposure to the railroad workers, he made a strong case that chrysotile was the overwhelming exposure to the machinists [Mancuso, 1989a,b, 1990].

A number of other epidemiological studies have been published but lack data that would allow calculation of pleural mesothelioma incidence. Bégin et al. [1992] described a series of mesothelioma cases in Canadian asbestos workers. All of these cases were seen and accepted by the Quebec Workman's Compensation Board for work-related compensation of industrial disease. There were 49 cases in miners and millers of the Quebec Eastern Township region. Twenty mesotheliomas occurred in miners and millers from Asbestos, where tremolite contamination was similar to background urban levels. Twenty-nine mesotheliomas occurred in workers from Thetford Mines, where higher levels of tremolite occur. The authors stated that, on the basis of the number of workers exposed at each mine site, the incidences in Asbestos and Thetford Mines were similar despite the differing levels of tremolite contamination. McDonald et al. [1980, 1993] conducted a cohort study of the miners and millers from Thetford Mines and Asbestos. Only 33 (25 in the period 1976–1988) mesotheliomas have been identified in the entire cohort of about 11,000 men, 80% of whom had died as of 1992. According to the authors, preliminary analysis of mesotheliomas suggests that the risk of mesothelioma was higher in the mine and mills at Thetford Mines (higher tremolite exposure) than in those at Asbestos (lower tremolite exposure). Their data, however, do not clearly support this conclusion, especially in the high exposure groups where the rates of mesothelioma were 0.97 per 1,000 person-years for Asbestos and 0.92 per 1,000 person-years for Thetford Mines.

A number of other studies have demonstrated risks of mesothelioma due to chrysotile exposure. Borow et al. [1973] reported 72 cases of malignant mesothelioma in persons exposed primarily to chrysotile in an asbestos mill. Fifty-three acceptable cases of chrysotile-induced mesotheliomas were identified by Churg et al. [1988]. Two malignant mesotheliomas were reported in a small group of former chrysotile miners and millers in Zimbabwe [Cullen and Baloyi, 1991]. A case series of 80 mesotheliomas in railroad rolling-stock machinists and others in the Italian

TABLE 1. Asbestos Cohort Studies

Reference	Industry	Primary asbestos exposure	Secondary asbestos exposure	Number in cohort	Number of deaths	Lung cancer deaths	Excess lung cancers	Perit. mesoth.	Pleural mesoth.	Pl. meso/1,000 deaths	Pl. meso/xs lung cancers	Comments
Mancuso [1988]	Railroad machinists	Chrys	Possibly some amphibole	181	159	11	NA	1	14	88.1	NA	Expected lung cancer deaths were not reported. Primarily servicing of steam locomotives. Greater than 20 years since first employment. Mancuso [1988] emphasizes that principal exposure was lagging or removal of lagging, which was chrysotile. However, other jobs may have used amphiboles, so secondary exposure is possible.
Finkelstein [1984]	Cement products	Chrys/croc		685	136	29	21.4	8	11	80.9	0.51	20+ years from onset. Production and maintenance.
Jones et al. [1980]	Gas mask manufacture	Croc		951	166	12	5.7	4	13	78.3	2.28	20+ years from onset. Females only.
Talcott et al. [1988]	Cigarette filter manufacture	Croc		33	28	11	10.3	3	2	71.4	0.19	
Elmas and Simpson [1977]	Insulation (laggers)	Unknown mix		162	122	24	NA	5	8	65.6	NA	20+ years from onset. Eleven additional lung cancers or mesotheliomas could not be categorized. EPA [1986] lists 27 obs., 22 excess lung cancers for this cohort.
Peto et al. [1985]	Textiles	Chrys	Croc	145	123	20	14.5	0	7	56.9	0.40	Subcohort: men only, employed 20+ years with some service before 1933. High exposure group. Crocidolite made up 5% of asbestos used between 1932 and 1969.
McDonald and McDonald [1978]	Gas mask manufacture	Croc	Chrys	199	56	7	4.6	6	3	53.6	0.65	Males and females combined, 33-36 years since onset of exposure to crocidolite. Exposure to chrysotile likely to have occurred before and after. Cohort includes workers from three factories. Filter pad workers in Montreal (n = 32) were exposed to croc from 1/40 to 6/41 only. This factory used chrysotile since 1928 for manuf. of brake linings. Filter pad workers from Asbestos, Quebec (n = 113) were exposed to croc 1939-1941 only. This factory had been in operation since WWI processing chrysotile. Gas mask assembly was performed in Ottawa (n = 54). An additional two cases of pleural mesothelioma from Montreal plant were identified from a nat'l survey. Note that Table 2 in McDonald and McDonald [1978] incorrectly presents two pleural mesotheliomas.
Newhouse et al. [1985]	Textiles/cement products	Mixed amos/chrys/croc		700	274	37	32.0	11	14	51.1	0.44	Women only. Greater than 10 years follow-up.
Newhouse et al. [1985]	Laggers	Mixed amos/chrys/croc		1,400	157	38	27.3	6	7	44.6	0.26	Men only. Greater than 10 years follow-up. No complete data for 20+ years since 1st employ.
Selkoff et al. [1979a]	Shipyard	Chrys/amos		389	73	20	24.9	5	3	41.1	0.12	Shipyard insulator cohort; 20+ years from onset. Amosite added to chrysotile just before and during WWII.
Sluis-Cremer et al. [1992]	Mining	Croc		3,430	423	27	13.7	2	17	40.2	1.24	Cohort of miners exposed only to crocidolite. No subcohort data for 20+ years since 1st employ.
Nicholson [1976]	Production and textiles	Not stated		689	199	27	18.6	7	8	40.2	0.43	20+ years from onset.
Armstrong et al. [1988]	Mining/milling	Croc		6,506	820	91	55.5	1	32	39.0	0.57	Men only. Includes entire cohort. Update to Hobbs et al. (1980).
Newhouse et al. [1985]	Textiles/cement products	Mixed amos/chrys/croc		3,000	818	158	94.8	29	31	37.9	0.33	Men only. >10 years follow-up.
Seidman and Selkoff [1990]	Insulation	Chrys	Amos	17,800	4,951	1,168	899.3	285	173	34.9	0.19	Entire cohort. Workers were exposed to chrys in early years and chrys + amos in later years.
Rossiter et al. [1980]	Shipyards	Mixed		6,076	1,043	84	16.3	2	29	27.8	-1.78	
Albin et al. [1990]	Asbestos cement manufacture	Chrys	Croc/amos	1,456	592	35	15.6	0	13	22.0	0.83	
Seidman et al. [1986]	Insulation manuf.	Amos		820	366	76	62.8	9	8	21.9	0.13	20-40 elapsed years since onset of work.
Peto et al. [1985]	Textiles	Chrys	Croc	3,211	727	93	28.4		10	13.8	0.35	Subcohort of men first employed in 1933 or later, 20+ years since 1st employ.
Sluis-Cremer et al. [1992]	Mining	Mixed amph		675	154	NA	NA	3	2	13.0	NA	Cohort of miners exposed to mixed amphiboles. The number of pl. mesos could be two or three. Unclear.
Newhouse and Sullivan [1989]	Friction materials	Chrys	Croc	2,222	743	88	5.7	NA	9	12.1	1.58	20+ years from onset.
Kolonef et al. [1985]	Shipyards	Chrys	Amos	5,191	668	61	4.9	?	8	12.0	1.63	Nonexposed group excluded.
Acheson et al. [1984]	Insulation manufacture	Amos		4,820	333	57	27.4	1	4	12.0	0.15	Includes all latency periods. Includes two pl. mesoth. with less than 20 years since first exposure.
Acheson et al. [1982]	Gas mask manufacture	Croc		757	219	13	6.8	0	2	9.1	0.29	Crocidolite cohort only. Some civilian chrysotile gas masks were also made by this cohort.
Raffin et al. [1989]	Manuf. asb. cement	Chrys	Amos/croc	7,996	1,305	162	72.2	0	10	7.7	0.14	89% chrysotile used. 100% chrys 1928-1946.

TABLE II. Additional Studies Considered*

Acheson et al. [1982]—chrysotile cohort
Dement et al. [1982]
Finkelstein [1989]
Henderson and Enterline [1979]
Hughes and Weill [1980]
Hughes et al. [1987]
McDonald et al. [1980, 1993]
McDonald et al. [1983a]
McDonald et al. [1983b]
McDonald et al. [1984]
Nicholson et al. [1979]
Piofatto et al. [1990]
Puntoni et al. [1979]
Robinson et al. [1979]
Sivis-Cremer et al. [1992]—amosite cohort
Thomas et al. [1982]
Weill et al. [1979]
Weiss [1977]

*Studies which were reviewed but were not included in Table I due to low ratios of pleural mesotheliomas to total deaths.

railroad industry, where chrysotile was the primary exposure, has also been reported [Maltoni et al., 1991]. Fifty malignant mesothelioma cases have been identified in the manufacturing, insulation, and shipbuilding trades, and 21 cases in the construction and building maintenance trades [Begin et al., 1992]. In all of these trades, chrysotile constituted the primary exposure and amphiboles the secondary exposure. Sanden et al. [1992] conducted a cancer incidence study of shipyard workers exposed primarily to chrysotile, with lesser exposure to amosite and crocidolite. Eleven of the 168 cancers were pleural mesothelioma, including eight of the 70 cancers in persons with 20 or more years latency. In addition, eight cases of malignant mesothelioma were reported following household exposure to the dusty clothing of asbestos workers [McDonald and McDonald, 1980]. Three of these eight cases were children of chrysotile mine employees. The above data demonstrate that chrysotile exposure, even at the relatively low levels expected in household exposures, can cause malignant mesothelioma.

Gas Mask Studies

Studies of workers who assembled gas masks during World War II have been widely quoted as indicating that crocidolite is much more potent than chrysotile asbestos in causing mesothelioma [Doll and Peto, 1985; Harington, 1991]. Table III presents data abstracted from the three gas mask studies where workers have been exposed to one fiber type only [Jones et al., 1980; McDonald and McDonald,

1978; Acheson et al., 1982]. The expected number of lung cancer deaths for the McDonald and McDonald [1978] study was not given, but we have assumed it was one since it makes very little difference to the overall consideration of the studies.

The last row of Table III gives the summed data from the three gas mask studies. There were 19 pleural mesothelioma cases in the crocidolite group with a lung cancer excess of about 13.5. There was only one case in the chrysotile-only category, but the excess lung cancer number was only 1.2. Since chrysotile is a potent cause of lung cancer, this low excess makes it clear that the chrysotile gas mask workers had relatively low exposures. In fact, the total length of exposure to chrysotile in the Jones et al. study was shorter than 5 months. In the Acheson study, the exposure to chrysotile was probably much lower than the exposure to crocidolite, since the crocidolite filters were made by hand while the manufacture of chrysotile filters was mechanized. Thus these three studies provide no evidence whatsoever that crocidolite is more potent in causing mesothelioma than chrysotile asbestos.

Fiber Type Risk Comparisons

Hughes and Weill [1986] have suggested that crocidolite is about 14 times more potent than chrysotile in causing combined pleural and peritoneal mesotheliomas. This finding is based on combined data from selected cohorts with chrysotile, amosite, crocidolite, or mixed exposures. The results indicated that the number of mesotheliomas was 12% of the excess lung cancers among chrysotile-exposed populations, but 165% for crocidolite exposure, 22.2% for amosite exposure, and 65.9% for mixed fiber exposure.

Table IV presents our reanalysis of the above findings. The same cohorts are included, but the most recent follow-up data from these cohorts were used in the analysis. Where possible, data from subcohorts with 20+ years since first exposure were used. Furthermore, since it is generally agreed that chrysotile asbestos is not a potent cause of peritoneal mesotheliomas, only pleural mesotheliomas are included in the table. Our analysis indicates very different results from Hughes and Weill [1986]. The number of pleural mesotheliomas is 20% of the excess lung cancers among chrysotile-exposed populations, 72% for crocidolite exposure, 13% for amosite exposure, and 27% for mixed exposures. The longer follow-up period makes a large difference between the Hughes and Weill [1986] analysis and that presented here. Rather than appearing to be 14 times less potent than crocidolite, based on this selection of studies chrysotile may be only three or four times less potent in causing malignant mesothelioma. This is in close agreement with the conclusions of Nicholson [1991], who looked at comparative dose-response relationships of asbestos fiber

TABLE III. Pleural Mesotheliomas, Lung Cancer, and Excess Lung Cancers in Gas Mask Manufacturers Using Only Crocidolite or Only Chrysotile

	Crocidolite only			Chrysotile only		
	Pleural mesotheliomas	Lung cancer	Excess lung cancers	Pleural mesotheliomas	Lung cancer	Excess lung cancers
McDonald and McDonald [1978] ^a	1	2	1	—	—	—
Jones et al. [1980]	15	11	5.7	0	0	—
Acheson et al. [1982]	3	13	6.8	1	6	1.2
Total	19	26	13.5	1	6	1.2

^aOttawa cohort with exposure to crocidolite only.

types and included more studies than Hughes and Weill [1986]. His conclusion was: that "There appears to be no difference in the potency of chrysotile and amosite in producing mesothelioma. However, exposures to pure crocidolite, which has been and is rarely used in the U.S., may carry a two- to three-fold greater risk" [Nicholson, 1991].

To summarize the epidemiological findings as they relate to chrysotile and pleural mesothelioma, the following points can be made: (1) If crocidolite were much more potent, the highest mesothelioma risk cohorts should involve predominantly exposure to crocidolite. In fact, the highest risk cohorts do not show this differentiation. (2) Limited data concerning exposure of household members suggest chrysotile is a highly potent cause of mesothelioma. (3) The widely quoted gas mask workers studies do not provide evidence that crocidolite is more potent than chrysotile. (4) Considered overall, the evidence suggests chrysotile may be less potent than crocidolite by a factor in the range of 2–4. However, the epidemiological evidence does not support chrysotile being less potent than amosite.

A REVIEW OF AVAILABLE ANIMAL DATA

Chrysotile, amosite, crocidolite, and tremolite can cause pleural mesotheliomas in experimental animals exposed by inhalation, intrapleural injection, or surgical implantation. Table V summarizes data from long-term studies of experimental animals exposed via inhalation, the most relevant route for human exposure.

In order to get an overall incidence of pleural mesotheliomas in rats following inhalation, incidence data were added together for each of the three asbestos types (i.e., chrysotile, amosite, and crocidolite). The overall incidence of pleural mesothelioma in rats exposed via inhalation is 1.8% (13/733) for chrysotile, 1.3% (5/377) for amosite, and 1.2% (4/328) for crocidolite. Thus, inhalation studies in rats do not support the argument that chrysotile is far less potent than amphiboles in pleural mesothelioma causation.

Since only one inhalation experiment has been done for tremolite, it is not included in this comparison.

Intrapleural injection studies have also demonstrated that chrysotile is a potent cause of pleural mesotheliomas in rats [Reeves et al., 1971; Wagner et al., 1973]. In fact, Wagner et al. found that finely milled chrysotile was more potent than the crocidolite and amosite samples tested.

Surgical pleural implantation of fine chrysotile, crocidolite, amosite, or tremolite fibers also induced significant numbers of pleural sarcomas in rats [Stanton et al., 1972, 1981]. The cumulative incidence of deaths with mesothelioma from chrysotile, amosite, and two types of crocidolite was similar at the maximum dose level of 40 mg [Stanton et al., 1972].

In conclusion, there is clear evidence in animal inhalation and pleural injection/implantation studies that chrysotile asbestos causes pleural mesothelioma. Indeed, if one considers the dose of asbestos in terms of mass, chrysotile asbestos is generally the more potent fiber when compared to crocidolite and amosite. However, the data do not permit estimation of potency per fiber. The data for tremolite is quite limited, but do not support the conclusion that tremolite is a more potent mesothelial carcinogen than chrysotile.

THE STANTON AND AMPHIBOLE HYPOTHESES REVISITED

Two lines of evidence have led some researchers to believe that chrysotile is not an important cause of pleural mesothelioma in asbestos workers, and that the risk is attributable to amphibole exposure. The "Stanton Hypothesis" suggests that mesothelioma incidence is strongly correlated with longer, thinner fibers. The "Amphibole Hypothesis" states that amphibole fibers are responsible for causing mesothelioma, since these fibers are found in the lungs of mesothelioma cases at autopsy, but chrysotile fibers are not. The evidence leading to these hypotheses is summarized below.

TABLE IV. Mesothelioma in Populations Exposed to Different Fiber Types^{a,b}

Fiber type	Observed deaths	Lung cancer		Pleural mesothelioma	
		Observed	Excess	Observed	As % of excess lung cancer
Chrysotile ^c	10,345	726	186.9	39	20.3
Amosite ^d	1,163	133	90.2	12	13.3
Crocidolite ^e	1,042	110	66.8	48	71.9
Mixed fiber ^f	9,532	1,722	1,106.2	301	27.2

^aBased on Table 1 of Hughes and Weill [1986].^bIncludes subcohorts with 20+ years since first employment, where possible.^cMcDonald et al. [1983, 1984, 1993], McDonald and McDonald [1980], Rubino et al. [1979], Piolatto et al. [1990], Weiss [1977], Acheson et al. [1982], Thomas et al. [1982].^dSeidman et al. [1979, 1986], Acheson et al. [1984].^eHobbs et al. [1980], Armstrong et al. [1988], McDonald and McDonald [1978], Jones et al. [1980].^fMcDonald et al. [1983], Berry and Newhouse [1983], Newhouse and Sullivan [1989], Selikoff et al. [1979], Seidman and Selikoff [1990], Acheson et al. [1982], Newhouse and Berry [1979], Newhouse et al. [1985], Finkelstein [1983, 1984], Elmes and Simpson [1977], Thomas et al. [1982], Rossiter and Coles [1980].

Stanton and his colleagues conducted a series of experiments in which a number of durable minerals in the form of respirable particles were implanted in the pleura of rats for periods of more than 1 year [Stanton and Wrench, 1972; Stanton, 1973; Stanton et al., 1977, 1981]. Significant numbers of pleural sarcomas were induced in rats with a wide variety of fine, durable fibers including chrysotile, crocidolite, amosite, and tremolite. The two earlier studies showed no difference in potency between standard UICC samples of chrysotile and crocidolite [Stanton and Wrench, 1972; Stanton, 1973]. The primary conclusion of these studies was that the ability of mineral particles to cause tumors is mostly a function of the dimensional properties of the particles, rather than physicochemical properties.

The later studies, which did not include chrysotile, attempted to further characterize the importance of dimensional aspects of fibers [Stanton et al., 1977, 1981]. According to the authors, the incidence of malignant mesenchymal neoplasms correlated well with the dimensional distribution of the particles. The probability of pleural sarcoma correlated best with the number of fibers that measured 0.25 μm or less in diameter and more than 8 μm in length. Relatively high correlations were also observed with fibers in other categories having a diameter up to 1.5 μm and a length of greater than 4 μm .

This evidence led to the "Stanton Hypothesis," which states that durable fibers (provided they subscribe to well defined ranges of diameter and length), of which asbestos is but one sample, cause cancer irrespective of their physicochemical nature simply because they are fibers. Stanton also stated, however, that direct application of the results of his experiments to the problems in humans would be unwise given the deficiencies in the method of application and the massive amounts of fibers used (standard dose, 40 mg). In fact, if one were to exclude all fiber types other than asbes-

tos from Stanton's data, there appears to be little or no relationship between the probability of tumor and the number of particles measuring $\leq 0.25 \mu\text{m}$ diameter and $\geq 8 \mu\text{m}$ length (Fig. 1).

Other researchers have studied the correlation between dimensional properties of fibers and mesothelioma. In experiments similar to Stanton's, Jaurand [1991] determined the percentage of mesotheliomas occurring after intrapleural inoculation of 20 mg asbestos samples into rats. She found a fairly good correlation ($r = 0.643$, $p < 0.01$) between the risk of mesothelioma and the number of "index" fibers (i.e., $\leq 0.25 \mu\text{m}$ diameter and $\geq 8 \mu\text{m}$ length) inoculated according to Stanton's criteria. However, there was only a 30% difference (20% vs. 50%) between the percentage of mesotheliomas produced by samples with the smallest number of index particles compared to samples with a higher number of index particles. Furthermore, when Jaurand [1991] combined all of her available data from previous studies of amosite, crocidolite, and chrysotile [Monchaux et al., 1981], there was no correlation between the percentage of mesotheliomas and the number of index particles ($r = 0.164$).

Despite Stanton's warning and the findings described above, many researchers have utilized the Stanton hypothesis to link mesothelioma cases to particular asbestos fiber types and sizes. Churg, for example, stated: "Given the very high exposures experienced by the Quebec workforce, the short size and low aspect ratio of the tremolite fibers found in the ore may be a fortunate accident which 'protects' these workers from mesothelioma" [Churg, 1988].

Churg's statement, however, also assumes that it is the tremolite, not the chrysotile, that is responsible for those mesotheliomas that did occur. This assumption is based on the finding that, although tremolite comprises only a tiny fraction of the asbestos dust in the Quebec mines and mills,

TABLE V. Long-Term Asbestos Inhalation Studies in Animals

Reference	Species	Fiber type	Dose ^{a,b} mg/m ³	Number tested	No. of pleural mesotheliomas
Reeves et al. [1971]	Rats	Amos	~48	63	0
		Croc	~48	61	0
		Chrys	~48	49	0
	Rabbits	Amos	~48	20	0
		Croc	~48	18	0
		Chrys	~48	26	0
	G. pigs	Amos	~48	17	0
		Croc	~48	33	0
		Chrys	~48	21	0
	Hamsters	Amos	~48	50	0
		Croc	~48	45	0
		Chrys	~48	49	0
Wagner et al. [1974]	Rats	Amos	11-14	146	1 ^c
		Croc	10-13	141	3 ^d
		Chrys (Can.) ^e	10-12	137	4
		Chrys (Rh.) ^f	10-15	144	0
Reeves et al. [1974]	Rats	Chrys	~50	34	1
		Croc	~50	43	0
		Amos	~50	43	0
	Gerbils	Chrys	~50	40	2
		Croc	~50	31	0
		Amos	~50	45	0
Davis et al. [1978]	Rats	Chrys (Rh.)	2	42	0
		Chrys (Rh.)	10	40	0
		Amos	10	43	0
		Croc	5	43	1
		Croc	10	40	0
		Tremolite (Kor.) ^g	?	40	2
Davis et al. [1985]	Rats	Short amos	10	42	0
Davis et al. [1986a]	Rats	Long amos	10	40	2
		WDC yarn ^h	4	41	0
Davis et al. [1986b]	Rats	Factory WDC ⁱ	4	44	0
		Chrys yarn ^j	4	42	1
		Exp WDC ^k	4	43	4
		Exp WDC/RD ^l	4	37	1
	Rats	Short chrys	10	40	0
		Long chrys	10	40	2
Davis and Jones [1988]	Rats	Chrys		733	13 (1.8%)
		Amos		377	5 (1.3%)
		Croc		328	4 (1.2%)

^aNo pleural mesotheliomas were observed in any control group.^bSimilar doses in mg/m³ may be very different in terms of fibers/ml.^cMesothelioma occurred with just 1 day exposure (>2 years followup).^dOne mesothelioma occurred with just 1 day exposure (>2 years followup).^eRh, Rhodesian.^fCan, Canadian.^gKor, Korean.^h"WDC" is wet dispersed chrysotile.ⁱDust from factory air.^jStandard chrysotile textile yarn.^kExperimental WDC process.^lExperimental WDC "reversed daylight."

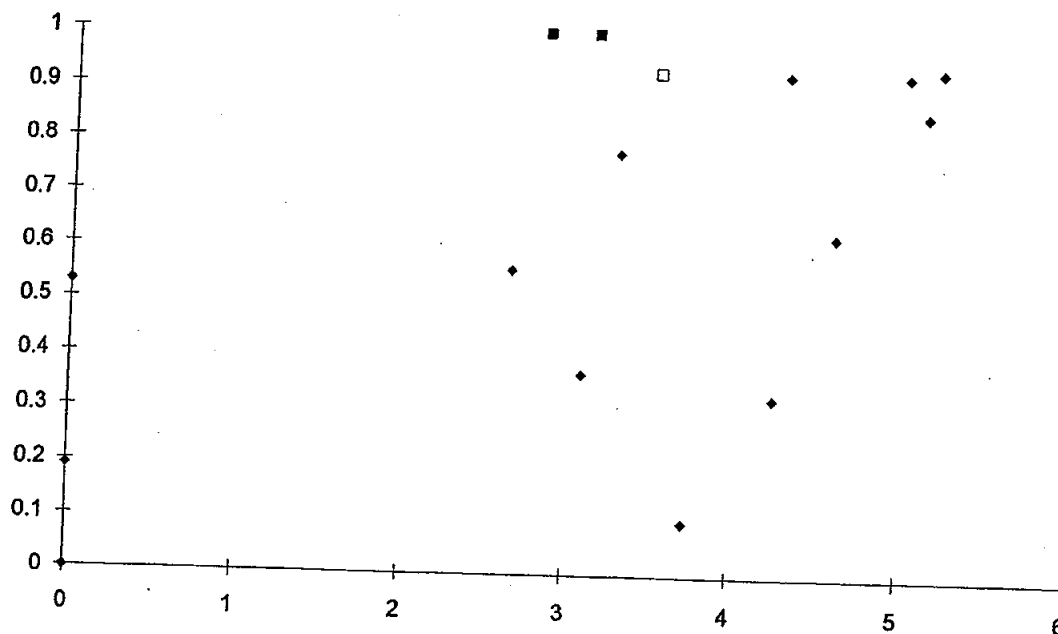


FIGURE 1. Stanton et al. (1981) data for asbestos fibers only. X-axis: Log number particles measuring $\leq 0.25 \mu\text{m}$ width by $>8 \mu\text{m}$ length per microgram. Y-axis: Probability of tumor. ■, tremolite; □, amosite; +, crocidolite.

high tremolite lung burdens were associated with the presence of mesothelioma in miners and millers from Thetford Mines [Churg, 1994]. After adjustment for the presence of tremolite, no correlations between chrysotile concentration and disease could be found.

This leads us to the "amphibole hypothesis," which attributes the mesotheliomas observed in various groups of workers to the asbestos fibers present in their lungs at the time of death rather than to the fiber exposure earlier in life [McDonald et al., 1989; Mossman et al., 1990; Churg, 1988]. The "amphibole hypothesis" is based on the findings that workers exposed to asbestos have more amphiboles in their lungs than chrysotile at autopsy. This occurs because chrysotile fibers (but not amphiboles) break down and split apart longitudinally in tissue, leading to a loss of fibers in lung tissues that are visible by electron microscopy [Nicholson and Landrigan, 1994]. Some suggest that some (if not most) of the chrysotile fibers further fragment into shorter fibers and are then cleared from the lungs [Churg, 1994].

A number of studies have examined fiber content in lungs of mesothelioma cases. Those of Churg et al. [1984] and McDonald et al. [1989] are often referenced in support of the "amphibole hypothesis." Other important studies include Roggli et al. [1993], Morinaga et al. [1989], Rogers et al. [1991], and Sakai et al. [1994]. In fact, the results of these studies are inconsistent, as demonstrated in the following reviews.

Lung tissues of six mesothelioma cases from the Quebec chrysotile mining regions were examined by Churg et al. [1984]. The five cases that had only chrysotile ore components in their lungs had larger amounts of tremolite (i.e., tremolite/actinolite/anthophyllite) than chrysotile. The mean levels of chrysotile and tremolite in mesothelioma cases were higher than their respective mean levels in nine chrysotile miners without mesothelioma or the mean levels in nonexposed controls. Assuming that the fibers present in lung tissue at autopsy are responsible for mesothelioma, this study would support the conclusion that tremolite is responsible for the mesotheliomas occurring in this cohort.

McDonald et al. [1989] examined lung tissue samples from 78 mesothelioma cases in Canada and from matched referents. Chrysotile fiber distributions in the two series were similar. Relative risk was related to the concentration of long amphibole fibers. The proportion of long amphibole and chrysotile fibers was higher in cases than referents. According to the authors, amphibole asbestos fibers could explain most mesothelioma cases in Canada, and other inorganic fibers, including chrysotile, very few. McDonald et al. [1989] concluded that fibrous tremolite probably explained most cases in the Quebec mining region.

In a more recent study, Roggli et al. [1993] analyzed the mineral fiber content of the lungs in 94 patients with malignant mesothelioma from the United States. A large proportion of the cases were either insulators or shipyard workers. Only fibers that were greater than or equal to $5 \mu\text{m}$

in length were included in the analysis. Amosite was identified in 76 cases (81%), the noncommercial amphiboles (primarily tremolite) were identified in 52 cases (55%), chrysotile was detected in 20 cases (21%), and crocidolite in 15 cases (16%). Another five cases (5%) could not be distinguished between amosite and crocidolite. According to the authors, tremolite fibers are probably a marker for the much greater numbers of chrysotile fibers which were deposited but subsequently cleared.

The authors found that, assuming it is the fibers that accumulate within the lung that are responsible for the development of mesothelioma, the order of importance of fibers is amosite > tremolite > chrysotile = crocidolite. However, they were unable to exclude a greater role for the long chrysotile fibers found in their cases, especially since they probably constitute only a small fraction of the long fibers actually deposited. One issue raised was that the methods used might have underestimated the numbers of chrysotile fibers 5 μ m or greater in length, because chrysotile tends to undergo longitudinal splitting with many of the resulting fibers having diameters less than 0.1 μ m. The techniques used in Roggli et al. primarily detected fibers that are 0.2 μ m or greater in diameter.

A study of asbestos fiber content of lungs with mesothelioma in Osaka, Japan was conducted by Morinaga et al. [1989]. Chrysotile was observed in 12 of the 23 mesothelioma cases, amosite in 13, crocidolite in three, and actinolite-tremolite in three cases examined. Six of the mesothelioma cases had only chrysotile fibers. This study provides evidence that, if indeed it is the fibers present in the lung at death that are responsible for mesothelioma, then chrysotile asbestos is a potent cause of this cancer.

Rogers et al. [1991] examined lung tissues from 221 definite and probable cases of malignant mesothelioma reported to the Australian Mesothelioma Surveillance Program, and from an age-sex frequency-matched control series of 359 postmortem cases. A progressive increase in relative risk with increasing fiber content was observed for all fiber content measures. The relative risks for chrysotile, crocidolite, and total amphibole fibers which were 10 μ m or longer were greater than the corresponding risks for fibers less than 10 μ m in length. When cases and controls were compared in relation to exposure to single-fiber types only (all lengths), increased relative risks were observed for both chrysotile and crocidolite.

Pulmonary fiber content was analyzed by Sakai et al. [1994] in 16 patients with malignant mesothelioma and in 16 case-matched controls. Amphibole, chrysotile, and nonasbestos fiber contents were significantly higher in patients than in the control subjects.

Summary of Lung Content Studies

The "amphibole hypothesis" is based on (1) the assumption that the fibers present in the lungs at death caused

the mesothelioma, and (2) the finding that workers exposed to asbestos have more amphiboles in their lungs than chrysotile at autopsy. Chrysotile fibers break down and split apart longitudinally in tissue and can be cleared from the lungs, while amphibole fibers are less attacked by body fluids and can be detected in the lungs of workers years after exposure [Nicholson and Landrigan, 1994]. In fact, complete fragmentation of a single chrysotile fiber may produce 1,000 fibrils [Wagner et al., 1973], and these fibrils may be so thin that they are no longer visible by electron microscopy in lung tissue.

Results of the lung content studies described above are inconsistent, and do not resolve the question of the importance of fiber type in mesothelioma causation. Some studies report significant amounts of chrysotile fibers in lung tissue. Furthermore, the results of Morinaga et al. [1989] demonstrate that mesothelioma can occur in the absence of amphibole fibers, since six cases had only chrysotile fibers in their lung tissues.

The limitations of using lung content studies in determining the role of chrysotile in mesothelioma causation are as follows: (1) The methods used often exclude fibers less than 5 μ m in length. (2) The potential for carcinogenic effects induced by large numbers of short fibers has not been investigated. (3) The methods may have underestimated the number of long thin chrysotile fibers actually present in the lungs due to an inability to detect very thin fibers. (4) The number of chrysotile fibers counted constitute only a minute proportion of the long fibers actually deposited and subsequently cleared. (5) Finding a significant number of tremolite fibers would indicate a major exposure to chrysotile, since tremolite is only a minor contaminant of chrysotile.

Dement [1991] makes the obvious point that measurements of lung fiber burdens made many years after first exposure may bear no relationship to the carcinogenic events that took place long before clinical manifestation of disease (lung cancer or mesothelioma). In addition, the fiber levels of tremolite measured in lung tissues of workers exposed to chrysotile may be a surrogate measure of cumulative dose of chrysotile. Case [1991], on the other hand, states: "*It is presumably necessary for fibers to be present in order for them to exert a carcinogenic effect!*" This point is often missed by those who regard tremolite—the more potent carcinogen—simply as a 'marker' for chrysotile."

However, we cannot presume that the fibers present in the lungs at death are responsible for mesothelioma. In view of the long latency between asbestos exposure and mesothelioma diagnosis (average of about 32 years in all studies), it is more likely that the effective target organ dose involves fibers in contact with the pleura many years before diagnosis. Data concerning fibers present in the pleural space are considered below.

Pleural Content Studies

A number of studies have addressed pleural fiber content, which is likely to be more biologically relevant to the development of asbestos-related pleural mesothelioma than lung tissue content.

One study comparing the retention of asbestos fibers in parenchymal and pleural tissues found that lung parenchymal retention is not a good indicator of pleural retention [Sébastien et al., 1980]. Although amphibole-type fibers longer than 8 μm were present in lung parenchyma, in parietal pleural tissues short chrysotile fibers greatly outnumbered long fibers of the amphibole type. The retention of asbestos dusts in the parietal pleura was related to type and size: 84% of the chrysotile fibers in the parietal pleura were from 0.4 to 4 μm in length and from 0.03 to 0.25 μm in diameter. If the fiber content of the pleura is responsible for pleural mesothelioma, then this study suggests that chrysotile fibers would be more important than amphiboles in causation of this cancer.

Tissue samples from 13 North American insulators were examined in order to investigate translocation of asbestos fibers [Kohyama and Suzuki, 1991]. These cases included three of asbestosis, three lung cancers, two malignant pleural mesotheliomas, and five malignant peritoneal mesotheliomas. The authors concluded that (1) translocation of inhaled asbestos fibers from the lung to other organs, such as the pleura and the peritoneum, seemed to occur frequently among asbestos insulation workers, although the route of the translocation has not been completely investigated; (2) chrysotile seemed to be more actively cleared from the lung and translocated into extra pulmonary tissues, compared with amosite; (3) chrysotile fibers cleared from the lung were not later eliminated from the host. The authors suggested that biological effects of the translocated asbestos fibers may be significant, and translocated chrysotile fibers may play an important role in the induction of either malignant mesothelioma and/or hyaline plaques. Asbestos fibers detected in both mesothelial tissue and hyaline plaques were mainly chrysotile.

Data from a study of lungs and pleurae of shipyard workers were reported by Bignon et al. [1978]. Larger fibers, often amphibole, were found in the lung tissue. In the pleura, the fibers were generally chrysotile, but shorter and thinner.

Le Bouffant [1980] observed a preferential migration of chrysotile fibers to the pleura, with a significant increase and accumulation in the pleura in comparison with the lung parenchyma. The median percentage of chrysotile fibers was 3% in the lung and 33% in the pleura. Similar results have been demonstrated in rats [Viallat et al., 1986]. Following intratracheal injection of rats with small amounts of UICC chrysotile, the shortest fibrils (mean lengths 0.44–1.32 μm , diameter 0.03 μm) reached the pleura very rapidly

and could be retrieved from the pleural fluid of rats within 1 month.

In summary, pleural content studies demonstrate that chrysotile fibers preferentially reach the pleura and are the predominant fiber found at this target site in asbestos-exposed humans. These findings are clearly more pertinent than lung content findings, and support chrysotile asbestos being a potent cause of pleural mesothelioma.

CONTRIBUTION OF CHRYSOTILE ASBESTOS TO PLEURAL MESOTHELIOMA INCIDENCE

In considering the contribution of chrysotile to pleural mesothelioma incidence, three factors will be addressed: (1) the relative potency of the three commercial asbestos fiber types; (2) the proportion of pleural mesotheliomas due to asbestos exposure; and (3) the extent of chrysotile production and use.

Potency of Chrysotile

To summarize the evidence presented concerning the potency of chrysotile asbestos in causing pleural mesothelioma, the following points can be made: (1) Studies of asbestos-exposed workers provide evidence that the chrysotile and crocidolite forms of asbestos are major causes of pleural mesothelioma in humans. Crocidolite asbestos may be 2–4 times more potent than chrysotile and amosite. (2) In rodents, chrysotile, amosite, and crocidolite asbestos have similar potencies, both in inhalation studies and in pleural injection studies. (3) Reexamination of the data on which the Stanton Hypothesis is based demonstrates that the data do not support the hypothesis that long thin amphibole asbestos fibers are the most potent in causing mesotheliomas. (4) Studies of lung tissue on which the "Amphibole Hypothesis" is based are inconsistent. In any case, findings in lung tissue at the time of diagnosis have no relevance to causal events which take place decades earlier. (5) Pleural content studies demonstrate that chrysotile fibers preferentially reach the pleural space, which is important since the pleura is the target site.

Based on these points it can be concluded that chrysotile asbestos is a potent cause of pleural mesothelioma. In light of the evidence regarding their relative potencies, it is reasonable to make the same regulatory policies for each of the three primary asbestos fiber types.

Proportion of Mesotheliomas Due to Asbestos

There has been wide variation in estimates of the proportions of mesotheliomas attributable to asbestos exposure. For example, Peterson et al. [1984] reviewed the literature

and noted that the proportions linked to asbestos exposure ranged from 13% in two studies [Ratzer et al., 1967; Brenner et al., 1982] to 100% in one study at the other extreme [Cochrane and Webster, 1978]. They concluded that there were large numbers of apparently nonasbestos-related malignant mesotheliomas.

Closer examination of the evidence does not support this conclusion. The studies which find a low proportion of cases linked to asbestos exposure tend to use poor exposure ascertainment methods, such as reviewing medical records [Ratzer et al., 1967; Brenner et al., 1982]. Assessment of the proportion of cases due to asbestos requires careful exposure ascertainment methods. This point was made very clearly by Cochrane and Webster [1978], who noted that "a history of exposure to asbestos can be established in a significant number of cases if histories are taken from the patient and recorded by a medical specialist with experience in the field of occupational medicine." In their own study, histories were taken from patients by one or other of the authors, usually by both. Where confirmation of exposure to asbestos was necessary, it was obtained from executive and government sources. All interviews were repeated at least once. These authors reported asbestos exposure in all but one of the 70 cases, and the one exception was a carpenter who claimed he had "worked with asbestos sheeting only very occasionally, and although he had always kept asbestos filling for screw holes on his workbench, he did not feel that this, or any other exposure, had been meaningful" [Cochrane and Webster, 1978].

Another early study with carefully obtained work histories found that 85% of 246 cases could be linked to asbestos exposure [Greenberg and Davies, 1974]. Living subjects were interviewed where possible. Occupational histories were also sought from coroners and from former employers and workmates. The final classification was made by two medical advisors in consultation. If one focuses attention solely on those epidemiological studies which have obtained careful work histories, then it is clear that the large majority of mesotheliomas in adult males are attributable to asbestos exposure. Since additional cases may occur from unknown occupational exposures, it is likely that at least 80% of pleural mesothelioma cases in adult males are attributable to asbestos exposure. That a large proportion is due to asbestos is also consistent with the evidence that the rate of mesothelioma prior to the 1930s was extremely low in the United States and in Europe [Mark and Yokio, 1991].

Production and Use of Asbestos in the U.S.

Chrysotile represents approximately 95% of the total world production of all forms of asbestos, with Canada its largest producer [Mancuso, 1988]. Amosite and crocidolite

accounted for only 5% of the asbestos usage in the U.S. over the years (Table VI) (Minerals Yearbook, 1936-1950). For example, the percent amphibole usage ranged from $\leq 1\%$ in 1935 to a peak of $\leq 5.9\%$ ($\leq 26,121$ tons amphiboles/445,902 tons total asbestos consumed) in 1943, then decreased to less than 2% by 1950. During this period the U.S. depended mainly on Canada for its supply of nonspinning (short chrysotile) fiber and upon South Africa, Canada, and Russia for nearly all of its spinning (long chrysotile and amphibole) asbestos. The U.S. produced only small amounts of both chrysotile and amphiboles.

Chrysotile had a wide variety of uses in the U.S. during the 1935-1945 period. The higher grade, long fibers were used in woven brake linings, textiles, and sheet packing. Lower grade, short fibers were used in asbestos shingles, paper, molded brake linings, fireproofing, floor tiles, etc. Rhodesian chrysotile was used for electric insulation, gaskets, and flameproof navy cable construction. Chrysotile was also used extensively in heat insulation [Minerals Yearbook, 1936-1950].

During the war years, amphiboles had specialized uses in the U.S. Amosite was used for insulation around steam machinery on warships, special pipe coverings, and block insulation. Crocidolite was used for asbestos-cement pressure pipes, chemical filters, acid-resistant packings, and gas masks [Minerals Yearbook, 1936-1950].

CONCLUSION CONCERNING THE CONTRIBUTION OF CHRYSOTILE ASBESTOS TO MESOTHELIOMA INCIDENCE

The three points made above can be summarized as follows: (1) chrysotile asbestos is a potent cause of pleural mesothelioma; (2) the large majority of mesothelioma is attributable to asbestos exposure; and (3) chrysotile asbestos has been the major fiber type used. Based on this evidence, we conclude that chrysotile asbestos is by far the main contributor to pleural mesothelioma causation in the U.S. and other countries in which it has been the predominant fiber type. Crocidolite may be 2-4 times more potent, but there is no valid evidence that amosite is more potent than chrysotile. Even considering an extreme that crocidolite and amosite were 10 times more potent than chrysotile, the extent of use of chrysotile means that it would still be the main contributor to pleural mesothelioma causation.

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TABLE VI. Estimated Quantities of Asbestos (Short Tons) Imported or Consumed in the United States*

Year	Canadian chrysotile imported ^a	U.S. chrysotile produced	African amphiboles imported ^b	U.S. amphiboles produced	Total consumed in U.S. ^c	Percent that is chrysotile
1935	154,200	NA ^d	945	NA	174,655	99.5
1936	226,080	10,520	2,080	404	250,922	99.0
1937	276,002	13,284	4,247	612	316,260	98.5
1939	223,840	14,686	6,359	450	255,547	97.3
1940	225,653	17,481	8,752	1,693	262,199	96.0
1941	389,391	20,144	21,447	2,252	438,741	94.6
1942	386,647	13,109	20,424	2,208	434,121	94.8
1943	385,655	3,900	24,007	2,114	445,902	94.1
1944	353,228	6,296	19,162	317	407,148	95.2
1945	355,768	13,340	13,247	250	377,875	96.4
1946	442,073	4,438	6,324	437	459,752	98.5
1949	470,783	NA	22,720	NA	535,132	95.8
1950	678,358	NA	14,805	NA	728,785	98.0

*Data for years 1935-1950 obtained from the Minerals Year Book (1936-1950).

^aIncludes crude and milled fibers, as well as "stucco and refuse."

^bMay include some small amount of African Chrysotile.

^cIncludes all imported as well as domestic-produced amphiboles and chrysotile consumed in that year.

^dNA, data not available.

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REFERENCES

- Acheson ED, Gardner MJ, Pippard EC, Grime LP (1982): Mortality of two groups of women who manufactured gas masks from chrysotile and crocidolite asbestos: A 40-year follow-up. *Br J Ind Med* 39:344-348.
- Acheson ED, Gardner MJ, Winter PD, Bennett C (1984): Cancer in a factory using amosite asbestos. *Int J Epidemiol* 13:3-10.
- Albin M, Jakobsson K, Attewell R, Johansson L, Welinder H (1990): Mortality and cancer morbidity in cohorts of asbestos cement workers and referents. *Br J Ind Med* 47:602-610.
- Amandus HE, Wheeler R (1987): The morbidity and mortality of vermiculite miners and millers exposed to tremolite-actinolite: Part II. Mortality. *Am J Ind Med* 11:15-26.
- Armstrong BK, DeKlerk NH, Musk AW, Hobbs MST (1988): Mortality in miners and millers of crocidolite in Western Australia. *Br J Ind Med* 45:5-13.
- Baris YI, Artvinli M, Şahin AA, Bilir N, Kalyoncu F, Sébastien P (1988): Non-occupational asbestos related chest diseases in a small Anatolian village. *Br J Ind Med* 45:841-842.
- Bégin R, Gauthier JJ, Desmeules M, Ostiguy G (1992): Work-related mesothelioma in Quebec, 1967-1990. *Am J Ind Med* 22:531-542.
- Berry G, Newhouse ML (1983): Mortality of workers manufacturing friction materials using asbestos. *Br J Ind Med* 40:1-7.
- Bignon J, Sébastien P, Gaudichet A, Bonnaud G (1978): Measurement of asbestos retention in the human respiratory system related to human effects. In: Workshop on Asbestos: Definition and Measurement Methods. Gaithersburg, Maryland. NBS Special Publication, pp 95-119.
- Borow M, Conston A, Livornese L, Schalet N (1973): Mesothelioma following exposure to asbestos: A review of 72 cases. *Chest* 64:641-646.
- Brenner J, Sordillo PP, Magill GB, Golbey RB (1982): Malignant mesothelioma of the pleura. *Cancer* 49:2431-2435.
- Case BW (1991): Health effects of tremolite. *Ann NY Acad Sci* 643:491-504.
- Churg A (1988): Chrysotile, tremolite, and malignant mesothelioma in man. *Chest* 93:621-628.
- Churg A, Green F (1990): Re: Mesothelioma in railroad machinists. *Am J Ind Med* 17:523-524.
- Churg A, Wiggs B, DePaoli L, Kampe B, Stevens B (1984): Lung asbestos content in chrysotile workers with mesothelioma. *Am Rev Respir Dis* 130:1042-1045.
- Cochrane JC, Webster I (1978): Mesothelioma in relation to asbestos fibre exposure. *S Afr Med J* 54:279-281.
- Cullen MR, Baloyi RS (1991): Chrysotile asbestos and health in Zimbabwe: I. Analysis of miners and millers compensated for asbestos-related diseases since independence (1980). *Am J Ind Med* 19:161-169.
- Davis JMG, Jones AD (1988): Comparisons of the pathogenicity of long and short fibres of chrysotile asbestos in rats. *Br J Exp Pathol* 69:717-737.
- Davis JMG, Beckett ST, Bolton RE, Collings P, Middleton AP (1978): Mass and number of fibers in the pathogenesis of asbestos-related lung disease in rats. *Br J Cancer* 37:673-688.
- Davis JMG, Addison J, Bolton RE, Donaldson K, Jones AD, Miller BG (1985): Inhalation studies on the effects of tremolite and brucite dust in rats. *Carcinogenesis* 6:667-674.

- Davis JMG, Addison J, Bolton RE, Donaldson K, Jones AD, Smith T (1986a): The pathogenicity of long versus short fibre samples of amosite asbestos administered to rats by inhalation and intraperitoneal injection. *Br J Exp Pathol* 67:415-430.
- Davis JMG, Addison J, Bolton RE, Donaldson K, Jones AD (1986b): Inhalation and injection studies in rats using dust samples from chrysotile asbestos prepared by a wet dispersion process. *Br J Exp Pathol* 67:113-129.
- Dement JM (1991): Carcinogenicity of chrysotile asbestos: Evidence from cohort studies. *Ann NY Acad Sci* 643:15-23.
- Dement JM, Harris RL, Symons JM, Shy CM (1982): Estimates of dose-response for respiratory cancer among chrysotile asbestos textile workers. *Ann Occup Hyg* 26:869-887.
- Dement JM, Harris RL, Symons MJ, Shy CM (1983): Exposures and mortality among chrysotile asbestos workers. Part I: Exposure estimates. *Am J Ind Med* 4:399-419.
- Dement JM, Brown DP, Okun A (1994): Follow-up study of chrysotile asbestos textile workers: Cohort mortality and case-control analyses. *Am J Ind Med* 26:431-447.
- Doll R, Peto J (1985): "Asbestos—Effects on Health of Exposure to Asbestos." London: Her Majesty's Stationery Office, Health and Safety Commission.
- Elmes PC, Simpson MJC (1977): Insulation workers in Belfast. A further study of mortality due to asbestos exposure (1940-75). *Br J Ind Med* 34:174-180.
- EPA (U.S. Environmental Protection Agency) (1986): "Airborne Asbestos Health Assessment Update." Washington, DC: Office of Health and Environmental Assessment, Document No EPA-600/8-84-003F.
- Finkelstein MM (1983): Mortality among long-term employees of an Ontario asbestos-cement factory. *Br J Ind Med* 40:138-144.
- Finkelstein MM (1984): Morality among employees of an Ontario asbestos-cement factory. *Am Rev Respir Dis* 129:754-761.
- Finkelstein MM (1989): Mortality among employees of an Ontario factory manufacturing insulation materials from amosite asbestos. *Am J Ind Med* 15:477-481.
- Greenberg M, Lloyd Davies TA (1974): Mesothelioma register 1967-1968. *Br J Ind Med* 31:91-104.
- Harington JS (1981): Fiber carcinogenesis: Epidemiologic observations and the Stanton hypothesis. *J Natl Cancer Inst* 67:977-989.
- Harington JS (1991): The carcinogenicity of chrysotile asbestos. *Ann NY Acad Sci* 643:465-472.
- Henderson VL, Enterline PE (1979): Asbestos exposure: Factors associated with excess cancer and respiratory disease mortality. *Ann NY Acad Sci* 330:117-126.
- Hobbs MST, Woodward SD, Murphy B, Musk AW, Elder JE (1980): The incidence of pneumoconiosis, mesothelioma and other respiratory cancer in men engaged in mining and milling crocidolite in Western Australia. In Wagner JC (ed): "Biological Effects of Mineral Fibres." Lyon, France: International Agency for Research on Cancer, Scientific Publication No 30, pp 615-625.
- Hughes J, Weill H (1980): Lung cancer risk associated with manufacture of asbestos-cement products. In Wagner JC (ed): "Biological Effects of Mineral Fibres." Lyon, France: International Agency for Research on Cancer, Scientific Publication No 30, p 627.
- Hughes JM, Weill H (1986): Asbestos exposure—quantitative assessment of risk. *Am Rev Respir Dis* 133:5-13.
- Hughes JM, Weill H, Hammad YY (1987): Mortality of workers employed in two asbestos cement manufacturing plants. *Br J Ind Med* 44:161-174.
- Huncharek M (1994): Asbestos and cancer: Epidemiological and public health controversies. *Cancer Invest* 12:214-222.
- Jaurand MC (1991): Observation on the carcinogenicity of asbestos fibers. *Ann NY Acad Sci* 643:258-270.
- Jones JSP, Smith PG, Pooley FD, Berry G, Sawie GW, Madeley RJ, Wignall BK, Aggarwal A (1980): The consequences of exposure to asbestos dust in a wartime gas-mask factory. In Wagner JC (ed): "Biological Effects of Mineral Fibres." Lyon, France: International Agency for Research on Cancer, Scientific Publication No 30, pp 637-653.
- Kohyama N, Suzuki Y (1991): Analysis of asbestos fibers in lung parenchyma, pleural plaques, and mesothelioma tissue of North American insulation workers. *Ann NY Acad Sci* 643:27-52.
- Kolonel LN, Yoshizawa CN, Hirohata T, Myers BC (1985): Cancer occurrence in shipyard workers exposed to asbestos in Hawaii. *Cancer Res* 45:3924-3928.
- Langer AM, Constantopoulos SH, Nolan RP, Moutsopoulos HM (1987): Association of Metsovo lung and pleural mesothelioma with exposure to tremolite-containing whitewash. *Lancet* 1:965-967.
- LeBouffant L (1980): Physics and chemistry of asbestos dust. Biological effects of mineral fibres. In Wagner JC (ed): "Biological Effects of Mineral Fibres." Lyon, France: International Agency for Research on Cancer, Scientific Publication No 30, pp 15-33.
- Lippmann M (1988): Asbestos exposure indices. *Environ Res* 46:86-106.
- Maltoni C, Pinto C, Mobiglia A (1991): Mesotheliomas following exposure to asbestos used in railroads: The Italian cases. *Toxicol Ind Health* 7:1-45.
- Mancuso TF (1988): Relative risk of mesothelioma among railroad machinists exposed to chrysotile [published erratum appears in *Am J Ind Med* (1989) 15:125]. *Am J Ind Med* 13:639-657.
- Mancuso TF (1989a): Response to Dr. CG Ohlson. *Am J Ind Med* 15:353-356.
- Mancuso TF (1989b): Response to Dr. C McDonald and Dr. A McDonald. *Am J Ind Med* 15:489-490.
- Mancuso TF (1990): Response to Drs. Churg and Green. *Am J Ind Med* 17:525-530.
- Mark EJ, Yokio T (1991): Absence of evidence for a significant background incidence of diffuse malignant mesothelioma apart from asbestos exposure. *Ann NY Acad Sci* 643:196-204.
- McDonald AD, McDonald JC (1978): Mesothelioma after crocidolite exposure during gas mask manufacture. *Environ Res* 17:340-346.
- McDonald AD, McDonald JC (1980): Malignant mesothelioma in North America. *Cancer* 46:1650-1656.
- McDonald AD, Fry JS, Woolley AJ, McDonald JC (1983a): Dust exposure and mortality in an American chrysotile textile plant. *Br J Ind Med* 30:361-367.
- McDonald AD, Fry JS, Woolley AJ, McDonald JC (1983b): Dust exposure and mortality in an American factory using chrysotile, amosite and crocidolite in mainly textile manufacture. *Br J Ind Med* 40:368-374.
- McDonald AD, Fry JS, Woolley AJ, McDonald JC (1984): Dust exposure and mortality in an American chrysotile asbestos friction products plant. *Br J Ind Med* 41:151-157.
- McDonald JC, McDonald A (1989): Mesothelioma in railroad workers. *Am J Ind Med* 15:487-490.
- McDonald JC, McDonald AD, Armstrong B, Sebastian P (1986): Cohort study of mortality of vermiculite miners exposed to tremolite. *Br J Ind Med* 43:436-444.

- McDonald JC, Armstrong B, Case B, Doell D, McCaughey WT, McDonald AD, Sebastian P (1989): Mesothelioma and asbestos fiber type. Evidence from lung tissue analyses. *Cancer* 63:1544-1547.
- McDonald JC, Liddell FDK, Dufresne A, McDonald AD (1993): The 1891-1920 birth cohort of Quebec chrysotile miners and millers: mortality 1976-1988. *Br J Ind Med* 50:1073-1081.
- Minerals Yearbook (1936-1950): Washington, DC: United States Department of the Interior, Bureau of Mines.
- Monchaux G, Bignon J, Jaurand MC, Lafuma J, Sebastian P, Masse R, Hirsch A, Goni J (1981): Mesothelioma in rats following inoculation with acid leached chrysotile asbestos and other mineral fibres. *Carcinogenesis* 2:229-236.
- Morinaga KM, Kohyama N, Yokoyama K, Yasui Y, Hara I, Sasaki M, Suzuki Y, Sera Y (1989): Asbestos fibre content of lungs with mesothelioma in Osaka, Japan: A preliminary report. In "Nonoccupational Exposure to Mineral Fibers." Lyon, France: International Agency for Research on Cancer, Scientific Publications No 90, pp 438-443.
- Mossman BT, Bignon J, Corn M, Seaton A, Gee JB (1990): Asbestos: Scientific developments and implications for public policy. *Science* 247:294-301.
- Newhouse ML, Berry G (1979): Patterns of mortality in asbestos factory workers in London. *Ann NY Acad Sci* 330:53-60.
- Newhouse ML, Sullivan KR (1989): A mortality study of workers manufacturing friction materials: 1941-86. *Br J Ind Med* 46:176-179.
- Newhouse ML, Berry G, Wagner JC (1985): Mortality of factory workers in East London 1933-80. *Br J Ind Med* 42:4-11.
- Nicholson WJ (1976): Case Study 1: Asbestos—the TLV approach. *Ann NY Acad Sci* 271:152-169.
- Nicholson WJ (1991): Comparative dose-response relationships of asbestos fiber types: Magnitudes and uncertainties. *Ann NY Acad Sci* 643:74-84.
- Nicholson WJ, Landrigan PJ (1994): The carcinogenicity of chrysotile asbestos. *Adv Mod Environ Toxicol*, xxii:407-423.
- Nicholson WJ, Selikoff IJ, Seidman H, Lillis R, Foirmy P (1979): Long-term mortality experience of chrysotile miners and millers in Thetford Mines, Quebec. *Ann NY Acad Sci* 330:11-21.
- Ohlson CG (1989): Is chrysotile a significant risk factor for mesothelioma? *Am J Ind Med* 15:351-356.
- Peterson JT, Greenberg SD, Buffler PA (1984): Non-asbestos-related malignant mesothelioma. *Cancer* 54:951-960.
- Peto J (1980): Lung cancer mortality in relation to measured dust levels in an asbestos textile factory. In Wagner JC (ed): "Biological Effects of Mineral Fibres." Lyon, France: International Agency for Research on Cancer, Scientific Publication No 30, pp 829-836.
- Peto J, Doll R, Hermon C, Binns W, Clayton R, Goffe T (1985): Relationship of mortality to measures of environmental asbestos pollution in an asbestos textile factory. *Ann Occup Hyg* 29:305-355.
- Piolatto G, Negri E, La Vecchia C, Pira E, Decarli A, Peto J (1990): An update of cancer mortality among chrysotile asbestos miners in Balangero, northern Italy. *Br J Ind Med* 47:810-814.
- Puntoni R, Vercelli M, Merlo F, Valerio F, Santi L (1979): Mortality among shipyard workers in Genoa, Italy. *Ann NY Acad Sci* 330:353-357.
- Raffin E, Lynge E, Juel K, Korsgaard B (1989): Incidence of cancer and mortality among employees in the asbestos cement industry in Denmark. *Br J Ind Med* 46:90-96.
- Ratzer ER, Pool JL, Melamed MR (1967): Pleural mesotheliomas: Clinical experiences with thirty-seven patients. *Am J Radiol* 99:863-880.
- Reeves AL, Puro HE, Smith RG, Vorwald AJ (1971): Experimental asbestos carcinogenesis. *Environ Res* 4:496-511.
- Reeves AL, Puro HE, Smith RG (1974): Inhalation carcinogenesis from various forms of asbestos. *Environ Res* 8:178-202.
- Robinson C, Lemen R, Wagoner JK (1979): Mortality patterns, 1940-1975 among workers employed in an asbestos textile friction and packing products manufacturing facility. In Lemen R, Dement JM (eds.): "Dusts and Disease." Illinois: Pathotox Publishers, Inc., pp 131-143.
- Rogers AJ, Leigh J, Berry G, Ferguson DA, Mulder HB, Ackad M (1991): Relationship between lung asbestos fiber type and concentration and relative risk of mesothelioma. A case-control study. *Cancer* 67:1912-1920.
- Roggli VL, Brody AR (1984): Changes in numbers and dimensions of chrysotile asbestos fibers in lungs of rats following short-term exposure. *Exp Lung Res* 7:133-147.
- Roggli VL, George MH, Brody AR (1987): Clearance and dimensional changes of crocidolite asbestos fibers isolated from lungs of rats following short-term exposure. *Environ Res* 42:94-105.
- Roggli VL, Pratt PC, Brody AR (1993): Asbestos fiber type in malignant mesothelioma: An analytical scanning electron microscopic study of 94 cases. *Am J Ind Med* 23:605-614.
- Rossiter CE, Coles RM (1980): HM Dockyard, Devonport: 1947 mortality study. In Wagner JC (ed): "Biological Effects of Mineral Fibres." Lyon, France: International Agency for Research on Cancer, Scientific Publication No 30, pp 713-721.
- Rubino GF, Piolatto G, Newhouse ML, Scansetti G, Aresini GA, Murray R (1979): Mortality of chrysotile asbestos workers at the Balangero mine, Northern Italy. *Br J Ind Med* 36:187-194.
- Sakai K, Hisanaga N, Huang J, Shibata E, Ono Y, Aoki T, Takagi H, Ando T, Yokio T, Takeuchi Y (1994): Asbestos and nonasbestos fiber content in lung tissue of Japanese patients with malignant mesothelioma. *Cancer* 73:1825-1835.
- Sanden A, Jarvholm B, Larsson S, Thiringer G (1992): The risk of lung cancer and mesothelioma after cessation of asbestos exposure: A prospective cohort study of shipyard workers. *Eur Respir J* 5:281-285.
- Sébastien P, Janson X, Guadichet A, Hirsch A, Bignon J (1980): Asbestos retention in human respiratory tissues: Comparative measurements in lung parenchyma and in parietal pleura. In Wagner JC (ed): "Biological Effects of Mineral Fibres." Lyon, France: International Agency for Research on Cancer, Scientific Publication No 30, pp 237-246.
- Seidman H, Selikoff IJ (1990): Decline in death rates among asbestos insulation workers 1967-1986 associated with diminution of work exposure to asbestos. *Ann NY Acad Sci* 609:300-317.
- Seidman H, Selikoff IJ, Hammond EC (1979): Short-term asbestos work exposure and long-term observation. *Ann NY Acad Sci* 330:61-89.
- Seidman H, Selikoff IJ, Gelb SK (1986): Mortality experience of amosite asbestos factory workers: Dose-response relationships 5 to 40 years after onset of short-term work exposure. *Am J Ind Med* 10:479-514.
- Selikoff IJ, Lillis R, Nicholson WJ (1979a): Asbestos disease in United States shipyards. *Ann NY Acad Sci* 330:295-311.
- Selikoff IJ, Hammond EC, Seidman H (1979b): Mortality experience of insulation workers in the United States and Canada. 1943-1976. *Ann NY Acad Sci* 330:91-116.
- Sluis-Cremer GK, Liddell FDK, Logan WPD, Bezuidenhout BN (1992): The mortality of amphibole miners in South Africa, 1946-80. *Br J Ind Med* 49:566-575.
- Stanton MF (1973): Some etiological considerations of fibre carcinogenesis. In: "Biological Effects of Asbestos." Lyon, France: International Agency for Research on Cancer, Scientific Publication No 8, pp 289-294.

- Stanton MF, Wrench C (1972): Mechanisms of mesothelioma induction with asbestos and fibrous glass. *J Natl Cancer Inst* 48:797-821.
- Stanton MF, Layard M, Tegeris A, Miller E, May M, Kent E (1977): Carcinogenicity of fibrous glass: Pleural response in the rat in relation to fiber dimension. *J Natl Cancer Inst* 58:587-603.
- Stanton MF, Layard M, Tegeris A, Miller E, May M, Morgan E, Smith A (1981): Relation of particle dimension to carcinogenicity in amphibole asbestos and other fibrous minerals. *J Natl Cancer Inst* 67:965-975.
- Talcott JA, Thurber WA, Kantor AF, Gaensler EA, Danahy JF, Antman KH, Li FP (1989): Asbestos-associated diseases in a cohort of cigarette-filter workers. *N Engl J Med* 321:1220-1223.
- Thomas HF, Benjamin IT, Elwood PC, Sweetnam PM (1982): Further follow-up study of workers from an asbestos cement factory. *Br J Ind Med* 39:273-276.
- Viallat JR, Rayboud F, Passarel M, Boutin C (1986): Pleural migration of chrysotile fibers after intratracheal injection in rats. *Arch Environ Health* 41:282-286.
- Wagner JC (1991): The discovery of the association between blue asbestos and mesotheliomas and the aftermath. *Br J Ind Med* 48:399-403.
- Wagner JC, Berry G, Timbrell V (1973): Mesotheliomata in rats after inoculation with asbestos and other materials. *Br J Cancer* 28:173-187.
- Wagner JC, Berry G, Skidmore JW, Timbrell V (1974): The effects of the inhalation of asbestos in rats. *Br J Cancer* 29:252-269.
- Wagner JC, Chamberlain M, Brown RC, Berry G, Pooley FD, Davies R, Griffiths DM (1982): Biological effects of tremolite. *Br J Cancer* 45:352-360.
- Weill H, Hughes J, Waggenspack C (1979): Influence of dose and fiber type on respiratory malignancy risk in asbestos cement manufacturing. *Am Rev Respir Dis* 120:345-354.
- Weiss W (1977): Mortality of a cohort exposed to chrysotile asbestos. *J Occup Med* 19:737-740.

EXHIBIT 50

Mesothelioma from Chrysotile Asbestos: Update

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PURPOSE: There are different mineral classes of asbestos, including serpentines and amphiboles. Chrysotile is the main type of serpentine and by far the most frequently used type of asbestos (about 95% of world production and use). There has been continuing controversy over the capability of chrysotile asbestos to cause pleural and peritoneal mesothelioma. This review is to help clarify the issue by detailing cases and epidemiology studies worldwide where chrysotile is the exclusive or overwhelming fiber exposure.

METHODS: A worldwide literature review was conducted of asbestos and associated mesothelioma including case series, case-control and cohort epidemiology studies searching for well documented chrysotile asbestos associated mesothelioma cases.

RESULTS: Chrysotile asbestos exposures have occurred in many countries around the world from mining, manufacturing and community exposures. There have been many documented cases of mesothelioma from those exposures.

CONCLUSIONS: Chrysotile asbestos, along with all other types of asbestos, has caused mesothelioma and a world-wide ban of all asbestos is warranted to stop an epidemic of mesothelioma.

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INTRODUCTION

Wagner et al. (1) discovered mesothelioma of the pleura and peritoneum from asbestos exposure in 1960. Fifty years later there is overwhelming evidence that asbestos is responsible for this fatal cancer. Mesothelioma from asbestos involves a quickly fatal disease that has a very long latent period, and causative asbestos exposures may only have had to be low. Although it is a very rare cancer as compared with most, epidemics of mesothelioma have been reported in the United States (2) and worldwide (3) and potentially continuing into the future if asbestos continues to be used.

There is overwhelming documentation by classic studies by Selikoff et al. (4) and others (5) of asbestos as an occupational cause of asbestosis, pleural plaques, lung cancer, pleura and peritoneal mesothelioma, larynx cancer, and other cancers. Environmental cancer's most famous synergism was shown by Selikoff et al. (6) and Hammond et al. (7) for occupational asbestos exposure and cigarette smoking in the incidence of lung cancer. Although cigarettes are paramount in the lung cancer–asbestos connection, cigarettes have no place in mesothelioma causation.

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Asbestos has two main classes, the serpentines (of which chrysotile is the most common type) and the amphiboles (of which crocidolite, amosite, tremolite, anthophyllite, and actinolite are the main types). A total of 95% of world asbestos production has been chrysotile, largely in the past from Canada, but also from mines in several other countries around the world. Some toxicologists and other scientists have sought to delay policy (8) implementation of preventive medicine to ban all asbestos, stating that chrysotile is not causative for mesothelioma, whereas all other types are. For approximately 30 years there has been the “amphibole hypothesis,” the assertion that chrysotile asbestos was incapable of causing mesothelioma (9).

By 2011, there are numerous occupational epidemiology and registry and case studies clearly linking all types of asbestos, including chrysotile, to pleural and peritoneal mesothelioma. The global 15-year (1994–2008) magnitude of mesothelioma is estimated to be 174,300 in a group of 56 countries that report the disease, and 38,900 for the same 15-year period by extrapolation to a group of 33 countries that do not systematically report the disease. The actual cases are probably much greater, as one mesothelioma is missed in every four or five reported cases, because of the difficulty in pathologic diagnosis (3).

There have been many risk assessments and reviews of asbestos and mesothelioma with differing conclusions, especially as to fiber type and causality (10–16). This review and commentary will lay out the studies and cases from all over the world, where the overwhelming evidence is that chrysotile asbestos was the primary or only asbestos exposure. It has been almost 10–15 years since similar review efforts

Selected Abbreviations and Acronyms

SMR = standardized mortality ratio
CI = confidence interval
OR = odds ratio

(13–15, 17, 18). There have been many new cases and studies of chrysotile asbestos-associated mesothelioma. Although it is clear to most agencies and scientists that all types of asbestos are causative for mesothelioma, there are still some remaining detractors (19), and thus the need for this review.

There is legitimate controversy in the scientific community as to the relative potency of differing types of asbestos in causing mesothelioma. The hypothesized fiber gradient potency in mesothelioma causation ranges between South African crocidolite (an amphibole type), other amphiboles, and chrysotile fibers from 500 to 1 (9) to 200 to 1 (20) to 10 to 1 (5) to 1 to 1 (15). Potency difference assertions will not be easily resolved, but even if chrysotile is much less potent than other types of asbestos, it is now the only type being used in many countries around the world, and thus it is of extreme public health importance to stop its use if it leads to fatal malignant mesothelioma. This review emphasize studies and cases in which chrysotile asbestos was the only, or overwhelming, asbestos exposure, and thus seeks to reclarify the issue that chrysotile asbestos is capable of being the associated asbestos exposure in malignant mesothelioma causation. It is of paramount importance to elucidate the chrysotile asbestos–mesothelioma connection because of its obvious implications for preventive medicine and public health. This review will begin with the U.S. epidemiology studies, and then will branch out to Canada, Mexico and then Europe, Asia, and Australia.

U.S. STUDIES

Illinois

Wolf et al. (21) examined clinical, radiologic, pathologic, and epidemiologic data on 32 patients with diffuse malignant mesothelioma diagnosed between 1968 and 1984 at a community hospital in Berwyn, Illinois. Thirty patients had a history of exposure through work ($n = 15$) and/or residence near an asbestos facility ($n = 27$). Two large chrysotile asbestos product manufacturing plants were within 4.8 km of the hospital. This case series of 32 patients had a clear high exposure to chrysotile because of where they lived or worked.

South Carolina Textile Plant

This asbestos manufacturing plant was located in Charleston, South Carolina (22), starting in 1896, and production of asbestos textiles (yarn and cloth) was 1909–1978.

Chrysotile asbestos was the primary material processed at the plant for textile production. The chrysotile asbestos used by the plant was received from Quebec, British Columbia, and Rhodesia. Small quantities of crocidolite were also used at the plant to make tape or braided packing from the 1950s to 1975. However, only 2000 pounds of total crocidolite was used, compared with the 6–8 million pounds per year of chrysotile used during the same period (23). The crocidolite was never carded, spun, or twisted, so Dement et al. (24) concluded that the predominant exposure to workers at this plant was to chrysotile asbestos. On the basis of this conclusion, the fraction amphibole in the workplace atmosphere is estimated to be at most 0.5% (0%–2%). Dement et al. (22) studied the cohort who worked at least 1 month during 1940–1967, including 1247 white men, 1229 white women, and 546 black men. Follow-up was carried out through 1990.

Hein et al. (25) extended follow-up for mortality through 2001. Twenty-one nonwhite women were added to the cohort, and 29 workers for which updated demographic information who had previously been excluded from analysis were added for a total of 3072 workers with vital status follow-up through 2001. Two deaths were certified as caused by mesothelioma on the death certificates of two white men who had latency periods of 37 and 34 years and who worked in the plant for 25 and 32 years (22). Both of these workers had primarily worked in the spinning operations part of the plant. Hein et al. (25) add a third mesothelioma to the two certified by Dement et al. (22). This third mesothelioma occurred in 1995, “nearly 50 years after the employee began working in the mule spinning department for approximately 2.5 years” (25).

North Carolina Textile Plants

Workers employed for at least 1 day between January 1, 1950 and December 31, 1973, in any of four plants in North Carolina, that produced asbestos textile products were enumerated by Loomis et al. (26). Vital status was ascertained through December 31, 2003. Historical exposures to asbestos fibers were estimated from work histories and 3578 industrial hygiene measurements taken 1935–1986. Mortality of the cohort of 5770 workers was compared with that of the national population via standardized mortality ratios (SMRs). Approximately 90% of the asbestos came from Canada, with smaller amounts from the United States and South Africa, and occasionally from Russia and Australia. According to available records, only chrysotile was used except for a separate operation in Plant 3, where a limited amount of amosite was carded, twisted, and woven between approximately 1963 and 1976. The other plant (Plant 2) produced friction products and other finished goods from purchased asbestos yarn and tape. Eight mesotheliomas were found in total, 4 pleural

and 4 peritoneal. This study provides evidence that workers exposed to chrysotile are at increased risk of mesothelioma, with an SMR of approximately 11 based on 4 deaths observed and 0.37 expected after mesothelioma began to be coded as a separate cause of death in 1999 with the 10th revision of the *International Classification of Diseases*.

U.S. Railroad Machinists

Mancuso (27, 28) reported on a cohort of 181 railroad machinists who worked 1920–1929 and were alive as of 1945 and were followed through 1986. Mancuso (29, 30) made a strong case that their railroad occupational exposures to asbestos were only to chrysotile. Fourteen mesotheliomas were found as of 1986 in this group. The mortality rate of 88.1 per 1000 deaths is one of the highest rates ever found for mesothelioma.

Plastics Manufacturing New Jersey

Dell and Teta (31) studied mortality through 1988 for 5932 male employees who worked for at least 7 months between January 1, 1946, and December 31, 1967, at a New Jersey plastics manufacturing and research and development plant. The cohort was followed through 1988. There were 1859 deaths. Among them were nine pleura mesothelioma deaths (five listed on the death certificate as underlying and four listed as contributory), which occurred with an average latent period of 33.4 years in this cohort who were primarily making phenolic resins. Asbestos, “usually chrysotile” (31) was used as a filler in the plastic molding process.

U.S. Brake Repair Workers

Langer and McCaughey (32) describe a case of diffuse pleural mesothelioma in a man whose sole exposure to asbestos was to the chrysotile during brake maintenance and repair. This 55-year-old man was admitted to hospital 1980 and died in 1981. Since the age of 19 he had serviced automobiles, including the replacement of brake linings. He had no other occupational history of exposure to asbestos or residential history near an asbestos plant. Postmortem digestion of tissue and electron diffraction revealed chrysotile fibrils. 10% of the fibrils were longer than 10 μm . No amphibole fibers were found. The authors estimate that only chrysotile had been used in brake pads since the 1940s.

Lemen (33) reviewed possible asbestos exposure from its use in brakes. Molded brake linings with chrysotile asbestos were introduced in 1927 (33) and were in virtually every car by 1940 and continued to be used in rear brake drums even after the introduction of disk brakes in the era of 1965–1975. Chrysotile comprised 40% to 50% of the brake lining. Most of the chrysotile fibers did not escape to the environment during driving brake use. The fibers ended up as a nonfibrous material called fosterite formed by the heat of the braking process (approximately 600°F). However, some

fibers remain unchanged and escape into the environment. Also, during repair and maintenance of brakes, there is potential for chrysotile exposure to the garage mechanics or those in the vicinity. There is a possibility that fosterite has the potential to affect health, but this has not been adequately investigated. The remaining fibers are short (<5 μm in length). There is some evidence that short fibers are less toxic than longer, thinner fibers—longer than 10 microns (34), which is been disputed by Dodson et al. (35) more recently. However, Lemen (33) emphasizes that even if short fibers are less toxic, that they are not without carcinogenic hazard. There was heightened interest in the chrysotile short fiber carcinogenicity question after the collapse of the World Trade Towers on September 11, 2001. Lemen’s (33) greatest concern was exposure to mechanics removing brakes or installing new brakes, including the practices of manipulation of brake pads with compressed air blowout, wire brushing or other methods of cleaning out old pads.

Connecticut Friction Plant

Finkelstein and Meisenkothen (36) describe six mesothelioma cases in the Connecticut Raybestos plant that made brake linings, transmission and other automotive friction disks, bands, and other materials. Workers in the plant were exposed to chrysotile asbestos during the period of 1940s to the 1980s.

Pennsylvania Textile

O’Donnell et al. (37) studied 55 asbestosis cases in workers who had worked in a Pennsylvania chrysotile textile factory who were patients in the Lancaster General Hospital 1940–1965. Five of the cases developed mesothelioma (three peritoneum, one pleura, and one both). The interval from initial exposure until the neoplasms were diagnosed in this series was 20–40 years. Mann et al. (38), in a previous study of these asbestosis cases, and three of the O’Donnell et al. (37) mesothelioma cases, found that the factory was using chrysotile.

California Naturally Occurring

California has large amounts of serpentine rock in the northern and central part of the state in the Sierra Nevada Coast and Klamath mountain ranges. Serpentine is the base mineral of chrysotile asbestos. Pan et al. (39) conducted a case–control study comparing 2908 incident malignant mesothelioma cases as compared with the same number of pancreatic controls matched by 5-year age group and sex from the California Cancer Registry. Occupational and residential histories were determined and compared. Both occupational exposure and proximity to asbestos sources was associated with mesothelioma incidence. The authors conclude that they confirmed their hypothesis of proximity

to nonoccupational asbestos (serpentine) was associated with malignant mesothelioma.

CANADA

Quebec Miners and Millers

McDonald et al (40) surveyed the Canadian Association of Pathologists and the Quebec Association of Laboratory Physicians for fatal cases of primary malignant tumors of the pleura or peritoneum between 1959 and 1967. They found a total of 165 cases: 113 pleural, 45 peritoneal, 3 pleural, and peritoneal and 4 pericardial. A case–control study was conducted in which they compared the mesothelioma cases with two control groups, one composed of primary lung cancer and one composed of secondary lung cancer cases. Relatives and friends of the deceased filled out questionnaires on occupation, residence, family history, smoking habits, and household dust exposure. An association between mesothelioma and definite or probable occupational exposure to asbestos was demonstrated, but could only be confirmed in 20% of the male cases and in one female case. The documented occupational exposure was more in the manufacturing and industrial application than in mining, indicating to the authors that chrysotile was less associated than other forms of asbestos. Although the authors' hypothesis is possible, the overwhelming occupational Quebec exposure to asbestos in this region was from extremely large chrysotile mines (Thetford and Asbestos) and its subsequent use in manufacture of products. In addition, residential exposure would be to chrysotile from general environmental contamination from the mines (ie, leakage from trucks, washing of workers clothes at home).

McDonald et al. (41) reported on the mesotheliomas in a widely reported study of a cohort of 9780 men who worked as chrysotile miners and millers in Quebec at the Thetford mines. Thirty-three mesotheliomas were observed in miners and millers whose work was with chrysotile asbestos. The overwhelming asbestos exposure to these men was chrysotile. Twenty-one autopsy lung specimens were examined on electron microscope, which showed the amphibole tremolite at about 8 times as chrysotile in 14 of the lungs specimens and 1.7 times greater in 5 of the specimens. The authors ran several statistical analyses attempting to attribute the distribution of mesothelioma cases to exposure to nonchrysotile tremolite instead of the cases' overwhelming exposure to chrysotile in time and space, calling it the tremolite hypothesis. The geographic and time statistical analyses had mixed results even though the authors conclude quite enthusiastically concerning their tremolite hypothesis. Whether it was the chrysotile or the chrysotile-tremolite combination that caused the mesothelioma cases is irrelevant, because the two occurred together, ie, Thetford

chrysotile often has roughly 1% tremolite, and if McDonald et al. (41) are correct that it is the 1% tremolite–99% chrysotile combination that is responsible for the mesotheliomas, then Thetford asbestos (99% chrysotile, 1% tremolite) is still the asbestos exposure to these cases of mesothelioma (whatever its exact geologic formula).

Canadian Case Reports

In 2010, there was a case report of peritoneal mesothelioma in a mill worker from a tremolite-free Canadian asbestos mine (42). He worked for 25 years as a mill worker in two different Carey mines and then 15 years additional as yield maintenance foreman. Born in 1923, he died 1990. There was no other known exposure to asbestos except chrysotile. Samples from this mining area have been consistently tremolite free.

Champion (43) reported on two cases of mesothelioma in two young men. One was the 31-year-old son of a pipe fitter in Scotland; there is no way to tell which fiber type was responsible. However, the second case, a 32-year-old man, had been born in Fulford, Quebec and had moved to Asbestos, Quebec, at age 3, where he lived for 23 years. For 10 years he worked “....as an asbestos mine prospector in Quebec and elsewhere in Canada....The patient in Case 2 had worked for many years in the Canadian mining industry and had lived in a mining town. He had been exposed only to chrysotile” (43).

Canadian Environmental Exposures from Quebec Chrysotile Mines

Camus et al. (44) described female mesothelioma cases first diagnosed from 1970 to 1989 from the area of the Quebec chrysotile mines of Thetford and Asbestos Canada. Ten pleura and one peritoneal mesothelioma cases were found in a survey of 817 female residents.

MEXICO

Aguilar-Madrid et al. (45) carried out a case-control study of 119 pleural malignant mesothelioma workers insured by the Mexican Institute of Social Security and 353 age-, sex-, and city-matched controls with the same type of insurance. The cases were immunohistopathologically confirmed by two certified pathologists. Occupational and sociodemographic histories were obtained. Asbestos used in Mexico is overwhelmingly chrysotile imported from Canada. Odds ratios for occupational exposure to asbestos for cases compared with controls were 3.7 (95% confidence interval [95% CI], 1.3–10.4) for the whole group and 14.3 (95% CI, 8–26) for the 96 cases as compared with 111 controls with the most certain data. The authors forecast an epidemic of

future mesothelioma cases if there is continued use of imported chrysotile asbestos in Mexico.

EUROPE

British Women Who Manufactured Gas Masks

Acheson et al. (46) reported on a 40-year follow-up of two groups of women who manufactured gas masks, one at Blackburn (n = 570) out of chrysotile for civilians working in 1939, and the other factory in Leyland and Preston (n = 757) working in 1939 manufacturing respirators for soldiers out of crocidolite and some chrysotile. Five death certificates mentioned mesothelioma, four in the crocidolite group, but one in the chrysotile-only Blackburn group as the underlying cause of death.

Italy

There is an open air chrysotile mine located in Balangero, Italy, which is located in the foothills of the Alps (near Turin, northern Italy). The mine and its associated milling, crushing, screening, and bagging plant began production of chrysotile asbestos in 1916 and, with the exception of the war years from 1939 to 1945, production increased each year. By the time it closed in 1990, the mine was producing 500 tons of chrysotile asbestos per day from the crushing of 9000 tons of serpentine rock (47). In an examination of several air samples using scanning electron microscopy, researchers did not find amphibole fibers at detectable concentrations. In addition to the asbestos being at least 99% chrysotile, a fibrous silicate known as balangeroite, accounted for 0.2%–0.5% of the total mass of samples as commercialized from the Balangero mine. Two mesothelioma deaths were observed, both in workers whose first exposure had occurred at least 20 years earlier. In continuing study of the same facility (2009), Pira et al. (48) found four pleura mesotheliomas as compared with 0.9 expected (4.67 SMR; 95% CI. 1.27–11.96) and 5 pleura and peritoneal mesotheliomas as compared with 1.6 expected (3.16 SMR; 95% CI, 1.02–7.36).

Mirabelli et al. (49) searched the Registry of Malignant Mesotheliomas of Piedmont and found four cases of pleural mesothelioma among blue-collar workers in the mine in addition to the original two reported (6 observed vs 1.5 expected; $p < .01$) They found three mesothelioma cases among white-collar workers in the mine, and five additional mesotheliomas in workers hired by subcontractors. In addition, three more cases were found among workers processing chrysotile outside the mine. Ten additional cases were found who had not worked in the mine (who might have been exposed to nonoccupational exposures such as mine tailings). In total, 14 mesothelioma cases were found among active workers in the mine and 13 exposed to Balangero

chrysotile outside the mine. Mirabelli et al. (49) consider the cluster of 14 mesothelioma cases they found among workers active in the mine and 13 among others “...exposed to Balangero chrysotile adds further evidence to the carcinogenicity of tremolite-free chrysotile” (49).

As to the balangeroite contaminant of chrysotile, a study was conducted Turci et al. (50). They incubated fibers in simulated phagolysosomal fluids with pure chrysotile, pure balangeroite, one sample chrysotile contaminated with balangeroite, and two chrysotile samples contaminated with tremolite. The authors concluded that the balangeroite cannot be considered solely responsible for the mesothelioma cases in Balangero.

A historical cohort study of the largest Italian asbestos textile factory that was in operation 1865–1986 in Grugliasco, Italy, was conducted by Mamo and Costa (51). The study cohort consisted of 1653 workers who were followed through the national mortality registry 1981–1995. SMRs were calculated using for comparison a workforce of manual workers in Turin. Statistically significant excesses for pleural mesothelioma (4 in males, SMR = 3322 men, 10 in women, 13248 females) were observed. This textile plant used the chrysotile mined in Balangero. The textiles were mostly composed of medium and long-fiber chrysotile asbestos, generally mixed with rubber, various resins and additives, and at times with metallic netting.

East Germany

Sturm et al. (52) describe the uses of asbestos and asbestos related diseases in the former East Germany. Applications included asbestos construction materials, sheets, boards, tiles, pipes, textiles, filters, seals, putties, filling and joint compounds, plastics, friction materials, and talcum powder. Almost all of the asbestos was chrysotile from the former Soviet Union and smaller quantities of “long-fibred grades” chrysotile from Canada and small amounts of crocidolite from Mozambique and Italy. Chrysotile asbestos from Russia was introduced into East Germany in the early 1960s to establish an asbestos-cement industry. Occupational diseases from 1970 to 1988 in the region were analyzed. 812 mesothelioma cases were investigated and “...due to the exact knowledge of the conditions of production it is possible for 481 cases exposed to asbestos to provide detailed information about the relevant grades of asbestos....On this basis sole exposure to chrysotile asbestos was determined to be the cause of disease in 67 cases....This clearly points to the mesothelioma-inducing potential of chrysotile asbestos from Russia...” (52).

Lithuania

Smalyte et al. (53) described the asbestos situation in Lithuania, where asbestos was used on industrial sites at very high levels until 1990. There were two factories that

have manufactured asbestos-cement pipes and plates in Lithuania from the 1950s. In both plants only chrysotile asbestos was used, and the asbestos came from mines in the Ural area of Russia and Kazakhstan. The content of tremolite fibers in Russian asbestos is much lower than in Canadian chrysotile (54). The asbestos consumption in both factories remained at the same level up to 1990, when it started to decline. Included in the study (53) were all the workers employed 3 months or more before 1986, from 1956 in one plant and from 1963 in the other. The year 1985 was chosen as the last year for entry because asbestos-related cancers have a long induction period, seldom less than 15 years. The authors studied complete data on 1887 workers. The study population (53) was followed from 1978 to the end of 2000. One case of pleural mesothelioma was found and the study showed no deaths from pneumoconiosis. No amphiboles were added to the Lithuanian asbestos-cement production; so the study is informative concerning chrysotile asbestos exposure and mesothelioma risk, with one observed case and 0.3 expected.

Everatt et al. (55) investigated retrospective occupational exposures to asbestos for 298 lung cancer and 4 mesothelioma patients admitted to the Institute of Oncology, Vilnius between November 1, 2003 and May 15, 2005. Occupational histories and lung burden studies were carried out. From the lung burden studies, only chrysotile fibers were found in Lithuania specimens as compared with specimens from other countries in Europe. This agrees with the importation of chrysotile asbestos from Russia for use in Lithuania. Of the four mesothelioma cases (3 men and 1 woman), the diagnosis was confirmed histologically or cytologically. The mean age of the three males was 60.7 and the one woman patient was 43 years of age. One of the male mesothelioma patients had an occupational exposure to chrysotile. The other three did not have documentable asbestos exposures. The authors emphasize the lack of recognition by physicians of occupational etiology of cancer in Lithuania, so over time there may have been many missed cases of mesothelioma.

MIDDLE EAST, AFRICA, ASIA, AUSTRALIA, PACIFIC

Egypt

An epidemiological and environmental study of asbestos and malignant pleural mesothelioma was conducted by Madkour et al. (56) in Shubra El-Kheima city in the greater Cairo area. The study was carried out near a large chrysotile asbestos manufacturing plant. It was constructed in 1948, and its main products were asbestos cement pipes and concrete. Workers in the plant were studied along with populations in six areas near the plant and a control agricultural population far geographically remote from the plant. The

subjects were picked by cluster sampling. Of the 322,109 people living in the area of the plant 3059 were sampled and 2913 participated in mass miniature radiography. Occupational histories were taken. Of the 543 plant workers 487 agreed to undergo mass miniature radiography. A control group in an agricultural area 40 km from the plant (Banha city) was also studied. A total of 1041 were sampled and 979 agreed to be in the study. None of these had any occupational history with asbestos exposure. For those subjects who had suspected abnormalities, they had full chest radiographs. For those that had abnormal chest x-rays they had high-resolution computerized scans. There were 83/2913 (2.8%) cases in the environmentally exposed group, 4/487 (0.8%) in the occupationally exposed group, and 1/979 (0.1%) in the control group. The risk of developing malignant pleural mesothelioma was 26 times greater among the occupationally and environmentally exposed groups compared with the nonexposed group. The number of cases was greater in the environmental area with the greatest concentration of airborne chrysotile asbestos fibers.

Zimbabwe

Cullen and Baloyl (57) reported on a study of 51 individuals who had been compensated for pneumoconiosis and who had exposure to chrysotile asbestos in Zimbabwe's mines or mills since that country's independence in 1980. A sample of more than 300 who had been compensated for pneumoconiosis were examined for occupational history and availability of complete medical and occupational records to select the sample of 51 for the study. The exposure period of the 51 included workers encompassing 1932–1986 and they were certified between 1980 and 1987. X-rays, demographic data, medical and occupational histories, and laboratory reports were examined in the 51 individuals. There were two cases of pathologically confirmed malignant mesothelioma (pleural), one of these found among 18 asbestosis cases.

Australia

Rogers et al. (58) reported on their study of the lung tissue of 221 definite and probable cases of malignant mesotheliomas reported to the Australian Mesothelioma Surveillance Program 1980–1985 and age-sex frequency matched control series of 359 postmortem cases. A total of 697 definite or probable mesotheliomas were diagnosed during the period, and lung tissue material for fiber analysis was available for 221. A total of 207 were pleural, and 14 were peritoneal. The postmortem lung tissue specimens were examined by light microscope and analytical transmission electron microscope and energy dispersive x-ray analysis. Fiber type and length greater or less than 10 μm were reported and only fibers larger than 2 μm were counted.

TABLE 1. Chrysotile asbestos mesothelioma studies

Authors	Location and facility type	Study type	Mesotheliomas
Wolf et al. 1990 (21)	Berwyn, Illinois hospital	Case series	32
Dement et al. 1994(22) and Hein et al. 2007 (25)	S. Carolina textile plant	Cohort	2
Loomis et al. 2009 (26)	North Carolina textiles	Cohort	4 pleural, 4 peritoneal
Mancuso 1983 (27), 1988 (28)	U.S. railroad machinists	Cohort	14
Dell and Teta 1995 (31)	New Jersey Plastics	Cohort	9
Langer & McCaughey 1982 (32)	Brake worker U.S.	Case report	1
Finkelstein & Mesenkenoth (36)	Conn. Automotive brakes and friction	Case series	6
O'Donnell et al. 1966 (37) and Mann et al. (38)	PA textile plant and hospital	Case series	5
McDonald 1994 (41)	Quebec CA asbestos mines	Cohort	38
Egilman and Menédez 2010 (42)	Canadian mill worker	Case report	1 peritoneal
Champion 1971 (43)	Quebec mine inspector	Case report	1
Camus et al. 2002 (44)	Quebec CA mine area females	Case series	10 pleural, 1 periton
Aguilar-Madrid et al. 2009 (45)	Mexico	Case-control	119
Acheson 1982 (46)	England gas mask workers	Case report	1
Piolatto et al. 1990 (47)	Balangero, Italy, mine	Cohort	2
Pira et al. 2009 (48)	Balangero, Italy, mine	Cohort	9
Mirabelli et al. 2008 (49)	Piedmont Italy Mesothelioma Registry	Case series	14 miners, 13 environ
Mamo and Costa 2004 (51)	Grugliasco, Italy, textile factory	Cohort	14
Sturm et al. 1994 (52)	East Germany	Cases	67
Smailyte et al. 2004 (53)	Lithuania cement pipe factories	Cohort	1
Everatt et al. 2007 (55)	Lithuania Institute of Oncology	Case series	4
Madkour et al. 2009 (56)	Cairo, Egypt, cement pipe factory	Cohort	4 factory, 83 environ
Cullen and Baloyl 1991 (57)	Zimbabwe mines and mills	Case series	2
Rogers et al. 1991 (58)	Australia mesothelioma surveillance	Case-control	25
Shiqu et al. 1988 (59)	Laiyuan, Hebei, China, mining area	Cohort	2 pleural, 1 periton
Cai et al. 2001 (60)	Chinese chrysotile miners	Cohort	4
Yano et al. 2001 (61)	Chongquin, Chinac textiles, cement and friction and heat-resistant materials	Cohort	2
Yano et al. 2009 (62)	Chongqing, China	Case report	1 peritoneal
Huilan and Zhiming 1993 (63)	China, 8 factories	Cohort	2
Baumann et al 2007(64), 2010 (65)	New Caledonia Cancer Registry	Case-control	109

There was a subgroup of 25 cases (23 pleural and 2 peritoneal) where only chrysotile was found in the lungs. There was a significant trend in odds ratio with increasing chrysotile fiber content. Two of the cases had a definite history of exposure only to chrysotile, 11 had a history of mixed exposure, and 10 had no documented history of asbestos exposure, and 2 had no available history. "Analysis of a small group of cases and controls with only chrysotile found in the lungs also showed a statistically significant trend ($p < .005$) of an increasing relative risk of mesothelioma with increasing fiber content in lungs" (58).

China

Three cases of mesothelioma were observed in workers in a chrysotile plant located in Chongquin, Hebei Province in China in a retrospective mortality study covering the years of 1972–1981 (59). The plant opened in 1939 and continued to grow and expand the variety of products it produced, including textiles, asbestos cement products, friction materials, rubber products, and heat-resistant materials. In 1996, 6000 tons of raw chrysotile asbestos obtained from two mines in Sichuan, China, were used in this plant and through its history, chrysotile was the only type of asbestos

used in the plant. Commercial samples from the two mines at Sichuan exclusively used in the Chongquin chrysotile plant were analyzed by x-ray diffraction and transmission electron microscopy. The results showed the samples to contain less than 0.001% of tremolite fiber. The cohort comprised male workers employed before January 1972. A total of 515 men were selected for this cohort and followed up for 25 years through 1996. There were two reported cases of mesothelioma in the cohort, one pleural and the other peritoneal.

In a review of asbestos exposed miners in another region in China, Laiyuan, Cai et al. (60) report on a cohort study of 9950 chrysotile miners from five different mines. Four mesothelioma deaths were found from the workers for the Laiyuan miner after 15 years of follow-up.

Yano et al. (61) conducted a 25-year longitudinal study (1972–1996) in Chongquin, China. The study cohort comprised 515 male asbestos plant workers exposed to chrysotile only. The control cohort included 650 workers from an electronics plant. Two cases of malignant mesothelioma, one pleural and the other peritoneal, were found in the asbestos cohort.

Yano et al. (62) report the case of a 35-year-old chrysotile asbestos worker in Chongqing, China, who developed

mesothelioma after only 4 years of employment in an asbestos textile plant. In addition to the adult work, he had been “born and bred in a company residence of an asbestos plant and manually spun asbestos during school age.” (62). Only chrysotile was used in the plant.

Huilan and Zhiming (63) report the results of a retrospective cohort study of eight chrysotile factory workforces in China. A total of 5893 workers in the eight plants who had retired or left the plants between 1972 and 1986 were traced to 1986 for cause of death. The rate of follow-up was 97.1%. Two pleural mesothelioma deaths were documented in this chrysotile-only exposed cohort.

New Caledonia

Very high incidences of malignant mesothelioma have been found in the Island of New Caledonia (64). The age-standardized incidence rate for mesothelioma for men was 4.6 per 100,000 per year in the 1996–2005 period and 3.1 for women. Baumann et al. (64) studied the possible association between pleural mesothelioma and a traditional lime, called “Po,” to cover houses. 68 pleural mesothelioma cases were studied from the tumor registry from 1984 to 2002. For each case, two controls were selected from the cancer registry matched by gender, age, and date of diagnosis. Po, ethnicity, serpentine in the soil, and other factors were investigated. The only significant factor in a linear regression of ethnicity, Po, and other factors, was serpentine (the base rock of chrysotile asbestos) in the soil $p = .017$.

Baumann et al. (65) further studied all mesothelioma cases (109) from the New Caledonia Cancer Registry from 1984 to 2008. Factors that were investigated were demographic variables, residential history, school, and occupational history. The most significant finding was the association with living near roads covered by serpentine, followed by the number and proximity of serpentine quarries and the size of the surface area containing serpentines. There are also locations on the island with a tremolite-actinolite type of asbestos. The odds ratio (OR) for the serpentine (antigorite) area was great (OR, 20.667; 95% CI, 4.028–106.03) as compared with the tremolite-actinolite area (OR, 1.714; 95% CI 0.664–4.423).

DISCUSSION

This review sought to search the world epidemiology literature on mesothelioma to catalogue the case-series, cohort, and case-control studies in which the asbestos exposure appeared to be overwhelmingly to the chrysotile type. Mesothelioma is a rare cancer, but as illustrated in Table 1 (21, 22, 25–28, 31, 32, 36–38, 41–49, 51–53, 55–65), there have been cases in which chrysotile is the exclusive or

overwhelming asbestos exposure from all over the world. Many members of the mainstream scientific community have concluded from the evidence that there is no “safe” level of exposure to asbestos of any type. “...an occupational history of brief or low-level exposure should be considered sufficient for mesothelioma to be designated occupationally related...” to asbestos exposure (66).

In addition to the “amphibole hypothesis,” there have been scientific disagreements about the biopersistence of chrysotile in the pleura and its capability to cause mesothelioma, and the capability of fibers less than 10 μm to cause cancer (34). The review by Dodson et al. (35) describes the work of Pott et al. (67) and others that makes it clear that small fibers are capable of carcinogenicity, and the work of Suzuki and Yuen (68) that chrysotile migrates to the pleura from the lung.

An occupational history of brief or low level exposure to asbestos is considered sufficient for mesothelioma to be considered as occupationally related, although many times the exposure is not documented because of mixed exposures to different substances in the construction trades or other work environments and the imperfect nature of retrospective recall of either the worker or the surviving relatives. We do know that many asbestos exposed individuals do not know they have been exposed when they have actually been exposed in the workplace or in the community. Thus, a mesothelioma labeled as “idiopathic” may be due to the fact that the victim’s exposure to asbestos is not known or documented.

The authors of multiple studies have shown that all levels of exposure to asbestos can increase the risk of mesothelioma. Because there is no known threshold, then current regulatory levels for asbestos may be capable of mesothelioma carcinogenicity. Brief or low exposures to asbestos are capable of mesothelioma carcinogenicity. It is universally accepted that it takes a greater exposure to asbestos to cause asbestosis than the amount needed for mesothelioma carcinogenicity. Thus, in worker groups, like brake workers, where there has been excess asbestosis, these workers have definitely been exposed to asbestos levels enough for mesothelioma carcinogenicity.

It is clear that all types of asbestos are capable of malignant mesothelioma carcinogenicity. Chrysotile asbestos may be less potent in this regard than certain types, for instance South African crocidolite, but given the widespread use and continuing exposure to chrysotile in many countries of the world, there have been projections of a continuing epidemic of mesothelioma (69).

SUMMARY

There are many well-documented cases of mesothelioma from chrysotile asbestos in case-reports and epidemiology studies from all over the world. The published studies most

certainly missed many cases of mesothelioma that have occurred from chrysotile asbestos exposure because of the difficult nature of the pathologic definitive diagnosis, the difficulty in documenting work exposures of the past, the absence of study of many workers who were exposed and left the industry without being included in the studies, and the environmental exposure that occurred to nonworkers. Thus, it is reasonable to assume that the total numbers of cases that are documented is just the tip of the iceberg of a potential world-wide environmental cancer epidemic of mesothelioma from asbestos, including chrysotile asbestos. There is general agreement among many scientists and health agencies that exposure to any type of asbestos (chrysotile or amphibole) can increase the likelihood of lung cancer, mesothelioma, and nonmalignant lung and pleural disorders (70–79).

Given the continued use of chrysotile asbestos in many countries worldwide, there have been projections of a continuing and increasing mesothelioma epidemic. In addition there are many safer, cheaper substitute materials available for each asbestos use, including plastic, cellulose, plant fibers, clay and wood fibers (80). Consequently, a number of the members of the scientific community have repeatedly called for a universal ban on the use of all types of asbestos as a mandatory measure to protect the public health (80). An analysis (81) of trends in global mesothelioma mortality rates over time, comparing countries that have banned asbestos to countries that have continued use, showed reduction in mortality in countries after adopting a ban. It is long past the time for a worldwide asbestos ban.

REFERENCES

- Wagner JC, Sleggs CA, Marchand P. Diffuse pleural mesothelioma and asbestos exposure in the northwestern Cape Province. *Br J Ind Med.* 1960;17:260–271.
- CDC. Malignant mesothelioma mortality—United States, 1999–2005. *MMWR Morb Mortal Wkly Rep.* 2009;58:393–396.
- Park E-K, Takahashi K, Hoshuyama T, et al. Global magnitude of reported and unreported mesothelioma. *Environ Health Perspect.* 2011;119:514–518.
- Selikoff IJ, Hammond EC, Seidman H. Mortality experience of insulation workers in the United States and Canada. *Ann NY Acad Sci.* 1979;330:91–116.
- Doll R, Peto J. Asbestos. Effects on Health of Exposure to Asbestos. London: Health and Safety Commission, Her Majesty's Safety Office; 1985.
- Selikoff IJ, Hammond EC, Churg J. Asbestos exposure, smoking and neoplasia. *JAMA.* 1968;204(2):106–112.
- Hammond EC, Selikoff IJ, Seidman H. Asbestos exposure, cigarette smoking and death rates. Asbestos exposure, cigarette smoking, and death rates. *Ann NY Acad Sci.* 1979;330:473–490.
- Kanarek MS. The delay of preventive medicine for asbestos caused disease in the 20th century. *Wisconsin Med J.* 2009;10:286–287.
- Mossman BT, Bignon J, Corn M, Seaton A, Gee JBL. Asbestos: Scientific developments and implications for public policy. *Science.* 1990;24:294–301.
- Hodgson JT, Darnton A. The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure. *Ann Occup Hyg.* 2000;44:565–601.
- Berman DW, Crump KS. A meta-analysis of asbestos-related cancer risk that addresses fiber size and mineral type. *Crit Rev Toxicol.* 2008;38:49–73.
- Silverstein MA, Welch LS, Lemen R. Developments in asbestos cancer risk assessment. *Am J Ind Med.* 2009;52:850–858.
- Landrigan PJ, Nicholson WJ, Suzuki Y, LaDou J. The hazards of chrysotile asbestos: A critical review. *Ind Health.* 1999;37:271–280.
- Stayner LT, Dankovic DA, Lemen R. Occupational exposure to chrysotile asbestos and cancer risk: A review of the amphibole hypothesis. *Am J Ind Med.* 1996;86:179–186.
- Nicholson WJ. The carcinogenicity of chrysotile asbestos—a review. *Industrial Health.* 2001;39:57–64.
- Yarborough CM. Chrysotile as a cause of mesothelioma: An assessment based on epidemiology. *Crit Rev Toxicol.* 2006;36:165–187.
- Smith AH, Wright CC. Chrysotile asbestos is the main cause of pleural mesothelioma. *Am J Ind Med.* 1996;30:252–266.
- Cullen MR. Chrysotile asbestos: Enough is enough. *Lancet.* 1998;351:1377–1378.
- McDonald JC. Epidemiology of malignant mesothelioma—An outline. *Ann Occup Hyg.* 2010;54:851–857.
- Berman DW, Crump KS. Update of potency factors for asbestos-related lung cancer and mesothelioma. *Crit Rev Toxicol.* 2008;38:1–47.
- Wolf KM, Piotrowski ZH, Engel JD, Bekeris LG, Palacios E, Fisher KA. Malignant mesothelioma with occupational and environmental asbestos exposure in an Illinois community hospital. *Arch Intern Med.* 1987;147:2145–2149.
- Dement J, Brown D, Okun A. Follow-up study of chrysotile asbestos textile workers: cohort mortality and case-control analyses. *Am J Ind Med.* 1994;26:431–447.
- Dement J, Harris R, Symons M, Shy C. Exposures and mortality among chrysotile workers. Part I: Exposure Estimates. *Am J Ind Med.* 1983a;4:399–419.
- Dement J, Harris R, Symons M, Shy C. Exposures and mortality among chrysotile workers. Part II: Mortality. *Am J Ind Med.* 1983b;4:421–433.
- Hein MJ, Stayner L, Lehman E, Dement JM. Follow-up study of chrysotile textile workers: Cohort mortality and exposure-response. *Occup Environ Med.* 2007;64:616–625.
- Loomis D, Dement JM, Wolf SH, Richardson DB. Lung cancer mortality and fiber exposures among North Carolina asbestos textile workers. *Occup Environ Med.* 2009;66:535–542.
- Mancuso TF. Mesothelioma among machinists in railroad and other industries. *Am J Ind Med.* 1983;4:501–513.
- Mancuso TF. Relative risk of mesothelioma among railroad machinists exposed to chrysotile. *Am J Ind Med.* 1988;13:639–657.
- Mancuso T. Response to Dr. C. McDonald and Dr. A. McDonald: Letter to the Editor. *Am J Ind Med.* 1989;15:489–490.
- Mancuso T. Response to Dr. C.-G. Ohlson: Letter to the editor. *Am J Ind Med.* 1989;15:353–356.
- Dell L, Teta J. Mortality among workers at a plastic manufacturing and research and development facility: 1946–1988. *Am J Ind Med.* 1995;28:373–384.
- Langer AM, McCaughey WTE. Mesothelioma in a brake repair worker. *Lancet.* 1982;2:1101–1103.
- Lemen RA. Asbestos in brakes: Exposure and risk of disease. *Am J Ind Med.* 2004;45:229–237.
- Stanton MF, Wrench C. Mechanisms of mesothelioma induction with asbestos and fibrous glass. *J Natl Cancer Inst.* 1972;48:797–821.
- Dodson RF, Atkinson MAL, Levin JL. Asbestos fiber length as related to potential pathogenicity: A critical review. *Am J Ind Med.* 2003;44:291–297.
- Finkelstein MM, Meisenkothen C. Malignant mesothelioma among employees of a Connecticut factory that manufactured friction materials using chrysotile asbestos. *Ann Occup Hyg.* 2010;54:692–696.
- O'Donnell WM, Mann RH, Grosh JL. Asbestos, an extrinsic factor in the pathogenesis of bronchogenic carcinoma and mesothelioma. *Cancer.* 1966;19:1143–1148.

38. Mann RH, Grosh JL, O'Donnell. Mesothelioma associated with asbestosis: A report of 3 cases. *Cancer*. 1966;19:521–526.
39. Pan XL, HW Day, W Wang, LA Beckett, MB Schenker (2005) Residential proximity to naturally occurring asbestos and mesothelioma risk in California. *Am J Respir Critical Care Med*. 2005;172:1019–1025.
40. McDonald AD, Harper A, El Attar OA, McDonald JC. Epidemiology of primary malignant mesothelial tumors in Canada. *Cancer*. 1970;26:914–919.
41. McDonald AD, Case BW, Churg A, et al. Mesothelioma in Quebec chrysotile miners and millers: Epidemiology and aetiology. *Ann Occup Hyg*. 1997;41:707–719.
42. Egilman D, Menéndez LM. A case of occupational peritoneal mesothelioma from exposure to tremolite-free chrysotile in Quebec, Canada: A black swan case. *Am J Ind Med*. 2011;54:153–156.
43. Champion P. Two cases of malignant mesothelioma after exposure to asbestos. *Am Rev Respir Dis*. 1971;103:821–826.
44. Camus M, Siemiatycki J, Case BW, Desy M, Richardson L, Campbell S. Risk of mesothelioma among women living near chrysotile mines versus USEPA asbestos risk model: Preliminary findings. *Ann Occup Hyg*. 2002;46(Suppl 1):95–98.
45. Aguilar-Madrid G, Perez ER, Juarez-Perez CA, Alvarado-Cabrero I, Rico-Mendez FG, Javier K-G. Case-control study of pleural mesothelioma in workers with social security in Mexico. *Am J Ind Med*. 2010;53:241–251.
46. Acheson ED, Gardner MJ, Pippard EC, Grime LP. Mortality of two groups of women who manufactured gas masks from chrysotile and crocidolite asbestos: A 40 year follow-up. 1982;39:344–348.
47. Piolatto G, Negri E, LaVecchia C, Pira E, Decarli A, Peto J. An update of cancer mortality among chrysotile asbestos miners in Balangero, Northern Italy. *Br J Ind Med*. 1990;47:810–814.
48. Pira E, Pelucchi C, Piolatto PG, Negri E, Belei T, La Vecchia C. Mortality from cancer and other causes in the Balangero cohort of chrysotile asbestos miners. *Occup Environ Med*. 2009;66:805–809.
49. Mirabelli D, Calisti R, Barone AF, Fornero E, Merletti F, Magnani C. Excess of mesotheliomas after exposure to chrysotile in Balangero, Italy. *Occup Environ Med*. 2008;65:815–819.
50. Turci F, Tomatis M, Compagnoni R, Fubini Z. Role of associated mineral fibres in chrysotile asbestos health effects: The case of Balangeroite. *Ann Occup Hyg*. 2009;53:491–497.
51. Mamo C, Costa, G. Mortality experience in an historical cohort of chrysotile asbestos textile workers. WS-E-03. Paper presented at the Global Asbestos Congress, Waseda University, Tokyo, Japan, November 19–21, 2004.
52. Sturm W, Menze B, Krause J, Thriene B. Use of asbestos, health risks and induced occupational diseases in the former East Germany. *Toxicol Lett*. 1994;72:317–324.
53. Smailyte G, Kurtinaitis J, Andersen A. Cancer mortality and morbidity among Lithuanian asbestos-cement producing workers. *Scand J Work Environ Health*. 2004;30:64–70.
54. Tossavainen A, Kovalevsky E, Vanhala E, Tuomi T. Pulmonary mineral fibres after occupational and environmental exposure to asbestos in the Russian chrysotile industry. *Am J Ind Med*. 2000;37:327–333.
55. Everatt RP, Smolianskiene G, Tossavainen C, Jankauskas R. Occupational asbestos exposure among respiratory cancer patients in Lithuania. *Am J Ind Med*. 2007;50:455–463.
56. Madkour MT, Bokhary MS, Allah HIA, Awad AA, Mahoud HF. Environmental exposure to asbestos-response relationship with mesothelioma. *Eastern Mediterranean Health J*. 2009;15:25–38.
57. Cullen MR, Baloyl RS. Chrysotile asbestos and health in Zimbabwe: I. Analysis of miners and millers compensated for asbestos-related diseases since independence. *Am J Ind Med*. 1991;19:161–169.
58. Rogers AJ, Leigh J, Berry G, Ferguson DA, Mulder HB, Ackad M. Relationship between lung asbestos fiber type and concentration and relative risk of mesothelioma: A case-control study. *Cancer*. 1991;67:1912–1920.
59. Shiqu Z, Yongxian W, Fusheng M, Hongshuen M, Wenzhi S, Zhenhuan J. Retrospective mortality study of asbestos workers in Laiyuan. In: Proceedings of the VII International Pneumoconiosis Conference Part II, August 23–26, 1988, Pittsburgh, PA. National Institute for Occupational Safety and Health; 1990:1242–1244. DHHS publication 90–109, part II.
60. Cai SX, Zhang C, Zhang H, Zhang X, Morinaga K. Epidemiology of occupational asbestos-related diseases in China. *Industrial Health*. 2001;39:75–83.
61. Yano E, Wang Z-M, Wang X-R, Wang M-Z, Lan Y-J. Cancer mortality among workers exposed to amphibole-free chrysotile asbestos. *Am J Epidemiol*. 2001;154:538–543.
62. Yano E, Wang Z-M, Wang X-R, et al. Mesothelioma in a worker who spun chrysotile asbestos at home during childhood. *Am J Ind Med*. 2009;52:282–287.
63. Huilan Z, Zhiming W. Study of occupational lung cancer in asbestos factories in China. *Br J Ind Med*. 1993;50:1039–1042.
64. Baumann F, Rougier Y, Ambrosi JP, Robineau BP. Pleural mesothelioma in New Caledonia: An acute environmental concern. *Cancer Detect Prev*. 2007;31:70–76.
65. Baumann F, Maurizot P, Mangeas M, Ambrosi J-P, Douwes J, Robineau BP. Pleural mesothelioma in New Caledonia: Associations with environmental risk factors. *Environ Health Perspect*. 2011;119:695–700.
66. Anonymous. Asbestos, asbestosis, and cancer: The Helsinki criteria for diagnosis and attribution. *Scan J Work Environ Health*. 1997;23:311–316.
67. Pott F, Huth F, Friedrichs KH. Tumorigenic effect of fibrous dusts in experimental animals. *Environ Health Perspect*. 1974;9:313–315.
68. Suzuki Y, Yuen SR. Asbestos tissue burden study on human malignant mesothelioma. *Industrial Health*. 2001;39:150–160.
69. LaDou J. The asbestos cancer epidemic. *Environ Health Perspect*. 2004;112:285–290.
70. American Conference of Governmental Industrial Hygienists. Asbestos, TLV. Chemical Substances. 7th ed. Documentation. Publication #7DOC-40. Cincinnati, OH: ACGIH; 2001.
71. Environmental Protection Agency. Airborne asbestos health assessment update. Washington, DC: U.S. EPA (EPA/600/8–84/003F); 1986.
72. International Agency for Research on Cancer. Asbestos. Monograph on the Evaluation of Carcinogenic Risk to Man. Lyon, France: IARC; 1988.
73. National Toxicology Program. Report on Carcinogens. 11th ed. Washington, DC: U.S. Department of Health and Human Services. Public Health Service; 2005.
74. World Health Organization Environmental Health Criteria 53: Asbestos and Other Natural Mineral Fibres. Geneva, Switzerland: WHO; 1986.
75. World Health Organization. Environmental Health Criteria 203: Chrysotile Asbestos. Geneva, Switzerland: WHO; 1998.
76. World Health Organization. Elimination of asbestos related diseases. Geneva, Switzerland: WHO; 2006.
77. Landrigan PJ, Soffritti M. Collegium Ramazzini call for an international ban on asbestos. *Am J Ind Med*. 2005;47:471–474.
78. Landrigan PJ. Asbestos—still a carcinogen. *N Engl J Med*. 1998;338:1618–1619.
79. U.S. Public Health Service. U.S. Department of Health and Human Services. Toxicological profile for asbestos. Atlanta, GA: Agency for Toxic Substances and Disease Registry; 2001.
80. Collegium Ramazzini. Asbestos is still with us: Repeat call for a universal ban. *J Occup Environ Med*. 2010;52:469–472.
81. Nishikawa K, Takahashi K, Karjalainen A, et al. Recent mortality from mesothelioma, historical patterns of asbestos use, and adoption of bans: A global assessment. *Environ Health Perspect*. 2008;116:1675–1680.

EXHIBIT 51

Brief Report

Occupational Asbestos Exposure Among Respiratory Cancer Patients in Lithuania

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Background Despite intensive use of asbestos, no cancer case has ever been diagnosed as asbestos related in Lithuania. This paper attempts to estimate the proportion of those occupationally exposed to asbestos among respiratory cancer patients.

Material and methods Occupational exposure to asbestos was assessed retrospectively for 298 lung cancer and four mesothelioma patients, admitted to the Institute of Oncology, Vilnius. The evaluation was based on personal interview data using an internationally established questionnaire covering most likely activities of asbestos exposure at the workplace. Cumulative exposure to asbestos at work was estimated in fiber years. Lung tissue asbestos fiber burden analysis was conducted by scanning transmission electron microscopy on 23 samples.

Results A cumulative asbestos exposure of ≥ 25 fiber years was found for 10 lung cancer patients (3.4%). They worked in foundries, construction, installation, shipyard, power plant, railway, asbestos cement, glass and chemical industry. In a further 56 lung cancer patients (18.8%) and for one (25%) mesothelioma patient, a cumulative exposure from 5 to 24.9 fiber years was assessed. Asbestos fibers were detected in 18 cases, the burden ranged from 0.1 to 4.1 million fibers/g dry lung tissue; concentrations exceeding 1 million f/g dry lung tissue were found in four cases. All fibers were chrysotile.

Conclusions Findings indicate that a fraction (3.4%) of the lung cancer cases could be attributed to heavy occupational exposure to asbestos using the Helsinki criterion of ≥ 25 fiber years. Therefore, approximately 50 lung cancer cases per year in Lithuania could be asbestos-related compensable occupational diseases. Am. J. Ind. Med. 50:455–463, 2007. © 2007 Wiley-Liss, Inc.

KEY WORDS: respiratory cancer; asbestos; occupational exposure; occupational cancer; Lithuania

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INTRODUCTION

Asbestos is one of the most dangerous industrial pollutants and causes asbestosis, lung cancer, mesothelioma, and non-malignant fibrosis of the pleura. Due to the long induction period (20–40 years), the associated risk remains high decades after exposure [Henderson et al., 2004]. It is estimated that occupational exposure to asbestos could be responsible for about 4–7% or more of lung cancers and 80–90% of pleural mesotheliomas in

men in industrialized countries [Tossavainen, 1997a; Mandi et al., 2000; Ameille et al., 2004]. Epidemiologic and toxicologic studies indicate that all types of asbestos, including chrysotile and amphiboles, cause malignant neoplasms; however, chrysotile fibers do not accumulate in lung tissue to the extent that amphiboles do, and they are removed more rapidly [Nicholson and Raffn, 1995; Yano et al., 2001].

All asbestos used in Lithuania (mainly chrysotile) was imported from Russia. About 700,000 tons of raw asbestos have been used in Lithuania since 1961 for asbestos-cement corrugated sheets and pipes, for the insulation of boilers and pipes, and for friction products [State Labour Inspection, 2001; Smailytė et al., 2003]. According to the International Information System on Occupational Exposure to Known or Suspected Carcinogens (CAREX) estimates, there were 7,451 workers exposed to asbestos in Lithuania in 1997, 3,120 (42%) of whom worked in the construction sector [Pajarskiene and Kauppinen, 2000; Kauppinen et al., 2001]. There were two factories manufacturing asbestos-cement pipes and tiles in the country. The Daugėliai building products factory used asbestos to manufacture corrugated asbestos-cement sheets from 1956 to 1997. Akmenės cementas manufactured asbestos-cement pipes and sheets from 1963 to 2000. The production rose from 3.3 million corrugated asbestos-cement sheets in 1956 to 103 million corrugated asbestos-cement sheets annually in the 1970s and 1980s. After an increase to 114 million corrugated asbestos-cement sheets by the end of the 1980s, production decreased to 8.18 million corrugated asbestos-cement sheets in 2000 when production was discontinued [Department of Statistics to the Government of the Republic of Lithuania (Statistics Lithuania), 2005, <http://www.std.lt/web/main.php>]. A historical cohort study investigating cancer risks among workers at two asbestos-cement factories did not find an increase in risk of respiratory cancer [Smailytė et al., 2004]. There were four main shipyards situated in Klaipėda, in western Lithuania, where asbestos was widely used. However, additional information about its use is unavailable.

Asbestos, regardless of fiber type, was classified as carcinogenic to humans (group I) by the International Agency for Research on Cancer in 1977 [IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, 1977]. In many European Union countries the use of asbestos was prohibited more than 10–20 years ago. When persons with heavy asbestos exposure are diagnosed as having an asbestos-related disease, they are entitled to compensation [Tossavainen, 1997b; Segura et al., 2003]. It is only recently that asbestos has been recognized as carcinogen in Lithuania. Until 1998, it was classified in the same group of hazardous chemicals as cement, clay, and mineral wool. Therefore, prior to 1998,

there were no regulations on the production and use of asbestos. Measurements of asbestos fibers in the air were initiated in 1999. The current limit level for the concentration of asbestos fibers in the air (0.6 fibers/cm³ for chrysotile and 0.3 f/cm³ for all other types of asbestos) must still be reduced to 0.1 f/cm³ to comply with EU Council Directive 2003/18/EC of March 27, 2003. The import and use of asbestos was banned completely in 2004.

Although some asbestos-induced respiratory diseases are recognized as occupational in Lithuania, no attention has been paid to asbestos-related cancer. No case of cancer has ever been diagnosed or compensated as an asbestos-related occupational disease [Everatt et al., 2006].

The aim of the present study is to assess the proportion of patients with lung cancer and mesothelioma who have had significant occupational exposure to asbestos.

MATERIALS AND METHODS

Three hundred two patients diagnosed as having lung cancer or mesothelioma and hospitalized at the Institute of Oncology of Vilnius University between November 1, 2003 and May 15, 2005 were enrolled for the study. Information on the demographic characteristics, occupations, and workplaces during the lifetime, as well as smoking habits, was obtained via personally interviewing the patients. A questionnaire compiled by a group of scientists from Justus-Liebig University, Giessen (Germany) was administered [Ahrens et al., 1993]. The questionnaire asked detailed questions about job tasks, location, duration, and frequency for every job activity involving asbestos exposure in the workplace. This information was supplemented by questions on lifetime occupational history and lifetime smoking habits. Information on the diagnosis was collected from medical records. All patients gave written consent to be included in the study.

The distribution of patients by sex, age, diagnosis, smoking habits, cumulative asbestos exposure, and type of activity was assessed. Exposure assessments were based on job descriptions and the BK-report “Faserjahre” [BK-Report, 1997]. This report provides estimates, compiled by a group of experts, of the concentrations of asbestos fibers for different types of occupations and workplaces in Germany. Cumulative exposure to asbestos at work was calculated and was expressed in fiber years as the product of intensity and duration of exposure summed over all work periods during the occupational history. One fiber year is defined as one year of full-time work in asbestos exposure of 1×10^6 asbestos f/m³ air, or

ten years of full-time work 0.1×10^6 asbestos f/m³ air, or any other combination resulting in a product of 1. A dose exceeding 25 fiber years has been estimated to cause a two-fold risk of lung cancer. This value is used for ascribing lung cancer to asbestos and for compensation of lung cancer in Germany; an equivalent occupational history is applied in Scandinavian and some other countries [Tossavainen, 1997b; Henderson et al., 2004].

In the analysis, four exposure categories were used: not exposed (or <0.01 fiber years), exposed: 0.01–4.9 fiber years, 5–24.9 fiber years, and ≥ 25 fiber years. Patients were divided according to smoking habits: never smokers, ex- (quitted ≥ 1 year before diagnosis) and active smokers.

Lung tissue specimens during surgery were obtained from 23 interviewed patients (20 lung cancer patients with information about occupational exposure in the past and three mesothelioma patients). For analysis of asbestos fibers and asbestos bodies in lung tissue, the lung sample was prepared for analysis by the method described previously [De Vuyst et al., 1998; Tossavainen et al., 2000]. Asbestos fiber analysis was conducted by scanning transmission electron microscopy to determine fiber types and concentration, expressed in millions of fibers per gram of dry lung. The analytical sensitivity was 0.1 million f/g dry lung tissue for fibers longer than 1 μ m. Arithmetic mean and minimal and maximal concentrations were calculated for different exposure categories. Counting of asbestos bodies in the lung tissue was performed by optical microscopy.

RESULTS

A total of 302 patients were interviewed including 298 lung cancer (92.9% men and 7.1% women) and four mesothelioma patients (3 men and 1 woman). The diagnosis was confirmed histologically or cytologically for all mesothelioma patients and for most lung cancer patients (281, or 94.3%). For 17 (5.7%) patients with lung cancer, the diagnosis was confirmed clinically. The distribution of basic patient characteristics is displayed in Table I. The mean age at diagnosis among lung cancer patients was 62.7 years (minimum 42, maximum 82) among men, and 62.5 (minimum 46, maximum 76) among women. For mesothelioma patients, the mean age was 60.7 (minimum 47, maximum 70) for men; the one woman patient was 43 years old. Three-quarters of patients were residents of the eastern part of Lithuania: 220 (72.8%) lived in the Vilnius, Panevėžys, or Utena districts. There were 25 patients (8.3%) from Alytus, 27 (8.9%) from Šiauliai, 9 (3.0%) from the Klaipėda district and few from the Kaunas, Telšiai, Tauragė, or Marijampolė districts. The distribution of the Lithuanian

population by district in the year 2004 was as follows: Vilnius 24.7%, Kaunas 20.0%, Klaipėda 11.1%, Šiauliai 10.6%, Panevėžys 8.6%, Marijampolė and Alytus 5.4% each, Utena, Telšiai 5.2% each, Tauragė 3.8% [Department of Statistics to the Government of the Republic of Lithuania (Statistics Lithuania), 2005, <http://www.std.lt/web/main.php>].

Table II presents the distribution of lung cancer patients according to cumulative asbestos exposure. Accordingly, 182 of 298 lung cancer patients (61.1%) were exposed to asbestos. The estimated average cumulative exposure to asbestos for these patients was 6.94 fiber years (minimum 0.01, maximum 102.4). A low cumulative asbestos exposure (<5 fiber years) was detected for most of the exposed—116 (38.9%) patients (40.8% of men and 14.3% of women). For 56 (18.8%) lung cancer patients (19.5% of men and 9.5% of women) cumulative exposure was from 5 to 24.9 fiber years. For 10 lung cancer patients (3.4%), cumulative asbestos exposure was estimated to be ≥ 25 fiber years. All patients heavily exposed to asbestos were men. Somewhat over one-third (116, or 38.9%) of lung cancer cases (36.1% of men and 76.2% of women) were not exposed occupationally to asbestos.

One of the four patients with malignant pleural mesothelioma had occupational asbestos exposure, assessed as 8.8 fiber years. He had worked as a tractor driver in a farm for 8 years, a machine operator in a TV-set producing company for 10 years, and foreman in a boiler house for 7 years. For the three remaining mesothelioma patients, the estimated cumulative exposure to asbestos was <0.01 fiber years. One of these patients was a computer specialist and lecturer for 15 years and a sales manager for 10 years; a second patient was a farm tractor driver for 32 years (Table V). The fourth mesothelioma patient was a woman who worked as farm worker for 29 years.

The mean age at diagnosis of male patients with cumulative exposure to asbestos ≥ 25 fiber years, 0.01 to 24.9 fiber years and no exposure was 63.9 (SD 7.0), 61.9 (SD 7.9), and 63.6 (SD 8.9) respectively. Among women, it was 59.0 (SD 11.5) and 62.0 (SD 9.8) (exposure categories 5–<25 fiber years and unexposed respectively).

Only three (1.1%) of lung cancer male cases were never smokers; the remainder were smokers (77.5%) or ex-smokers (21.4%). Among women with lung cancer, 85.7% never smoked. The mean number of pack years among smokers was 38.2 among men and 10.7 among women. All 10 patients heavily exposed to asbestos (≥ 25 fiber years) were current or ex-smokers (70 and 30%, respectively). Three out of four mesothelioma patients never smoked; there was one current smoker at the time of diagnosis.

TABLE I. Distribution of Lung Cancer and Mesothelioma Patients by Age and Smoking Status, Lithuania

	Men	Women	Total
Lung cancer			
Age:			
<50	14 (5.0%)	4 (19.0%)	18 (6.0%)
50–59	81 (29.2%)	5 (23.8%)	86 (28.9%)
60–69	122 (44.0%)	6 (28.6%)	128 (42.9%)
70–79	58 (20.9%)	6 (28.6%)	64 (21.5%)
≥80	2 (0.7%)	0	2 (0.7%)
Total	277	21	298
Smoking:			
Never	3 (1.1%)	18 (85.7%)	21 (7.0%)
Ex-smoker	60 (21.7%)	2 (9.5%)	62 (20.8%)
Current smoker	214 (77.2%)	1 (4.8%)	215 (72.2%)
Total	277	21	298
Mesothelioma			
Age:			
<50	1 (33.3%)	1 (100.0%)	2 (50.0%)
60–69	1 (33.3%)	0	1 (25.0%)
70–79	1 (33.3%)	0	1 (25.0%)
Total	3	0	4
Smoking:			
Never	2 (66.7%)	1 (100.0%)	3 (75.0%)
Current smoker	1 (33.3%)	0	1 (25.0%)
Total	3	0	4

The distribution of exposed patients by industry and occupational activities is shown in Table III. Heavily exposed patients (≥25 fiber years) had worked as fitter/maintenance technicians, welder, foreman, insulator, and electrician in foundries, construction, installation, shipyard, asbestos-cement products manufactory, glass industry, power plant, maintenance of railway coaches, and the chemical industry. The first year of their occupational exposure to asbestos was during the period

1958–1978. Four individuals (40%) were first exposed in or before 1960, five (50%) between 1961 and 1970, and one case in 1978. The mean time from the first exposure among this group was 38.8 years (minimum 26, maximum 47). The mean duration of exposure was 20.5 years (minimum 6, maximum 34). Patients with a cumulative exposure of 5–<25 fiber years had worked in construction, power station, shipping, asbestos-cement plant, installation, the heating industry as welders,

TABLE II. Distribution of Lung Cancer Patients by Cumulative Asbestos Exposure, Lithuania

Asbestos exposure category (fiber years)	Patients with lung cancer—number (%)		
	Men (n = 277)	Women (n = 21)	Total
Lung cancer			
Unexposed or <0.01	100 (36.1%)	16 (76.2%)	116 (38.9%)
Exposed, ≥0.01	—	—	—
0.01–0.9	70 (25.3%)	1 (4.8%)	71 (23.8%)
1–4.9	43 (15.5%)	2 (9.5%)	45 (15.1%)
5–24.9	54 (19.5%)	2 (9.5%)	56 (18.8%)
≥25	10 (3.6%)	0	10 (3.4%)
Total	277	21	298 (100%)

TABLE III. Distribution of the Lung Cancer and Mesothelioma Patients With a Cumulative Exposure ≥ 5 Fiber Years by Industry and Occupation, Lithuania

Industry and occupation	Exposure	
	5–24.9 fiber years	≥ 25 fiber years
Asbestos-cement products manufactory		
Fitter/maintenance technician		1
Laborer	2	
Construction industry		
Insulator		1
Foreman, technician	5	
Electrician	1	
Storeman	2	
Bricklayer	6	
Welder	4	
Crane operator, tractor driver	2	
Laborer	9	
Carpenter	1	
Plasterer	1	
Pipefitter	1	
Fitter/maintenance technician	1	
Foundry, metal products manufactory		
Welder		1
Fitter/maintenance technician	1	1
Metal worker	1	
Ship building and maintenance		
Fitter/maintenance technician		1
Ship mechanic	1	
Power station		
Fitter/maintenance technician		1
Electrician	1	
Heating trades, boiler house		
Boiler man, foreman	4	
Installation, maintenance		
Plumber	2	
Foreman		1
Fitter/maintenance technician	4	
Welder	1	
Concrete placer	1	
Maintenance of railway coaches		
Fitter/maintenance technician		1
Glass industry		
Sheet metal worker		1
Other industries		
Electrician	2	1
Motor vehicle mechanic	1	
Fitter/maintenance technician	1	
Miscellaneous	2	

plumbers, fitters/maintenance technicians, electricians, laborers, boiler man, asbestos-cement laborer etc. (Table III). The occupational histories of selected heavily exposed patients are presented in Table IV.

The results of the analyses of asbestos fiber and asbestos bodies in lung tissue, as well as occupational information, are presented in Table V. All 23 patients were men with a mean age of 62.0 (minimum 47, maximum 77) years. Asbestos fibers were detected in 18 cancer cases with concentrations ranging from 0.1 to 4.1 million f/g dry lung tissue. Concentrations exceeding 1 million f/g dry lung tissue, which indicate non-trivial exposure to asbestos dust according to the Helsinki Criteria, were detected in the lung tissue of 4 of 23 respiratory cancer patients. No concentrations were found

to be above 5 million amphibole f/g dry tissue, which, according to the Helsinki Criteria, is associated with a two-fold risk of lung cancer [Tossavainen, 1997b]. No amphiboles were detected in any of the samples.

Asbestos bodies in concentrations above the detection limit (6 AB/g wet lung tissue) were found in 8 patients out of 23 (range: 7–910 AB/g wet lung tissue). Concentrations above 100 AB/g wet lung were detected in the lung tissue of two respiratory cancer patients. The highest level of 4.1 million f/g dry tissue in patient no. 20 in Table V corresponded with the second highest concentration of AB in the lung (310 AB/g wet tissue) and with the high cumulative exposure of 18.8 fiber years estimated from the occupational history. Furthermore, all four lung cancer patients with high asbestos fiber

TABLE IV. Occupational Histories of Selected Lung Cancer Patients With Cumulative Exposure of ≥ 25 Fiber Years, Lithuania

No	Year of birth	Smoking habits	Occupational history			Type of exposure to asbestos	Duration of work with asbestos	Cumulative exposure (fiber years)
			Period	Occupation	Industry			
1	1941	Exsmoker, previously smoked 20 cig/day for 38 years	1962–1964	Helicopter pilot	Military		29,016 hr	46
			1965–1971	Electromechanic	Fishing ship	Insulation of wires with asbestos cord.		
			1971–2003	Fitter/maintenance technician, welder, electrician	Shipyard	Insulation of pipes, boilers, wires with asbestos materials.		
2	1934	Current smoker, 20 cig/day for 47 years, 10 cig/day for 3 years	1950–1958	Tractor driver	Autorepair shop		11,520 hr	42
			1958–1965	Locomotive machinist	Railway company			
			1965–1970	Fitter/maintenance technician	Agricultural machinery manufactory			
			1970–1991	Fitter/maintenance technician	Metallurgy industry	Repair of furnaces, pipes. Insulation of steam boilers, pipes, turbines. Use of asbestos materials		
3	1948	Current smoker, 15 cig/day for 26 years	1965–1969	Fitter/maintenance technician	Electronic equipment manufactory		3,937 hr	26
			1969–1974	Foreman	Land reclamation			
			1974–1978	Truck driver	Transport company	Carriage of sheets of asbestos-cement.		
			1978–1997	Foreman, driver	Construction	Insulation with asbestos powder.		
			1997–2001	Fitter	Construction			
			2001–2004	Fitter/maintenance technician	Industrial machinery manufactory			

TABLE V. Occupation, Cumulative Exposure, and Asbestos Fiber and Asbestos Body (AB) Concentration in the Lung Tissue of 23 Patients With Lung Cancer and Mesothelioma, Lithuania

No	Age	Occupation (industry)	Diagnosis	Cumulative exposure (fiber years)	Fiber concentration, (million f/g dry lung tissue)	AB concentration, (AB/g wet tissue)
1	52	Crane operator, welder (autorepair shop), toolmaker	LC	0.7	0.2	<6
2	65	Ship mechanic (ship's engine room)	LC	14.6	0.5	<6
3	77	Bricklayer, loader, storeman (construction)	LC	21.6	1.1	<6
4	58	Motor vehicle mechanic	LC	5.1	0.2	<6
5	62	Driver, motor vehicle mechanic, storeman	LC	0.9	0.4	<6
6	61	Welder (gas pipeline equipment, ferroconcrete constructions, and cement products manufactory)	LC	4.0	0.1	910
7	63	Machine operator (TV-set manufactory), construction worker	LC	16.7	0.2	<6
8	54	Electrician (construction, autorepair shop, farm)	LC	2.4	<0.1	<6
9	52	Fitter/maintenance technician (asbestos-cement products manufactory), farm worker	LC	60.0	<0.1	<6
10	64	Worker, foreman, engineer (construction)	LC	7.4	0.2	7
11	50	Carpenter (shipyard), driver	LC	0.8	<0.1	<6
12	71	Construction worker	LC	22.8	0.9	<6
13	56	Lorry driver, insulator (construction), fitter	LC	26.3	0.2	<6
14	64	Fitter/maintenance technician (heating company), toolmaker	LC	3.6	<0.1	21
15	62	Fitter/maintenance technician (power station)	LC	31.3	1.1	33
16	53	Plumber, bricklayer (construction)	LC	6.9	<0.1	<6
17	71	Electrician (chemical industry, municipal economy)	LC	52.7	2.1	38
18	68	Electrician (electricity company, construction, etc.)	LC	8.3	0.2	<6
19	70	Plumber, foreman (installation, construction)	LC	34.9	0.2	29
20	71	Plumber, fitter/maintenance technician (installation)	LC	18.8	4.1	310
21	47	Computer specialist, lecturer, sales manager	PM	<0.01	0.4	<6
22	70	Foreman (boiler house), tractor driver (agriculture), machine operator (TV-set producing company)	PM	8.6	0.1	<6
23	65	Tractor driver (agriculture)	PM	>0.01	0.2	46

LC, lung cancer; PM, pleural mesothelioma.

concentrations (i.e., >1 million f/g dry lung tissue) had high (i.e., ≥ 18.8 fiber years) cumulative asbestos exposure estimate (Table V). However, no significant statistical correlation between concentrations of asbestos fibers and cumulative exposure estimates derived from occupational history was observed (results not shown).

DISCUSSION

We investigated the frequency of asbestos exposure among lung cancer and mesothelioma patients from their reported lifetime occupational histories. The results of this study indicated 182 of 298 lung cancer patients (61.1%) and one of four mesothelioma patients (25%) admitted to the Institute of Oncology in Vilnius, Lithuania had experienced occupational exposure to asbestos. Furthermore, 3.4% of the study individuals had cumulative asbestos exposure estimated ≥ 25 fiber years and 18.8% had exposure from 5 to 24.9 fiber years. This is consistent with the data indicating the wide and uncontrolled use of asbestos in Lithuania during the years of the Soviet Union's exports [Smailytė et al., 2003]. The distribution of exposed cancer cases by industry, occupation, and latency period is similar to those reported in other studies where construction, asbestos-cement industry, ship building, and maintenance contributed the largest number of asbestos-related diseases [Mandi et al., 2000]. The proportion of heavily exposed (≥ 25 fiber years) patients was only slightly less than in Hungary, where 4% of lung cancer patients with an asbestos exposure of ≥ 25 fiber years were found, and was also somewhat lower than the estimates of asbestos-related lung cancers in different populations [Tossavainen, 1997a; Mandi et al., 2000; Ameille et al., 2004; Henderson et al., 2004].

Notably, one of the four mesothelioma patients was exposed to asbestos and had an 8.8 fiber years cumulative exposure estimate. Only chrysotile fibers were found. In contrast, results from studies in Hungary and Germany showed that amphibole fibers were present in 24% and 61% respiratory cancer patients respectively [Rödelsperger et al., 2001]. Our results are consistent with the fact that chrysotile asbestos containing only a small amount of tremolite/anthophyllite was used in Lithuania [Smailytė et al., 2003]. No observable correlation between asbestos fiber concentrations in lung tissue and cumulative exposure estimates is consistent with the known faster clearance rates of chrysotile fibers in comparison to amphiboles. Therefore, according to Helsinki Criteria, occupational histories are probably better indicator of lung cancer risk from chrysotile than fiber burden analysis. Furthermore, concentrations seldom exceeding reference values ($0.7\text{--}1.5 \times 10^6$ f/g dry lung) make interpretation complicated [De Vuyst et al., 1998].

Only 1% of male lung cancer patients in our study never smoked. The proportion of current smokers among male lung cancer patients in our study (77.2%) is higher than in the male population of Lithuania in general (51.5%). A number of studies indicated a combined (ranging from additive to multiplicative) effect of tobacco smoking and asbestos exposure in the causation of lung cancer. That three of the four mesothelioma patients never smoked is consistent with the fact that smoking is not related to the risk of mesothelioma.

Due to the extensive use of asbestos during the past decades and the long latency period for asbestos-related malignancies, asbestos-related morbidity will remain at least at the same level during the next 20 to 30 years in Lithuania, despite recent preventive measures and improved worker protection. There were 125 mesothelioma cases recorded in Lithuania in 1992–2001, with a current population of 3.4 million. The incidence rate was 3.5 cases/million among men and 1.7 cases/million among women [Smailytė et al., 2003; Department of Statistics to the Government of the Republic of Lithuania (Statistics Lithuania), 2005, <http://www.std.lt/web/main.php>]. Over 1,500 new lung cancer cases are diagnosed each year in Lithuania [Lithuanian Cancer Registry, 2005, http://www.is.lt/cancer_reg/]. The findings of our study indicate that past occupational asbestos exposure exceeds 25 fiber years in 3.4% of the lung cancer patients in Lithuania equaling approximately 50 compensable cases of occupational disease every year. The overall percentage of attributable cases is higher when lower exposures below 25 fiber years are taken into account. For example, in a Swedish case-control study, the risk of lung cancer increased 14% per fiber year of exposure which corresponds to a somewhat lower cumulative dose for the doubling of the risk; at 4 fiber years the risk was as high as 1.90 (95%CI = 1.32, 2.74) [Gustavsson et al., 2000, 2002].

The decision making on attribution and compensation favors the Helsinki Criteria approach in many countries. The cumulative exposure of 25 fiber years or more, as set forth in the Helsinki Criteria for lung cancer attribution to asbestos, was also applied in the present study.

One important limitation of the current study is the imprecision and accuracy of retrospective assessment of cumulative asbestos exposure in the absence of any measurement. Airborne asbestos fiber measurements prior to 1999 are not available in Lithuania. Therefore, the values for relevant work settings from the validated, large German database were used. Whether past conditions of asbestos exposure in Lithuania replicate the conditions in German workplaces over the past 40 years is not known. Occupational histories, which were obtained directly from cases using a standardized questionnaire, detailed data on job characteristics and

industry type and included 33 main specific questions addressing asbestos exposure with supplemental questions—such detail presumably increased the accuracy of the exposure estimates in contrast to an approach based on job titles only.

A second important limitation was the restricted geographic area of Lithuania from which cancer patients at the Institute of Oncology were drawn. Only a few study patients were residents of the northern or western parts of Lithuania. This selection likely resulted in an underestimation of the proportion of cases from the asbestos-cement industry and shipyards.

No asbestos-related occupational cancers have ever been diagnosed in Lithuania. This is due to the insufficient recognition by workers and physicians of the occupational etiology of cancer, the excessively complex, long and poorly functioning procedure of registration, and the unclear criteria for the certification of occupational cancer.

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REFERENCES

- Ameille J, Ruffie P, Bergeret A. 2004. Asbestos-related occupational cancers. *Rev Prat* 54(15):1649–1659.
- Ahrens W, Jöckel K-H, Brochard P, Bolm-Audorff U, Grossgarten K-H, Iwatsubo Y, Orlowski E, Pohlabein H, Berrino F. 1993. Retrospective assessment of asbestos exposure-I. Case-control analysis in a study of lung cancer: Efficiency of job-specific questionnaires and job exposure matrices. *Int J Epidemiol* 22(Suppl 2): 83–95.
- BK-Report 1/97. 1997. Hauptverband der gewerblichen Berufsgenossen-schaften. Faserjahre: Berufsgenossen-schaftliche hinweise zur Ermittlung der kumulativen Asbestfaserstaub-Dosis am Arbeitsplatz (Faserjahre) und Bearbeitungshinweise zur Berufskrankheit Nr 4104, Lungenkrebs-Kehlkopfkrebs* [calculation of cumulative exposure to asbestos in the recognition of lung cancer as occupational disease]. Germany: Sankt Augustin.
- De Vuyst P, Karjalainen A, Dumortier P, Pairon J-C, Monso E, Brochard, Teschler H, Tossavainen A, Gibbs A. 1998. Guidelines for mineral fibre analyses in biological samples: Report of the ERS Working Group. *Eur Respir J* 11:1416–1426.
- Everatt R, Jankauskas R, Kučiauskaitė A. 2006. Status of occupational cancer in Lithuania. *Int J Occup Environ Health* 12:24–27.
- Gustavsson P, Nyberg F, Pershagen G, Scheele P, Jakobsson R, Plato N. 2002. Low-dose exposure to asbestos and lung cancer: Dose-response relations and interaction with smoking in a population-based case-referent study in Stockholm, Sweden. *Am J Epidemiol* 155(11):1016–1022.
- Gustavsson P, Jakobsson R, Nyberg F, Pershagen G, Jarup L, Scheele P. Occupational exposure, lung cancer risk: A population-based case-referent study in Sweden. *Am J Epidemiol* 2000. 152:32–40.
- Henderson DW, Rödelberger K, Weitowitz HJ, Leigh J. 2004. After Helsinki: A multidisciplinary review of the relationship between asbestos exposure and lung cancer, with emphasis on studies published during 1997–2004. *Pathology* 36(6): 517–550.
- IARC. Monographs on the Evaluation of Carcinogenic Risks to Humans. 1977. Vol. 14. Asbestos. Lyon: International Agency for Research on Cancer. 106. p.
- Kauppinen T, Pajarskiene B, Podniece Z, Rjazanov V, Smerhovsky Z, Veidebaum T, Leino T. 2001. Occupational exposure to carcinogens in Estonia, Latvia, Lithuania and the Czech Republic in 1997. *Scand J Work Environ Health* 27(5):343–345.
- Lithuanian Cancer Registry. 2005. Cancer incidence in Lithuania in 2004 www.is.lt/cancer_reg/.
- Mandi A, Posgay M, Vadasz P, Major K, Rödelberger K, Tossavainen A, Ungvary G, Weitowitz H-J, Galambos E, Nemeth L, Soltész I, Egervary M, Böszörményi Nagy G. 2000. Role of occupational asbestos exposure in Hungarian lung cancer patients. *Int Arch Occup Environ Health* 73(8):555–560.
- Nicholson WJ, Raffin E. 1995. Recent data on cancer due to asbestos in the USA and Denmark. *Med Lav* 86:393–410.
- Pajarskiene B, Kauppinen T. 2000. Occupational exposure to carcinogens in Lithuania in 1997. Helsinki: Finnish Institute of Occupational Health.
- Rödelberger K, Mandi A, Tossavainen A, Brückel B, Barbisan P, Weitowitz HJ. 2001. Inorganic fibres in the lung tissue of Hungarian and German lung cancer patients. *Int Arch Occup Environ Health* 74:133–138.
- Segura O, Burdorf A, Luoman C. 2003. Update of predictions of mortality from pleural mesothelioma in the Netherlands. *Occup Environ Med* 60:50–55.
- Smalytė G, Filipauskienė J, Cicėnas S, Kurtinaitis J. 2003. Pleural mesothelioma incidence in Lithuania. *Public Health* 2(21):61–65. (in Lithuanian).
- Smalytė G, Kurtinaitis J, Andersen A. Cancer mortality and morbidity among Lithuanian asbestos-cement producing workers. *Scand J Work Environ Health* 2004. 30(1):64–70.
- State Labour Inspection. Careful, Asbestos! 2001. Vilnius: Garnelis. 32 p. (in Lithuanian).
- Department of Statistics to the Government of the Republic of Lithuania (Statistics Lithuania). 2005 <http://www.std.lt/web/main.php>.
- Tossavainen A, Kovalevsky E, Vanhala E, Tuomi T. 2000. Pulmonary mineral fibers after occupational and environmental exposure to asbestos in the Russian chrysotile industry. *Am J Ind Med* 37(4):327–333.
- Tossavainen A. 1997. Asbestos, Asbestosis and Cancer: Exposure criteria for clinical diagnosis. In: People and Work. Research Reports. Helsinki: Finnish Institute of Occupational Health. p. 8–27.
- Tossavainen A. 1997. Asbestos, asbestosis, and cancer: The Helsinki criteria for diagnosis and attribution. Consensus report. *Scand J Work Environ Health* 23:311–316.
- Yano E, Wang ZM, Wang XR, Wang MZ, Lan YJ. 2001. Cancer mortality among workers exposed to amphibole-free chrysotile asbestos. *J Epidemiol* 154(6):538–543.

EXHIBIT 52

Environmental exposure to asbestos and the exposure–response relationship with mesothelioma

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التعرض البيئي للأسبستوس والعلاقة بين التعرض والاستجابة وبين ورم المتوسطة
مختار طه مذكور، محمود سري البخاري، هاله إبراهيم عوض الله، عبد الحميد عوض، حسين فتحي محمود

الخلاصة: أجرى الباحثون دراسة وبائية وبيئية في منطقة شبرا الخيمة بمدينة القاهرة الكبرى، حول العلاقة بين التعرض والاستجابة للأسبستوس (الأميانت) وبين ورم المتوسطة الجنبوي الخبيث. وقد أجرى الباحثون تنظيراً شعاعياً لـ 487 شخصاً معرضين مهنيّاً للأسبستوس، و 293 شخصاً معرضين بيئياً له، ومجموعة شاهدة مكونة من 979 شخصاً ليس لهم سوابق تعرض. كما أخذ الباحثون خزعات جنبوية من الحالات المشتبه بها، وحددوا تركيز ألياف الأسبستوس المنقولة بالهواء في جميع المناطق. وشخصوا 88 حالة من ورم المتوسطة، 87 منها كانت ضمن المجموعة المعرضة. وتبين للباحثين أن اختطار ورم المتوسطة لدى المجموعة المعرضة بيئياً أعلى من المجموعتين الآخرين، كما أن الاختطار أعلى لدى الإناث منه لدى الذكور. وازداد انتشار ورم المتوسطة مع ازدياد التعرض التراكمي للأسبستوس.

ABSTRACT An epidemiological and environmental study was carried out in Shubra El-Kheima city, greater Cairo, of the exposure–response relationship between asbestos and malignant pleural mesothelioma. Radiological screening was done for 487 people occupationally exposed to asbestos, 293 environmentally exposed to asbestos and a control group of 979 with no history of exposure. Pleural biopsy was done for suspicious cases. The airborne asbestos fibre concentrations were determined in all areas. There were 88 cases of mesothelioma diagnosed, 87 in the exposed group. The risk of mesothelioma was higher in the environmentally exposed group than other groups, and higher in females than males. The prevalence of mesothelioma increased with increased cumulative exposure to asbestos.

Exposition environnementale à l'amiante et relation exposition–réponse avec le mésothéliome

RÉSUMÉ Une étude épidémiologique et environnementale a été réalisée à Shubra El-Kheima, dans la banlieue du Caire, sur la relation exposition–réponse entre l'amiante et le mésothéliome pleural malin. Un dépistage radiologique a été effectué sur 487 personnes exposées à l'amiante dans le milieu professionnel, 293 personnes exposées à l'amiante dans l'environnement et un groupe témoin de 979 personnes n'ayant jamais été exposées. Une biopsie pleurale a été réalisée sur les cas suspects. Les concentrations de fibre d'amiante dans l'air ont été établies dans toutes les zones. Quatre-vingt-huit cas de mésothéliome ont été diagnostiqués, dont 87 dans le groupe exposé. Le risque de mésothéliome était plus élevé dans le groupe soumis à une exposition environnementale que dans les autres groupes, et plus élevé chez les femmes que chez les hommes. La prévalence du mésothéliome augmentait en même temps que l'exposition cumulée à l'amiante.

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Introduction

Malignant pleural mesothelioma (MPM) is associated with environmental and occupational exposure to asbestos [1]. During the last 4 decades, numerous studies on MPM have been conducted [2,3]. However, the natural history of this tumour remains ill-defined or scarcely known. Particular topics that deserve further investigation include the proportion of cases attributable to asbestos, the spectrum of the population at risk, the length of the latency period, the impact of mild exposure to asbestos and the role of cofactors in the development of the tumour [4].

Epidemiological studies have linked occupational exposure to asbestos with mesothelioma [5–10]. Cohort studies have found increased incidence of and mortality from mesothelioma among asbestos workers employed in mining [5], textile manufacturing [6], insulation [7] and asbestos cement factories [8]. Exposure has been assessed by a variety of methods, but all studies reach the conclusion that the rate of mesothelioma increases as the level of exposure increases [10]. Non-occupational or environmental exposure to asbestos is also associated with an increased risk of mesothelioma [11]. Exposure is experienced by individuals living with asbestos workers [12] and those living near asbestos mines and mills [13] or factories manufacturing asbestos products [14]. The development of the disease has a long latency, with cases arising more than 10 years after first exposure, and numbers continue to rise exponentially with time since first exposure [15].

Since other factors such as level of exposure also determine the risk of mesothelioma [16], it is important to analyse all these factors to disentangle their separate effects. The prevalence of mesothelioma has been increasing throughout the industrialized world [17]. The incidence is predicted to

peak around 2020 [18]. This reflects industrial exposure to asbestos, which was common up to the 1980s, combined with a latent period between exposure to asbestos and development of mesothelioma averaging 30–40 years [17].

Data obtained from the information network of the General Organization for Industrialization in Egypt, showed that 14 asbestos factories were present in Egypt in the year 2004 [19]. These factories affect an area of approximately 5–7 km in radius, which explains the high incidence of mesothelioma in the neighbourhood of these factories. Workers employed since 1948 by the Egyptian asbestos company Sigwart at the mills in greater Cairo (El Maasara and Shubra El-Kheima) had an increased risk of mesothelioma, as did former residents of Shubra El-Kheima who were not directly employed in the milling of asbestos. In 2002, a high prevalence of pleuropulmonary disorders due to environmental asbestos exposure was reported in the immediate vicinity, 0.5–1.5 km, from an asbestos plant in south Cairo [20]. In Egypt, the ministerial council decided to ban asbestos imports in 2004 and the Sigwart plants were closed in November 2004. Therefore, the predicted incidence of mesothelioma in Egypt will reach its peak around 2040. However, no previous Egyptian study of environmental exposure to asbestos and the risk of mesothelioma has been able to utilize exposure levels to derive quantitative exposure–response relationships.

The aims of this study were: to evaluate the prevalence of MPM due to occupational and environmental (non-occupational) exposure to asbestos among persons who had worked in the asbestos manufacturing plant and in persons living in an area nearby the plant with potentially significant population exposure and to estimate the exposure–

response relationship between environmental exposure to asbestos and MPM.

Methods

Location

This epidemiological and environmental study was carried out in Shubra El-Kheima city, greater Cairo, to evaluate the prevalence of MPM. Shubra El-Kheima is an industrial city at the northern boundary of Cairo, just upwind from downtown Cairo. It has an area of about 30 km². This city was considered the focal point of the highest environmental exposure to ambient asbestos fibres due to the operation of a large asbestos manufacturing plant (the Sigwart Company plant) (Figure 1). The Sigwart plant is an asbestos manufacturing plant using chrysotile asbestos. It was constructed in 1948 and its main products were asbestos cement pipes and reinforced concrete products. The study included 6 areas in the near vicinity of Sigwart plant, and these areas were mapped according to the distance from the asbestos plant and the airborne asbestos fibre concentrations.

Sample

The people working in the plant were designated the occupationally exposed group and the population living in the 6 areas near the plant were defined as the environmentally exposed group. Sampling areas of airborne asbestos fibres and the wind direction and speed are shown in Figure 1.

Environmentally exposed group

The 6 areas which were defined in the near vicinity of Sigwart plant included El-Wehda El-Arabia, Manshiyat El-Gadida, Manshiyat El-Horriya, Ezbet Osman, Manshiyat Abdel Moneim Riad and Ezbet Rostom. For the purpose of calculating population statistics,

the 2000 census population data were obtained from the Egyptian Central Agency for Public Mobilization and Statistics. All sampling sites were located within 2 km of the asbestos plant. El-Wehda El-Arabia area



Figure 1 Map of Shubra El-Kheima city with superimposed direction and speed of wind. Sampling areas: (1) Asbestos plant (Sigwart store); (2) El-Wehda El-Arabia; (3) Manshiyat El-Horriya; (4) Ezbet Rostom; (5) Ezbet Osman; (6) Manshiyat El-Gadida; (7) Manshiyat Abdel Moneim Riad

includes 56 228 people and lies about 100 m walking distance of the asbestos plant. Manshiyat El-Gadida includes 20 000 people, Manshiyat El-Horriya includes 67 832 people, Ezbet Osman includes 25 000 people, Manshiyat Abdel Moneim Riad includes 128 215 people, finally, Ezbet Rostom includes 24 834 people. A total of 322 109 people are still living in these areas and are still exposed to asbestos.

Permission was taken from the health centres in these areas to do the study and in turn, the health visitors informed the population living in those areas to attend the centres to do a mass miniature radiography (MMR) scan. Considerable efforts were made to convince people of the importance of doing the MMR. Verbal consent was taken from all individuals included in the study.

The sample size was calculated as 3059 subjects using the *Epi-Info* program. Those who agreed to participate in the study were 2913 subjects who were chosen by cluster sampling, with a response rate of 95%. Details about occupation were taken, and subjects who were working in the plant or retired from the plant or had any history suggestive of occupational exposure to asbestos were excluded from the environmentally exposed group to avoid double registration.

Occupationally exposed group

Efforts were made to gain permission to do the study inside the asbestos plant and to convince the staff of the plant about the importance of having the MMR scan. The total number of staff working in the plant was about 543 people: 35 refused to participate in the study, 21 were lost during the study and the remaining 487 agreed to undergo the MMR. This group included workers dealing with asbestos manufacture in different processing sites (milling, manufacturing and cutting) and those working in the store,

industrial shops, administration, asbestos waste site and the gate of the plant. The study was done during working hours in the presence of the whole workforce of the plant. All the staff inside the asbestos plant were exposed to the hazards of asbestos as there were contiguous rooms for all staff inside the different sections of the plant and clerks delivered circulars from the administration staff to the workers at their duty sites and there was supervision of work performance by administration staff.

Control group

An agricultural area at Banha city about 40 km from the plant was included in the study as a control area. The sample size of the population included in the study in that area was calculated as 1041 subjects using the *Epi-Info* program. Those who agreed to be included in the study were 979 people chosen by cluster sampling, a response rate of 94%. Verbal consent was taken before doing the MMR. None of these individuals had a history of occupational or environmental exposure to asbestos.

Data collection: clinical

Full history taking

All participants were interviewed. Occupational history was taken in full detail. The place of birth and residence were recorded in chronological order. The duration of environmental exposure to asbestos was determined. Full details were taken from the environmentally exposed group regarding their place of residence and period of residence in Shubra El-Kheima city. Care was also taken to exclude those with a history of occupational exposure to asbestos or retired people who were working in an asbestos plant. No history of migration was recorded because levels of mobility from one area to another in Egypt are very low and so the period from first residence in the area until the

time of study was considered as the duration of environmental exposure.

Clinical examination

A thorough clinical examination was carried out for all subjects, with special emphasis on the respiratory system.

Mass miniature radiography

MMR was done for all studied groups. All the films were read by 2 qualified and experienced readers for diffuse parenchymatous disease and pleural diseases. We used MMR for the initial screening for the purpose of time and cost savings because of the large number of subjects in the study and also to avoid the health hazards of radiation to the community. This procedure is usually adopted by the Egyptian Ministry of Health surveys to detect cases with abnormal shadows and followed up with standard chest radiographs for confirmation.

Standard chest radiographs

Suspected cases with MMR abnormalities immediately underwent standard chest radiographs to confirm the presence of the abnormality.

High-resolution computerized scans

A high-resolution computerized scan (HRCT) of the chest was done for those persons with abnormal chest radiographs for better assessment and localization of the lesion.

Admission to Abbassia Chest Hospital

Subjects with abnormal MMR and abnormal HRCT were admitted to Abbassia Chest Hospital where pleural biopsy was done using thoracoscopy, limited thoracotomy or CT-guided biopsy.

Data collection: estimation of airborne asbestos fibres

The study was done in the period January 2003 to March 2004 inside the asbestos

plant when it was functioning at full capacity and after the plant was closed in November 2004. So the screening of workers and other aspects of the study were done before closure of the plant.

Air sampling and analytical methods

Each air sample was collected on a membrane filter (Millipore AA, 25 mm diameter) mounted on an open filter holder. The air sampling was carried out for 8 hours at a flow rate of 10 L/min. All the samples were prepared by the method of the Occupational Safety and Health Agency (OSHA7400).

Filters were placed onto the surface of clean glass slides and were cleared using acetone triacetin reagent. A clean cover slip was gently lowered on the wedge at a slight angle to reduce bubble formation. The filter segment was outlined with a glass marking pen to aid in microscopic evaluation.

Measurements were carried out using light microscopy, phase contrast with a blue filter, adjustable field iris, 10 × eyepiece and 40 × phase objective (total magnification 400 ×). Walton Beckett graticule type with 100 µm diameter was used to count asbestos fibres (field area of Walton Beckett graticule is 0.00785 mm²). The slide was centred on the stage of the calibrated microscope under the objective lens, and the plane of the filter was focused on the microscope.

Fibres longer than 5 µm which lay entirely within the Walton Beckett graticule were counted. Counting started from the top of the filter wedge and progressed along a radial line of the outer edge, shifted up-down on the filter and continued in the reverse direction. The graticule field was chosen randomly. During 6 unit continuous scans a range of focal planes was examined by moving the 5 focus knobs to detect very fine fibres which may be embedded in the filter.

Calculations

Average count was calculated by dividing the total fibre count by the number of fields observed. Fibre density (E) (fibres/mm²) was defined as the average count (fibres/field) divided by the field graticule area (AF) (0.00785 mm²):

$$E = \frac{F/nf - B/nb}{AF}$$

Where F/nf = average fibre count/graticule field, B/nb = mean field blank count/graticule field.

The concentration (C) (fibres/cm³) of fibres in the air volume (V) (L) using the effective collection area of the filter (AC) (385 mm²) was calculated as follows:

$$C = \frac{(E) \times (AC)}{V^{10^3}}$$

$$V = L/\text{min} \times \text{times} = 3.1 \times 30 = 93 \text{ L.}$$

Sampling sites

Inside the asbestos plant: 45 air samples were taken from all department, the milling site (8 samples), the manufacturing machine (7 samples), the cutting site (6 samples), asbestos waste site (5 samples), industrial shops (5 samples), the gate (4 samples), the administration office (5 samples), and the store (5 samples). The samples were collected in the working environment dealing with the manufacture of the asbestos pipes during different processes. The air samples were collected at a height of 1.5 m (breathing zone) above the ground level between 09:00 and 17:00 hours.

Outside the asbestos plant: air samples were collected at 6 different areas (5 samples each) in Shubra El-Kheima city around the plant in a radius of 2.5 km.

Agricultural area: air samples were collected from an agricultural area at Banha city, about 40 km from the plant.

Methods of estimation of individual exposure levels

Intensity of exposure was calculated according to airborne asbestos fibre concentration (f/mL). Duration of exposure was determined for all subjects. Duration of exposure was then combined with intensity of exposure to give a measure of cumulative exposure for each person in fibres per millilitre years (f/mL-years). Latency was estimated from the year of first exposure until the onset of symptoms.

Statistical methods

Data were analysed using SPSS, version 9. Statistical analysis was carried out using Student *t*-test, Mann-Whitney test, chi-squared test and Fisher test. Relative risks (RR) and 95% confidence intervals (95% CI) were calculated to determine the risk of MPM in exposed subjects.

Results

The demographic and exposure characteristics of asbestos-exposed subjects are shown in Table 1. There was a highly statistically significant difference between the environmentally and occupationally exposed groups as regards age, sex, duration of exposure (i.e. length of time resident in the area or employed in the factory) and prevalence of MPM cases ($P < 0.001$).

The classification of pleuropulmonary disorders in all study groups is shown in Table 2. There were 88 cases of MPM diagnosed, 87 in the exposed groups and 1 in the control group. MPM was more prevalent in the environmentally exposed group (83/2913, 2.8%) than the occupationally exposed group (4/487, 0.8%) and control group (1/979, 0.1%) (Table 3).

The mean age of patients with MPM was 51.3 [standard deviation (SD) 8.08] years;

Table 1 **Characteristics of groups occupationally and environmentally exposed to asbestos**

Characteristic	Occupationally exposed (n = 487)		Environmentally exposed (n = 2913)		Test	P-value
Mean (SD) age (years)	46.5 (3.9)		57.5 (8.9)		t = 740.07	< 0.001
Sex	No.	%	No.	%		
Male	487	100.0	1616	55.5	$\chi^2 = 350.56$	< 0.001
Female	0	0.0	1297	45.5		
Mean (SD) intensity of exposure to asbestos (f/mL)	0.59 (0.76)		0.38 (0.87)		Mann–Whitney test = 1.56	< 0.001
Duration of residence in area or employment in factory (years)	No.	%	No.	%		
0–10	47	10.0	307	10.5	$\chi^2 = 33.50$	< 0.001
11–20	107	22.0	616	21.2		
21–30	88	18.0	837	28.7		
31–40	47	30.0	618	21.2		
>40	9	20.0	535	18.4		
Malignant pleural mesothelioma						
+ve	4	0.8	83	2.8	$\chi^2 = 6.88$	< 0.001
–ve	483	99.2	2830	97.2		

n = total number of people examined.

54.1 (SD 8.45) years (range 39–70 years) for males and 49.5 (SD 7.39) years (range 35–60 years) for females.

The exposure characteristics of subjects positive and negative for MPM are shown

in Table 4. Exposure to asbestos was significantly higher among patients with MPM compared to non-MPM subjects.

The prevalence of MPM among the environmentally exposed group in differ-

Table 2 **Classification of pleuropulmonary disorders in groups occupationally and environmentally exposed to asbestos**

Disorder	Occupationally exposed (n = 487)		Environmentally exposed (n = 2913)		Non-exposed (n = 979)	
	No.	%	No.	%	No.	%
Malignant pleural mesothelioma	4	0.8	83	2.8	1	0.1
Pleural plaques	7	1.4	46	1.5	0	–
Diffuse pleural thickening	29	5.9	39	1.3	1	0.1
Benign pleural effusion	1	0.2	36	1.2	0	–
Bilateral pulmonary fibrosis	4	0.8	29	0.9	2	0.2
Pericardial calcification	1	0.2	11	0.3	0	–
Total	46	9.4	244	8.3	4	0.4

n = total number of people examined.

Table 3 Prevalence of malignant pleural mesothelioma (MPM) cases in the asbestos-exposed and non-exposed groups

Group	No. examined	MPM cases	
		No.	%
Occupationally exposed	487	4	0.8
Environmentally exposed	293	83	2.8
Non-exposed	99	1	0.1

ent areas is shown in Table 5. There was a statistically significantly higher prevalence of MPM cases in El-Wehda El-Arabia area (4.5%) compared to Ezbet Rostom area which had the lowest prevalence (1.2%) ($\chi^2 = 12.75$, $P = 0.03$).

The risk of developing MPM was 26 times greater among the occupationally and environmentally exposed groups compared to the non-exposed group (Table 6).

The duration of exposure to asbestos in cases of MPM in all studied groups is shown in Table 7. There was a significantly number of MPM cases in patients with environmental asbestos exposure of more than 40 years when compared to those with a shorter duration of exposure ($P < 0.001$). Figure 2 shows that the percentage of MPM cases increased with longer duration of exposure to asbestos fibres.

Fibre concentrations in the different sites inside the asbestos plant are shown in Table 8. There was a highly significant difference between fibre concentrations at the asbestos waste site versus other sites and versus the control area ($P < 0.001$). Also there was a highly significant difference between fibre concentrations at asbestos manufacturing sites (milling, cutting and industrial shops) versus the control area ($P < 0.001$). Airborne asbestos fibre concentrations in the surrounding areas outside the

Table 4 Characteristics of people with and without malignant pleural mesothelioma (MPM)

Characteristic	MPM				χ^2 and <i>P</i> values
	+ve (<i>n</i> = 88)		−ve (<i>n</i> = 4291)		
	No.	%	No.	%	
<i>Duration of residence in area or employment in factory (years)</i>					
0–10	0	0.0	406	9.5	$\chi^2 = 44.30$; <i>P</i> < 0.001
11–20	5	5.7	785	18.3	
21–30	14	15.9	992	23.1	
31–40	16	18.2	831	19.4	
> 40	53	60.2	1277	29.7	
<i>Age (years)</i>					
20–40	11	12.5	669	15.6	$\chi^2 = 27.59$; <i>P</i> < 0.001
41–50	23	26.1	2086	48.6	
51–60	47	53.4	1234	28.8	
> 60	7	7.9	302	7.0	
<i>Sex</i>					
Male	34	38.6	2606	60.7	$\chi^2 = 17.58$; <i>P</i> = 0.0021
Female	54	61.4	1685	39.3	

n = total number of people examined.

Table 5 Prevalence of malignant pleural mesothelioma (MPM) in the group environmentally exposed to asbestos in different areas

Area (distance from the asbestos plant)	No. exposed	No. examined	MPM cases	
			No.	%
El-Wehda El-Arabia (100 m)	56 228	873	39	4.5
Mansh yat El-Adi da (800 m)	20 000	644	17	2.6
Mansh yat El-Horriya (1 km)	67 832	335	8	2.4
Elbt Osman (1 km)	25 000	412	9	2.2
Mansh yat Abdel Moneim Riad (2 km)	128 215	318	6	1.9
Elbt Rostom (2.5 km)	24 834	331	4	1.2

Table 6 Risk of malignant pleural mesothelioma (MPM) in the asbestos-exposed and non-exposed groups

MPM	Exposed (n = 3400)		Non-exposed (n = 979)	
	No.	%	No.	%
+ve	87	2.6	1	0.1
-ve	3313	97.4	978	99.9

Relative risk = 25.68.

n = total number of people examined.

asbestos plant and number of MPM cases are shown in Table 9. The overall mean asbestos fibre concentration in the exposure areas was 0.38 (SD 0.87) f/mL. The number of cases of MPM was higher in El-Wehda El-Arabia area (39 cases), where the concentration of airborne asbestos fibres was higher (2.16 f/mL) compared with other areas ($P < 0.01$).

The distribution of various indices of estimated exposure for MPM and non-MPM cases is shown in Table 10. Nearly 50% of patients with MPM had cumulative exposure > 20 f/mL-years.

Discussion

In this study 88 cases of MPM were diagnosed, all except 1 in the asbestos-exposed groups. The finding of 1 mesothelioma case in the non-exposed group can be explained by Hillerdal in 1999 who discussed the

evidence that the tumour can occur even in the complete absence of asbestos, i.e. a spontaneously occurring tumour [2].

The mean age of MPM cases was 54.1 years. These results are in agreement with a study which reported that malignant mesotheliomas of the pleura may occur over a wide age range, but are most commonly observed in adults over the age of 50 years [21].

Our study showed a significant difference in age in all exposed groups including MPM cases between the occupationally exposed and environmentally exposed groups. This might be because workers inside the asbestos plant were exposed to higher concentrations of asbestos fibres than the environmentally exposed group, so the mesothelioma might occur at an earlier age than the environmentally exposed group or there might be retirement at an earlier age in addition to death from MPM at an earlier age in the workers.

The female predominance of MPM cases (61.4% versus 38.6%) in our study is in agreement with another study which found that out of 27 cases with malignant pleural mesothelioma, 18 cases were females (66.7%) and 9 cases were males (33.3%) [10].

In Egypt, one study found that the dust concentration in the environment of Sigwart factory was 3–20 f/mL [22]. Our results

Table 7 Duration of exposure to asbestos in cases of malignant pleural mesothelioma (MPM) in all study groups

Duration (years)	Occupationally exposed ^a (n = 487)						Environmentally exposed (n = 2913)						Non-exposed (n = 979)					
	Males			Females			Males			Females			Males			Females		
	No.	MPM +ve	MPM -ve	No.	MPM +ve	MPM -ve	No.	MPM +ve	MPM -ve	No.	MPM +ve	MPM -ve	No.	MPM +ve	MPM -ve	No.	MPM +ve	MPM -ve
0-10	47	0	47	261	0	261	122	0	122	17	0	17	35	0	35			
11-20	107	0	107	349	2	347	129	3	126	38	0	38	29	0	29			
21-30	88	0	88	457	7	450	142	7	135	53	0	53	28	0	28			
31-40	147	3	144	181	3	178	311	10	301	33	0	33	49	0	49			
> 40	98	1	97	368	17	351	593	34	559	395	1	394	302	0	302			

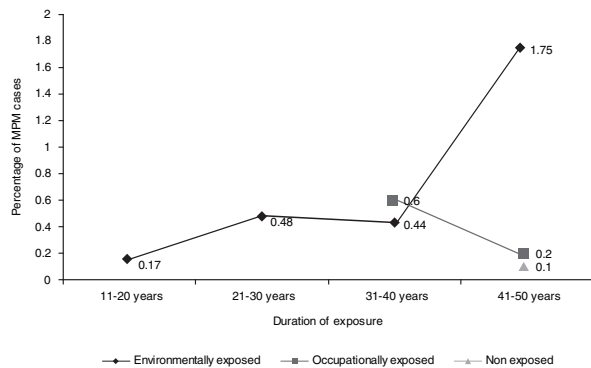
^aThere were no females occupationally exposed. $\chi^2 = 43.7, P < 0.001$.

Figure 2 Prevalence of malignant pleural mesothelioma according to the duration of exposure to asbestos fibres

showed a much lower mean concentration of 0.59 f/mL, presumably due to improvements in the technology of asbestos manufacturing and the use of closed systems along with the application of filters, frequent cleaning, suction systems and protective masks for the workers which led to a decrease in the concentration of the airborne asbestos fibres.

Environmental assessment of airborne asbestos fibre concentrations showed that the highest mean concentration (2.16 f/mL) was in the El-Wehda El-Arabia area which lies within 100 m of the asbestos plant and where the wind direction is towards that area. Fibre concentrations start to decrease further away from the plant. The overall mean asbestos fibre concentration in the exposure areas was 0.38 f/mL. This was in contrast with the findings of another study reporting a concentration of 7–13 f/mL in an area 0.5–1.5 km from the asbestos plant [20]. Therefore, it seems that exposure to asbestos fibres is not only limited to workers in factories but to those living in areas with environmental pollution from asbestos fibres.

In a study from Turkey the authors measured the airborne fibre concentration in a village environmentally exposed to asbestos, where they found that the mean concentration was 0.012 f/mL [23], a figure lower than ours. Their study and others [10,24] showed a higher rate of MPM cases among

Table 8 Asbestos fibre concentrations in the asbestos processing plant in greater Cairo and malignant pleural mesothelioma (MPM) cases by factory operation

Site no.	Operation	No. examined	No. of MPM cases	Fibre concentrations (f/mL-years)	
				Mean	SD
1	Milling	43	1	0.764	0.73
2	Manufacturing	89	0	0.250	0.11
3	Cutting	78	0	0.239	0.15
4	Store	23	0	0.183	0.21
5	Asbestos waste	45	3	2.330	1.30
6	Office	61	0	0.126	0.16
7	Industrial sbps	123	0	0.920	0.70
8	Gate	25	0	0.007	0.007
Total		487	4	0.590	0.76
Control		99	1	0.0021	0.013

F = 160; P < 0.001.

SD = standard deviation.

Table 9 Airborne asbestos fibre concentration in the surrounding areas outside the asbestos plant and number of malignant pleural mesothelioma (MPM) cases

Area (distance from the asbestos plant)	No. of MPM cases	Fibre concentration (f/mL)	
		Mean	SD
El-Wed a El-Arab a (100 m)	39	2.16*	0.16
El Mansh ya El Gida (800 m)	17	0.04	0.01
Mansh yet El Horriya (1 km)	8	0.021	0.0005
Elb Osman (1 km)	9	0.021	0.002
Mansh yet Abd E I Moneem Riyad (2 km)	6	0.025	0.004
Elb R ostom (2.5 km)	4	0.021	0.003
Total	83	0.38	0.87
Control	1	0.0021	0.013

F = 47.01; *P < 0.01.

SD = standard deviation.

those with higher intensity and cumulative exposure to asbestos. This was also confirmed in our study which showed a positive correlation between the asbestos fibre concentration and the number of MPM cases in all studied areas. It should be stressed that the high number of women detected with mesothelioma is due to the long duration of

residency near the asbestos plant with high permissible concentrations of asbestos.

The current study showed that MPM was more prevalent in the environmentally exposed group (2.8%) than in the occupationally exposed group (0.8%) reflecting the impact of environmental air pollution with asbestos on the prevalence of mesothelioma. This is in

Table 10 Distribution of various indices of estimated exposure of people with and without malignant pleural mesothelioma (MPM)

Measure of exposure	MPM				P-value
	+ve (n = 88)		-ve (n = 4291)		
	No.	%	No.	%	
<i>Estimated intensity of exposure (f/mL)</i>					
< 0.5	45	51.1	3350	78.1	$\chi^2 = 32.4; P < 0.01$
0.510. 75	0	0.0	0	0.0	
> 0.75	43	48.8	941	21.9	
<i>Estimated cumulative exposure (f/mL-years)</i>					
< 7.00	45	51.1	3130	73.0	
7.012 0	0	0.0	139	3.2	
> 20	43	48.8	1022	23.8	

n = total number of people examined.

agreement with a South African report which showed that one-third of the mesothelioma cases were exposed as residents living near asbestos mines and mills [25].

Comparing the prevalence of MPM among the environmentally exposed group in the different areas, our study showed that MPM was more prevalent in El Wehda El Arabia (4.5%), the nearest area near to the asbestos plant, than other areas further away. This agrees with the results of other studies which detected excess cases in the immediate neighbourhood of factories that processed asbestos, mainly from the same South African mines [26–28].

As regards monitoring of airborne asbestos fibre concentration, our study showed that the mean occupational airborne asbestos concentrations (0.59 f/mL) were significantly higher than the environmental concentrations (0.38 f/ mL). Similar results have been shown in previous reports on airborne asbestos concentrations in Europe and the United States of America [29].

Conclusion

This study provides additional quantitative information on the relative risks of pleural mesothelioma in subjects environmentally exposed to asbestos. Of special interest is the 26-fold excess risk of pleural mesothelioma due to environmental exposure. The central role of latency and of cumulative exposure in determining the risk of mesothelioma is of special importance. The present study has an important message. The mesothelioma epidemic will affect areas without major industrial exposure to asbestos. Though the importation of raw asbestos into Egypt was banned at the end of 2004, the threat of developing mesothelioma will remain for a considerable period of time due to the latency period. Therefore, a high index of suspicion is needed for early detection of mesothelioma in persons with environmental exposure to asbestos.

Successful interventions have already been made by the government of Egypt

to prevent further exposure to asbestos by placing a ban on its use. The focus now shifts to small informal workshops which use asbestos with a high risk of environmental exposure. Despite technical difficulties, the process of replacing asbestos with safer materials, especially in small informal workshops, is essential to prevent further

release of asbestos into the environment. Industries with harmful environmental and health impacts are heavily regulated in the developed countries and these industries are migrating to the developing world. Therefore great caution is needed, especially in the construction industry with the growing use of asbestos-based cement products.

References

1. Selcuk ZT et al. Malignant pleural mesothelioma due to environmental mineral fiber exposure in Turkey. Analysis of 135 cases. *Chest*, 1991, 102(3):796.
2. Hillerdal G. Mesothelioma: cases associated with non-occupational and low dose exposure. *Occupational environmental medicine*, 1995, 52:431-43.
3. Giarelli L, Bianchi C. Geography of mesothelioma: expected findings and paradoxes. *European journal of oncology*, 2000, 56 (suppl. 2):7781.
4. Bianchi C et al. Asbestos exposure in malignant mesothelioma of the pleura: A survey of 557 cases. *Industrial health*, 2001, 39:617.
5. McDonald CC et al. The 1891-1920 birth cohort of Quebec chrysotile miners and millers. Mortality 1968-88. *British journal of industrial medicine*, 1993, 50:1073-81.
6. Yano E et al. Cancer mortality among workers exposed to amphibole free chrysotile asbestos. *American journal of epidemiology*, 2001, 154:538-43.
7. Selikoff IJ, Hammond EC, Sediman H. Mortality experience of insulation workers in the United States and Canada, 193-196. *Annals of the New York Academy of Sciences*, 1979, 330:9-16.
8. Ulvestad B et al. Cancer incidence among workers in the asbestos cement producing industry in Norway. *Scandinavian journal of work environment and health*, 2002, 28(6):411-7.
9. Dement M, Brown DP, Olson A. Follow up study of chrysotile textile workers: cohort mortality and case-control analyses. *American journal of industrial medicine*, 1979, 26:431-47.
10. Hansen J et al. Environmental exposure to crocidolite and mesothelioma exposure-response relationships. *American journal of respiratory critical care medicine*, 1997, 157:69-75.
11. Duberstein H, Sediman H, Selikoff IJ. Mortality experience of family contacts of asbestos factory workers. *Annals of the New York Academy of Sciences*, 1991, 643:416-8.
12. Dodoli D et al. Environmental baseline exposure and occurrence of pleural mesothelioma. *American journal of industrial medicine*, 1992, 21:681-7.
13. Reid GD et al. Mortality of an asbestos-exposed birth cohort: a pilot study. *South African medical journal*, 1990, 78:684-6.
14. Hammond EC, Garfinkle L, Selikoff IT. Mortality experience of residents in the neighbourhood of an asbestos factory. *Annals of the New York Academy of Sciences*, 1979, 330:417-22.
15. Dekker NH, Armstrong BK. Cancer mortality in relation to crocidolite at Wittenoom

- George in Western Australia. *British journal of industrial medicine*, 1994;65:296.
16. Hauptmann M et al. The exposure-time response relationship between occupational asbestos exposure and lung cancer in two German case-control studies. *American journal of industrial medicine*, 2002;41:89.
 17. Britton M. The epidemiology of mesothelioma. *Seminars in oncology*, 2002, 29:825.
 18. White C. Annual deaths from mesothelioma in Britain to reach 2000 by 2010. *British medical journal*, 2003;325:1417.
 19. Kazan-Allen L. Asbestos: the environmental hazard. In: *Proceedings of the International Conference Asbestos Risk Reduction and Measurement of Asbestos Fibre Concentration, Cracow, Poland, September 28-29, 2006*. Kraków, Faculty of Materials Science and Ceramics, AGH University of Science and Technology (www.ceramika.agh.edu.pl/azbest06/2.pdf, accessed 11 August 2008)
 20. Tag-El-Din MA et al. Environmental airborne asbestos pollution and pleuropulmonary disorders in South Cairo. *Egyptian journal of chest diseases and tuberculosis*, 2002, 51(2):1606.
 21. Shrad D et al. Pneumothorax and malignant mesothelioma in patients over the age of 40. *Thorax*, 1994;6584.
 22. El-Shaar ARA et al. *Epidemiological study of asbestos-related diseases among Egyptian workers exposed to asbestos* [MD thesis]. Cairo, Department of Industrial Medicine and Occupational Health, Al-Azhar University, 1989.
 23. Metintas S et al. Malignant mesothelioma due to environmental exposure to asbestos. Follow up of a Turkish cohort living in a rural area. *Chest*, 2002, 122:2224-9.
 24. Browne K. Asbestos-related mesothelioma, factors discriminating between pleural and peritoneal sites. *British journal of industrial medicine*, 1986, 40:145-9.
 25. Wagner D, Sleggs CA, Marchand P. Diffuse pleural mesothelioma and asbestos exposure in the north western Cape Province. *British journal of industrial medicine*, 1980, 37:260-71.
 26. Selden A et al. Exposure to tremolite asbestos and respiratory health in Swedish dolomite workers. *Occupational environmental medicine*, 2001, 58:670-7.
 27. Hain E et al. Katamnestiche Untersuchungen zur Genese des Mesothelioms. Bericht über 150 Fälle aus dem Hamburger Raum [Retrospective study of 150 cases of mesothelioma in Hamburg area]. *Internationales Archiv für Arbeitsmedizin*, 1974, 33:15-37.
 28. Magnani C et al. Malignant pleural mesothelioma and non-occupational exposure to asbestos in Castale Monferrato, Italy. *Occupational and environmental medicine*, 1995, 52:362-7.
 29. Burdett GJ et al. Mean concentrations of airborne asbestos in the non-occupational environment. *Annals of occupational hygiene*, 1980, 28:31-8.

EXHIBIT 53

Latency periods in asbestos-related mesothelioma of the pleura

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Latency periods (time intervals elapsing between first exposure to asbestos and death) were examined in 421 cases of malignant pleural mesothelioma, diagnosed in the Trieste-Monfalcone area, Italy. Occupational data were collected from the patients or from their relatives by personal or telephone interviews. Routine lung sections were examined for asbestos bodies in 370 cases. Latency periods, calculated in 312 cases, ranged from 14 to 72 years (mean 48.7, median 51). Latency periods differed significantly from one occupational group to another. Mean latency periods were 29.6 among insulators, 35.4 among dock workers, 43.7 in a heterogeneous group defined as various, 46.4 in non-shipbuilding industry workers, 49.4 in shipyard workers, 51.7 among women with a history of domestic exposure to asbestos, and 56.2 in people employed in maritime trades. The ANOVA test indicated a correlation between latency periods and occupational groups. Latency periods in people with asbestos bodies visible in routine lung sections did not differ from those seen in cases with no evidence of asbestos bodies. These data suggest that intensity of exposure is a relevant, but not the only, factor in determining the duration of latency periods.

Key words: Asbestos exposure, environmental cancer, latency periods, mesothelioma, pleura, shipbuilding industry.

Introduction

Latency periods in asbestos-related mesothelioma may be defined as the time intervals elapsing between the first exposure to asbestos and the time of death (or alternatively of the first symptoms, or of the diagnosis). Latency periods in asbestos-related mesothelioma show wide variations (Lanphear and Buncher, 1992).

Some findings suggest that the intensity of the exposure to asbestos does not completely explain the differences in latency periods (Bianchi *et al*, 1993b, 1994). To obtain more data on the mechanisms involved in latency periods, we analysed a large series of malignant pleural mesotheliomas, diagnosed in the Trieste-Monfalcone area.

Trieste-Monfalcone district is a narrow coastal strip, located in north-eastern Italy, on the border of

Slovenia. In the past this area has been characterized by a high concentration of shipbuilding industries. A very high incidence of asbestos-related mesothelioma has been documented in Trieste (Giarelli *et al*, 1992, 1994), as well as in Monfalcone (Bianchi *et al*, 1993b).

Methods

A series of 421 malignant pleural mesotheliomas, diagnosed at Trieste University and at Monfalcone Hospital during 1968-96, were studied. Mesothelioma was diagnosed on, or confirmed by, necropsy findings in 374 cases. In a further 43 cases the pathological diagnosis was made on pleural biopsy specimens, and in the remaining four cases on cytological examination of the pleural fluid.

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Occupational histories were obtained from the patients themselves or from their relatives by personal or telephone interviews.

In 370 cases routine lung sections, generally obtained at necropsy and sometimes at surgery, were histologically examined for asbestos bodies.

The classification of a given case as asbestos-related was mainly based on the occupational data. However, in most of the cases, the existence of previous non-trivial exposure to asbestos was documented by objective signs (pleural plaques and/or lung asbestos bodies).

Statistical analysis was performed using Epi Info, version 5, from the Centers for Disease Control (Atlanta, Georgia). The ANOVA test was used to analyse the distribution of latency periods in the various occupational groups. Student's *t* test was used to compare mean latency periods among people with and without asbestos bodies in routine lung sections.

Results

Over 90% of the cases were classified as asbestos-related. However, precise chronological data about the first exposure to asbestos were obtained for 312 patients (292 men and 20 women, aged between 32 and 91 years). In such cases latency periods ranged from 14 to 72 years, most between 40 and 59 years (Figure 1). The different occupational groups showed substantial differences in latency periods (Figure 2). Insulators and dock workers generally had latency periods below 40 years. At the other extreme, the latency periods of women with histories of domestic exposure to asbestos (they had cleaned the work clothes of people occupationally exposed), and the latency periods of patients employed in maritime trades, were generally higher than 40 years. Intermediate values were observed in the remaining categories. The mean latency periods in the above occupational groups ranged from 29.6 to 56.2 years (Table 1).

The ANOVA test indicated a correlation between latency period and occupational groups ($P < 0.000001$).

Of 287 patients for whom both latency period data and routine lung sections were available, 198 (69%) showed asbestos bodies. The prevalence of positive findings varied largely from one category to another, ranging from 27% to 100% (Table 1). The latency periods in patients with asbestos bodies in routine lung sections are reported in Table 1. Mean latency period in people with asbestos bodies visible in

Latency periods in mesothelioma

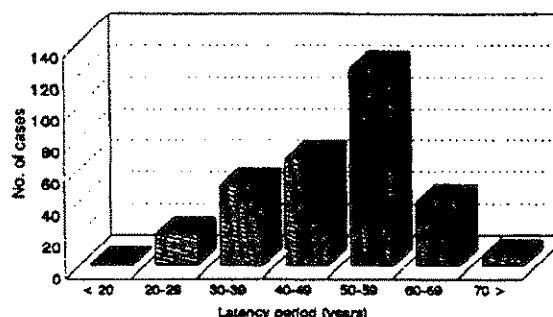


Figure 1. Latency periods in 312 cases of malignant pleural mesothelioma.

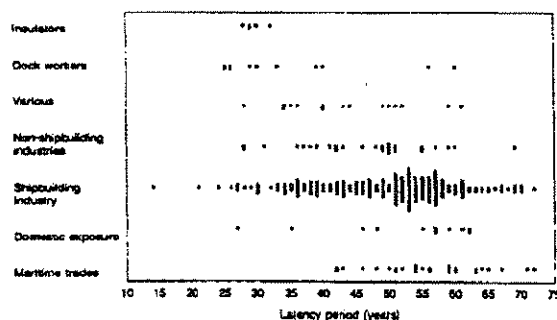


Figure 2. Latency periods by occupation in 312 cases of malignant pleural mesothelioma.

Table 1. Mean latency periods by occupation and presence of asbestos bodies in routine lung sections

Occupation	No of cases	Mean LP	Cases with AB (%)	Mean LP in the cases with AB
Insulators	5	29.6	80.0	30.0
Dock workers	11	35.4	100.0	35.4
Various	15	43.7	50.0	48.0
Non-shipbuilding industry	27	46.4	56.0	47.0
Shipbuilding industry	216	49.4	74.0	49.9
Domestic exposure	11	51.7	27.3	60.7
Maritime trades	27	56.2	52.2	56.0
Total	312	48.7	69.0	48.9

AB = Asbestos bodies
LP = Latency period

routine lung sections did not differ from that observed in cases with an absence of asbestos bodies.

Discussion

In general, the intervals elapsing between the time in which the exposure to a given carcinogenic agent occurs (or begins to occur), and the time at which cancer develops, vary extensively. Lymphoproliferative lesions (sometimes neoplastic in nature) that occur after organ transplantation may develop a few months after transplantation (London *et al*, 1995). At the other end of the spectrum, the development of mesothelioma may require incubation periods of 70 years. Intervals between some years and some decades are seen with radiogenic cancer (Mark *et al*, 1994; Nikiforov and Gnepp, 1994; Salvati *et al*, 1994).

When studying latency period in asbestos-related mesothelioma, the first point to assess is whether a given case is related to asbestos. Exposure to asbestos is guaranteed for several 'classic' occupations, but new, previously unrecognized, occupational groups at risk for asbestos disease have also emerged (Huncharek, 1992; Giarelli *et al*, 1994). In addition, there are many grey areas, where exposure cannot be excluded. It is therefore important that the classification based on the work history is corroborated by markers of exposure (pleural plaques, lung asbestos bodies). Such markers may also give reliable information about the intensity of the exposure (Bianchi *et al*, 1991).

As the workplace is the source of the exposure in most asbestos-related mesotheliomas, it is not generally difficult to determine the onset of the exposure. However, the first exposure may be difficult or impossible to establish exactly in the case of non-occupational exposure.

In previous studies on mesothelioma in the Trieste-Monfalcone area, latency periods were defined as time intervals between first exposure and death (Giarelli *et al*, 1992, 1994; Bianchi *et al*, 1994), and as time intervals between first exposure and diagnosis of the tumour (Bianchi *et al*, 1993b). In the present analysis the former definition was adopted, because in various cases, retrospectively examined, the time of the diagnosis (and/or of the first symptoms) could not be accurately determined.

The present data show that latency periods markedly differ among various occupational groups. The shortest mean latency periods were seen among insulators and dock workers. Insulation workers were by far the most heavily exposed to asbestos; in fact, they handled asbestos daily. Dock workers had

been employed in the port of Trieste, where they frequently loaded and unloaded asbestos. Previous inquiries revealed that heavy pollution occurred in such workplaces (Giarelli *et al*, 1994). The severe degree of exposure to asbestos these people had, is also indicated by the very high prevalence of cases with asbestos bodies visible in routine lung tissue sections.

The longest mean latency periods were found among men employed in maritime trades and among women with domestic exposure to asbestos. Both these categories generally experience exposures of relatively low intensity, the amounts of lung asbestos bodies frequently being below 1,000 per gram of dried tissue, and more rarely of some thousands/gram (Bianchi *et al*, 1991).

The data for the most heavily exposed people as well as those for the groups with the lowest exposures are exactly the same as would be expected, if an inverse correlation exists between the intensity of exposure to asbestos and the duration of latency period. Obviously, this conclusion is weakened by the fact that in the present series some groups (notably the insulators) were small in number.

The findings on shipyard workers are not easy to explain in terms of a dose-effect correlation. It is true that within this category the degrees of exposures are scattered along a very wide spectrum. However, the intensity of exposure among shipyard workers is high, as indicated by the high prevalence of large pleural plaques (71.7%), the high prevalence of asbestos bodies in lung sections (42.8%) and by the numbers of asbestos bodies in lung tissue (frequently over 10,000/gram) (Bianchi *et al*, 1991). On the whole, exposure to asbestos among shipyard workers seems to be similar to that experienced by insulators rather than like that experienced by sailors. Therefore, the long latency period seen in a large proportion of shipyard workers is quite unexpected. The hypothesis that mesothelioma involves a sub-category of shipyard workers with relatively mild exposures (the most heavily exposed persons having pulmonary asbestosis and lung cancer) should be considered. However, the high percentage of shipyard workers with asbestos bodies, visible in routine lung sections (Table 1), indicates that these patients had had heavy exposures. Moreover, latency periods in shipyard workers with asbestos bodies in routine lung sections did not differ from latency periods among those without asbestos bodies. These data suggest that latency periods among shipyard workers do not depend on the intensity of exposure alone.

Latency periods in mesothelioma

The type and amount of asbestos could help to determine the duration of the latency period. Investigations performed on pleura and lung tissues from people who had worked in the Monfalcone shipyards showed both amphibolic and chrysotilic fibres (Dodson *et al*, 1990). This clearly indicates that 'mixed' exposure occurred in the shipyards of this area. The remaining main categories of worker were also presumably exposed to various types of asbestos.

Another point to be considered is the possible association between latency period and smoking. Asbestos may induce both malignant mesothelioma and lung carcinoma, the latter in smokers. The smoking habits in a given population exposed to asbestos will influence the proportion of mesotheliomas and lung carcinomas. Smoking could also influence the latency periods in mesothelioma. For instance, being a non-smoker (or light smoker) might induce longer survival, and therefore could favour the development of mesothelioma after a long latency period. Investigation of pleural mesothelioma and lung carcinoma simultaneously would help resolve this. While previous findings (Bianchi *et al*, 1993a) suggest that in our area mesothelioma patients do not differ in their smoking habits from the general population, this topic requires further investigation.

The discussion about latency period is not of simply academic interest. Despite bans on (or limitations in) the use of asbestos, the incidence of malignant mesothelioma is increasing in various industrialized countries (Bégin *et al*, 1992; Facchini *et al*, 1993; Iwatsubo *et al*, 1994; Damhuis and Planteydt, 1995; De Vos Irvine, 1995; Peto *et al*, 1995; Leigh *et al*, 1996). In recent decades, the intensity of exposure has been reduced in many workplaces. However, more people have been exposed (for instance in the construction industry), and this indicates that a new wave of mesotheliomas is to be expected (Peto *et al*, 1995). On the other hand, the results obtained by various treatments for mesothelioma are not encouraging (de Pangher Manzini *et al*, 1993; Shin *et al*, 1995). In this context, how to prevent mesothelioma in healthy people previously exposed to asbestos becomes a major issue. If the factors responsible for the duration of latency period are identified, a way could be found to modify this duration. As the longest latency period in asbestos-related mesothelioma is very close to the mean duration of human life, the prolongation of the latency period could mean preventing the development of the tumour.

References

- Bégin R, Gauthier JJ, Desmeules M, Ostiguy G (1992). Work-related mesothelioma in Quebec, 1967-1990. *Am J Industrial Med* 22: 531-42.
- Bianchi C, Brollo A, Ramani L, Bertè R (1991). Exposure to asbestos in Monfalcone, Italy. A necropsy-based study. In *Autopsy in Epidemiology and Medical Research* (eds Riboli E, Delendi M); IARC, Lyon, pp. 127-40.
- Bianchi C, Brollo A, Ramani L, Zuch C (1993a). Asbestos exposure in pulmonary and pleural malignancies. A study of 307 cases. In *Proceedings of the Eighth International Conference on Occupational Lung Diseases* (eds Hurych J, Lesage M, David A); ILO, Geneva, pp. 335-40.
- Bianchi C, Brollo A, Ramani L, Zuch C (1993b). Asbestos-related mesothelioma in Monfalcone, Italy. *Am J Industrial Med* 24: 149-60.
- Bianchi C, Giarelli L, Grandi G, Brollo A (1994). Malignant mesothelioma of the pleura. A survey of 357 cases. In *Proceedings of the XVI International Cancer Congress* (eds Rao RS, Deo MG, Sanghvi LD); Monduzzi, Bologna, pp. 1239-42.
- Damhuis RAM, Planteydt HT (1995). Trends in incidence of pleural mesothelioma in the Rotterdam area. *Int J Cancer* 60: 883.
- de Pangher Manzini V, Brollo A, Franceschi S, De Mattheis M, Talamini R, Bianchi C (1993). Prognostic factors of malignant mesothelioma of the pleura. *Cancer* 72: 410-7.
- De Vos Irvine H (1995). Mesothelioma. *Lancet* 345: 1233.
- Dodson RF, Williams MG Jr, Corn CI, Brollo A, Bianchi C (1990). Asbestos content of lung tissue, lymph nodes, and pleural plaques from former shipyard workers. *Am Rev Respir Dis* 142: 843-47.
- Facchini U, Branzaglia P, Ludwig N, Riboldi L, Bertazzi PA (1993). Rischio amianto: uno studio sui certificati di morte per mesotelioma della pleura, anni 1969-1988. *Acta Oncologica* 14: 221-31.
- Giarelli L, Bianchi C, Grandi G (1992). Malignant mesothelioma of the pleura in Trieste, Italy. *Am J Industrial Med* 22: 521-30.
- Giarelli L, Bianchi C, Grandi G (1994). Asbestos-related mesothelioma of the pleura in Trieste, Italy. In *The Identification and Control of Environmental and Occupational Diseases* (eds Mehlman MA, Upton A); Princeton Scientific Publishing Co, Princeton, pp. 343-51.
- Huncharek M (1992). Changing risk groups for malignant mesothelioma. *Cancer* 69: 2704-11.
- Iwatsubo Y, Pairen JC, Archambault de Beaune C, Chammings S, Bignon J, Brochard P (1994). Pleural mesothelioma: a descriptive analysis based on a case-control study and mortality data in Ile de France, 1987-1990. *Am J Industrial Med* 26: 77-88.
- Lanphear BP, Buncher CR (1992). Latent period for malignant mesothelioma of occupational origin. *J Occupational Med* 34: 718-21.
- Leigh J, Hull B, Davidson P (1996). *The Incidence of Mesothelioma in Australia 1992 to 1994. Australian Mesothelioma Register Report, 1996*. Australian Mesothelioma Register, Sydney.

- London NJ, Farmery SM, Will EJ, Davison AM, Lodge JPA (1995). Risk of neoplasia in renal transplant patient. *Lancet* 346: 403-6.
- Mark RJ, Poen J, Tran LM, Fu YS, Selch MT, Parker RG (1994). Postirradiation sarcomas. A single-institution study and review of the literature. *Cancer* 73: 2653-62.
- Nikiforov Y, Gnepp DR (1994). Pediatric thyroid cancer after the Chernobyl disaster. Pathomorphologic study of 84 cases (1991-92) from the Republic of Belarus. *Cancer* 74: 748-66.
- Peto J, Hodgson JT, Matthews FE, Jones JR (1995). Continuing increase in mesothelioma mortality in Britain. *Lancet* 345: 535-9.
- Salvati M, Puzzilli F, Bristot R, Cervoni L (1994). Post-radiation gliomas. *Tumori* 80: 220-3.
- Shin DM, Fossella FV, Umsawasdi T et al (1995). Prospective study of combination chemotherapy with cyclophosphamide, doxorubicin, and cisplatin for unresectable or metastatic malignant pleural mesothelioma. *Cancer* 76: 2230-6.