This is a reproduction of a library book that was digitized by Google as part of an ongoing effort to preserve the information in books and make it universally accessible.

Google™ books

https://books.google.com



Toxicological Profile for

ASBESTOS
(Update)

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

Digitized by Google

UNIVERSITY OF
ILLINOIS LIBRARY
AT URBANA-CHAMPAIGN
VETERINARY MEDICINE

FEB 21 1996

Digitized by Google

TOXICOLOGICAL PROFILE FOR ASBESTOS

Prepared by:

Sciences International, Inc.
Under Subcontract to:

Research Triangle Institute
Under Contract No. 205-93-0606

Prepared for:

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

August 1995

Digitized by Google

DISCLAIMER

The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/5

UPDATE STATEMENT

A Toxicological Profile for Asbestos was released on April 1993. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary, but no less than once every three years. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology/Toxicology Information Branch
1600 Clifton Road NE, E-29
Atlanta, Georgia 30333

Digitized by Google

Digitized by Google

615.925392 24
T667
Jet. Med.

FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The original guidelines were published in the Federal Register on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature (that has been peer-reviewed) that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

Each toxicological profile begins with a public health statement, that describes in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protect public health will be identified by ATSDR and EPA. The focus of the profiles is on health and toxicologic information; therefore, we have included this information in the beginning of the document.

Each profile must include the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects.

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects.

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the federal, state, and local levels, interested private sector organizations and groups, and members of the public.

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The availability of the revised priority list of 275 hazardous substances was announced in the Federal Register on February 28, 1994 (59 FR 9486). For prior versions of the list of substances, see Federal Register notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17, 1990 (55 FR 42067); and October 17, 1991 (56 FR 52166); and October 28, 1992 (57 FR 48801).

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/8

Foreword

Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

This profile reflects our assessment of all relevant toxicologic testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, the Centers for Disease Control and Prevention (CDC), and other federal agencies. It has also been reviewed by a panel of nongovernment peer reviewers and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.



David Satcher, M.D., Ph.D.
Administrator
Agency for Toxic Substances and
Disease Registry

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/9

CONTRIBUTORS

CHEMICAL MANAGER(S)/AUTHOR(S):

Michael Brown, M.P.H.
ATSDR, Division of Toxicology, Atlanta, GA

LCDR William D. Henriques, M.S.P.H.
ATSDR, Division of Toxicology, Atlanta, GA

Patricia M. Bittner, M.S.
Sciences International, Inc., Alexandria, VA

THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Green Border Review. Green Border review assures the consistency with ATSDR policy.

2. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying endpoints.

3. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific minimal risk levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

Digitized by Google

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/11

PEER REVIEW

A peer review panel was assembled for asbestos. The panel consisted of the following members:

1. Dr. Lincoln Polissar, Associate Professor, Department of Biostatistics, University of Washington, Seattle, WA

2. Dr. Marty Kanarek, Associate Professor, Department of Preventive Medicine, University of Wisconsin, Madison, WI

3. Dr. Andrew L. Reeves, Professor Emeritus, Department of Occupational and Environmental Health, Wayne State University, Detroit, MI

4. Dr. Irving Selikoff, Professor Emeritus, Mount Sinai School of Medicine, New York, NY

5. Dr. Brooke Mossman, Professor, Department of Pathology, College of Medicine, University of Vermont

6. Dr. Neil Johnson, Experimental Pathologist, Inhalation Toxicology Research Institute, Kirkland Air Force Base, Albuquerque, NM

These experts collectively have knowledge of asbestos's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(i)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/12

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/13

CONTENTS

FOREWORD v

CONTRIBUTORS vii

PEER REVIEW ix

LIST OF FIGURES xv

LIST OF TABLES xvii

1. PUBLIC HEALTH STATEMENT 1
   1.1 WHAT IS ASBESTOS? 1
   1.2 WHAT HAPPENS TO ASBESTOS WHEN IT ENTERS THE ENVIRONMENT? 2
   1.3 HOW MIGHT I BE EXPOSED TO ASBESTOS? 2
   1.4 HOW CAN ASBESTOS ENTER AND LEAVE MY BODY? 4
   1.5 HOW CAN ASBESTOS AFFECT MY HEALTH? 4
   1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO ASBESTOS? 6
   1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH? 7
   1.8 WHERE CAN I GET MORE INFORMATION? 8

2. HEALTH EFFECTS 9
   2.1 INTRODUCTION 9
   2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE 9
      2.2.1 Inhalation Exposure 10
         2.2.1.1 Death 12
         2.2.1.2 Systemic Effects 12
         2.2.1.3 Immunological and Lymphoreticular Effects 26
         2.2.1.4 Neurological Effects 27
         2.2.1.5 Reproductive Effects 27
         2.2.1.6 Developmental Effects 27
         2.2.1.7 Genotoxic Effects 27
         2.2.1.8 Cancer 28
      2.2.2 Oral Exposure 32
         2.2.2.1 Death 33
         2.2.2.2 Systemic Effects 33
         2.2.2.3 Immunological and Lymphoreticular Effects 34
         2.2.2.4 Neurological Effects 40
         2.2.2.5 Reproductive Effects 40
         2.2.2.6 Developmental Effects 40
         2.2.2.7 Genotoxic Effects 41
         2.2.2.8 Cancer 41
      2.2.3 Dermal Exposure 44
         2.2.3.1 Death 46

Digitized by Google

2.2.3.2 Systemic Effects . . . 46
2.2.3.3 Immunological and Lymphoreticular Effects . . . 46
2.2.3.4 Neurological Effects . . . 46
2.2.3.5 Reproductive Effects . . . 46
2.2.3.6 Developmental Effects . . . 46
2.2.3.7 Genotoxic Effects . . . 46
2.2.3.8 Cancer . . . 46
2.3 TOXICOKINETICS . . . 46
2.3.1 Absorption . . . 47
2.3.1.1 Inhalation Exposure . . . 47
2.3.1.2 Oral Exposure . . . 47
2.3.1.3 Dermal Exposure . . . 48
2.3.2 Distribution . . . 48
2.3.2.1 Inhalation Exposure . . . 48
2.3.2.2 Oral Exposure . . . 49
2.3.2.3 Dermal Exposure . . . 50
2.3.2.4 Other Exposure . . . 50
2.3.3 Metabolism . . . 50
2.3.3.1 Inhalation Exposure . . . 50
2.3.3.2 Oral Exposure . . . 51
2.3.3.3 Dermal Exposure . . . 51
2.3.3.4 Other Exposure . . . 51
2.3.4 Excretion . . . 52
2.3.4.1 Inhalation Exposure . . . 52
2.3.4.2 Oral Exposure . . . 53
2.3.4.3 Dermal Exposure . . . 53
2.3.4.4 Other Exposure . . . 53
2.3.5 Mechanisms of Action . . . 53
2.4 RELEVANCE TO PUBLIC HEALTH . . . 58
2.5 BIOMARKERS OF EXPOSURE AND EFFECT . . . 70
2.5.1 Biomarkers Used to Identify or Quantify Exposure to Asbestos . . . 71
2.5.2 Biomarkers Used to Characterize Effects Caused by Asbestos . . . 73
2.6 INTERACTIONS WITH OTHER SUBSTANCES . . . 74
2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE . . . 76
2.8 METHODS FOR REDUCING TOXIC EFFECTS . . . 76
2.8.1 Reducing Peak Absorption Following Exposure . . . 77
2.8.2 Reducing Body Burden . . . 77
2.8.3 Interfering with the Mechanism of Action for Toxic Effects . . . 77
2.9 ADEQUACY OF THE DATABASE . . . 78
2.9.1 Existing Information on Health Effects of Asbestos . . . 79
2.9.2 Identification of Data Needs . . . 79
2.9.3 On-going Studies . . . 86

3. CHEMICAL AND PHYSICAL INFORMATION . . . 91
3.1 CHEMICAL IDENTITY . . . 91
3.2 PHYSICAL AND CHEMICAL PROPERTIES . . . 91

4. PRODUCTION, IMPORT, USE, AND DISPOSAL . . . 95
4.1 PRODUCTION . . . 95

Digitized by Google

4.2 IMPORT/EXPORT 97
4.3 USE 97
4.4 DISPOSAL 98

5. POTENTIAL FOR HUMAN EXPOSURE 99
5.1 OVERVIEW 99
5.2 RELEASES TO THE ENVIRONMENT 101
5.2.1 Air 101
5.2.2 Water 101
5.2.3 Soil 103
5.3 ENVIRONMENTAL FATE 103
5.3.1 Transport and Partitioning 103
5.3.2 Transformation and Degradation 104
5.3.2.1 Air 104
5.3.2.2 Water 104
5.3.2.3 Sediment and Soil 104
5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT 104
5.4.1 Air 104
5.4.2 Water 106
5.4.3 Sediment and Soil 106
5.4.4 Other Environmental Media 107
5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE 107
5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES 109
5.7 ADEQUACY OF THE DATABASE 109
5.7.1 Identification of Data Needs 110
5.7.2 On-going Studies 112

6. ANALYTICAL METHODS 113
6.1 BIOLOGICAL MATERIALS 114
6.2 ENVIRONMENTAL SAMPLES 115
6.3 ADEQUACY OF THE DATABASE 115
6.3.1 Identification of Data Needs 119
6.3.2 On-going Studies 120

7. REGULATIONS AND ADVISORIES 121

8. REFERENCES 125

9. GLOSSARY 189

APPENDICES

A. USER'S GUIDE A-1

B. ACRONYMS, ABBREVIATIONS, AND SYMBOLS B-1

C. RISK ASSESSMENT SUMMARY C-1

Digitized by Google

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/17

LIST OF FIGURES

2-1. Levels of Significant Exposure to Asbestos - Inhalation (Human Studies) 18
2-2. Levels of Significant Exposure to Asbestos - Inhalation (Animal Studies) 22
2-3. Levels of Significant Exposure to Asbestos - Oral 38
2-4. Summary of Calculated Gastrointestinal Cancer Risks from Ingestion of Asbestos 45
2-5. Existing Information on Health Effects of Asbestos 80
3-1. Basic Polysilicate Structures of Asbestos 92
5-1. Frequency of NPL Sites with Asbestos Contamination 100

Digitized by Google

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/19

LIST OF TABLES

2-1. Levels of Significant Exposure to Asbestos - Inhalation (Human Studies) 13
2-2. Levels of Significant Exposure to Asbestos - Inhalation (Animal Studies) 19
2-3. Levels of Significant Exposure to Asbestos - Oral 35
2-4. Summary of NTP Lifetime Asbestos Feeding Studies 43
2-5. Genotoxicity of Asbestos *In Vivo* 63
2-6. Genotoxicity of Asbestos *In Vitro* 64
2-7. On-going Studies on the Health Effects of Asbestos 87
3-1. Chemical Identity of Asbestos 93
3-2. Physical and Chemical Properties of Asbestos 94
4-1. Facilities That Manufacture or Process Asbestos 96
5-1. Releases to the Environment from Facilities That Manufacture or Process Asbestos 102
5-2. Summary of Typical General Population and Occupational Exposures 108
6-1. Analytical Methods for Determining Asbestos in Biological Samples 116
6-2. Analytical Methods for Determining Asbestos in Environmental Samples 118
7-1. Regulations and Guidelines Applicable to Asbestos 122

Digitized by Google

Digitized by Google

1. PUBLIC HEALTH STATEMENT

This statement was prepared to give you information about asbestos and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1,408 hazardous waste sites as the most serious in the nation. These sites comprise the "National Priorities List" (NPL): Those sites which are targeted for long-term federal cleanup activities. Asbestos has been found in at least 58 of the sites on the NPL. However, the number of NPL sites evaluated for asbestos is not known. As EPA evaluates more sites, the number of sites at which asbestos is found may increase. This information is important because exposure to asbestos may cause harmful health effects and because these sites are potential or actual sources of human exposure to asbestos.

When a substance is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. This release does not always lead to exposure. You can be exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking substances containing the substance or by skin contact with it.

If you are exposed to a substance such as asbestos, many factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such as age, gender, nutritional status, family traits, life-style, and state of health.

1.1 WHAT IS ASBESTOS?

Asbestos is the name applied to a group of six different fibrous minerals (amosite, chrysotile, crocidolite, and the fibrous varieties of tremolite, actinolite, and anthophyllite) that occur naturally in the environment. Nonasbestos (nonfibrous) forms of tremolite, actinolite, and

Digitized by Google

anthophyllite also are found naturally. The most common mineral type is white (chrysotile), but others may be blue (crocidolite), gray (anthophyllite), or brown (amosite). These minerals are made up of fibers that vary in length and may be straight or curled. Asbestos fibers do not have any detectable odor or taste. Asbestos can be found naturally in soil and rocks in some areas. Asbestos fibers are resistant to heat and most chemicals. Because of this property, asbestos fibers have been mined for use in a wide range of man-made products, mostly in building materials, friction products, and heat-resistant fabrics. Because asbestos fibers may produce adverse health effects in exposed persons, all new uses of asbestos have been banned in the United States by the EPA. Uses for asbestos that were established before July 12, 1989, which include most of the uses listed above, are still allowable.

See Chapters 3 and 4 for more information on the properties and uses of asbestos.

1.2 WHAT HAPPENS TO ASBESTOS WHEN IT ENTERS THE ENVIRONMENT?

Asbestos fibers do not evaporate into air or dissolve in water. However, pieces of fibers can enter the air and water from the weathering of natural deposits and the wearing down of man-made asbestos products. Small fibers and fiber-containing particles may remain suspended in the air for a long time and be carried long distances by wind or water currents before settling. Larger fibers and particles tend to settle more quickly. Asbestos fibers are not able to move through soil. Asbestos fibers are not broken down to other compounds in the environment. Therefore, they can remain in the environment for decades or more. Asbestos fibers may build up in animals.

See Chapters 4 and 5 for more information on the behavior of asbestos in the environment.

1.3 HOW MIGHT I BE EXPOSED TO ASBESTOS?

You are most likely to be exposed to asbestos by inhaling asbestos fibers suspended in air. These fibers can come from natural outcroppings of asbestos or from the wearing down of

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/23

man-made products including insulation, ceiling and floor tiles, roof shingles, cement, and automotive brakes and clutches. However, these products do not always contain asbestos. Low levels of asbestos that are not likely to be harmful to your health can be detected in almost any air sample. For example, in rural areas, an average of around 0.03–3 fibers are usually present in a cubic meter (f/m^3) of outdoor air[a]. (A cubic meter is about the amount of air you breathe in 1 hour.) Higher levels are usually found in cities, where there may be 2–300 f/m^3.

Close to an asbestos mine or factory, levels could reach 2,000 f/m^3 or higher. Levels could also be above average near a building that contains asbestos products and is being torn down or renovated or near a waste site where asbestos is not properly covered up or stored to protect it from wind erosion.

In indoor air, the concentration of asbestos depends on whether asbestos was used for insulation, ceiling or floor tiles, or other purposes, and whether these asbestos-containing materials are in good condition or are deteriorated and easily crumbled. Concentrations measured in homes, schools, and other buildings that contain asbestos range from 0.7 to 6,000 f/m^3. People who work with asbestos (for example, miners, insulation workers, automobile brake mechanics) without proper protection are likely to be exposed to much higher levels of asbestos particles in air.

You can also be exposed to asbestos by drinking fibers present in water. Even though asbestos does not dissolve in water, fibers can enter water by being eroded from natural deposits or piles of waste asbestos, from asbestos-containing cement pipes used to carry drinking water, or from filtering through asbestos-containing filters. Most drinking water

---

[a] The fiber count depends on how the fibers are measured. Values in air are reported as phase contrast fibers per cubic meter. This is the same measure as used to describe health effects in Section 1.5. The values in water are reported as transmission electron microscope fibers. This method is more sensitive than phase contrast microscopy, so values in air and water are not comparable.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/24

supplies in the United States have concentrations less than 1 million fibers per liter (MFL). However, in some locations, water samples may contain 10–300 MFL or even higher.

See Chapters 2 and 5 for more information on how you could be exposed to asbestos.

1.4 HOW CAN ASBESTOS ENTER AND LEAVE MY BODY?

If you breathe asbestos fibers into your lungs, some of the fibers will be deposited in the air passages and on the cells that make up your lungs. Most fibers are removed from your lungs by being carried away or coughed up in a layer of mucus to the throat, where they are swallowed into the stomach. This usually takes place within a few hours. Fibers that are deposited in the deepest parts of the lung are removed more slowly. In fact, some fibers may move through your lungs and can remain in place for many years and may never be removed from your body.

If you swallow asbestos fibers (either those present in water or those that are moved to your throat from your lungs), nearly all the fibers pass along your intestines within a few days and are excreted in the feces. A small number of fibers may penetrate into cells that line your stomach or intestines and a few penetrate all the way through and get into your blood. Some of these become trapped in other tissues and some are removed in your urine.

If you get asbestos fibers on your skin, very few of these fibers, if any, pass through the skin into your body.

See Chapter 2 for more information on how asbestos enters and leaves your body.

1.5 HOW CAN ASBESTOS AFFECT MY HEALTH?

Information on the health effects of asbestos in people comes mostly from studies of people who were exposed in the past to high levels of asbestos in the workplace. Workers who

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/25

breathe in asbestos may develop a slow buildup of scar-like tissue in the lungs and in the membrane that surrounds the lungs. This scar-like tissue does not expand and contract like normal lung tissue and so breathing becomes difficult. Blood flow to the lung may also be decreased and this causes the heart to enlarge. This disease is called asbestosis. People with asbestosis have shortness of breath, often accompanied by a cough. This is a serious disease and can eventually lead to disability or death in people exposed to high amounts of asbestos. However, asbestosis is not usually of concern to people exposed to low levels of asbestos. Changes in the membrane surrounding the lung, called pleural plaques, are quite common in people occupationally exposed to asbestos and are sometimes found in people living in areas with high environmental levels of asbestos, but effects on breathing are usually not serious.

Asbestos workers have increased chances of getting two types of cancer: cancer of the lung tissue itself and mesothelioma, a cancer of the thin membrane that surrounds the lung and other internal organs. Lung cancer is usually fatal, while mesothelioma is invariably fatal within a few months of diagnosis. These diseases do not develop immediately, but appear only after a number of years. There is also some evidence from studies of workers that breathing asbestos can increase the chances of getting cancer in other locations (for example, stomach, intestines, esophagus, pancreas, kidneys), but this is less certain. Members of the public who are exposed to lower levels of asbestos may also have increased chances of getting cancer, but the risks are usually small and are difficult to measure directly.

The levels of asbestos in air that lead to lung disease depend on a large number of factors. The most important of these are (1) how long you were exposed, (2) how long it has been since your exposure started, and (3) whether you smoked cigarettes. Interactions between cigarette smoke and asbestos increase your chances of getting lung cancer. Also, there is a scientific debate concerning the differences in the extent of disease caused by different fiber types and sizes. Some of these differences may be due to the physical and chemical properties of the different fiber types. For example, several studies suggest that the amphiboles (tremolite, amosite, and especially crocidolite) may be more harmful than chrysotile. However, most data indicate that fiber size (length and diameter) is the most

Digitized by Google

important factor for cancer-causing potential, particularly for mesothelioma. Most studies indicate that long fibers (greater than about 1/5,000th of an inch) are more likely to cause injury than short fibers (less than about 1/10,000th of an inch). Generally, smaller fiber diameters or widths are associated with mesothelioma, while larger widths are associated with lung cancer.

The health effects from swallowing asbestos are unclear. Some groups of people who have been exposed to asbestos fibers in their drinking water have higher-than-average death rates from cancer of the esophagus, stomach, and intestines. However, it is very difficult to tell whether this is caused by asbestos or by something else. Animals that were given very high doses of asbestos in food did not get more fatal cancers than usual, although some extra nonfatal tumors did occur in the intestines of rats in one study.

Several government offices and regulatory agencies have considered all the evidence regarding the carcinogenicity of asbestos. The Department of Health and Human Services (DHHS) has determined that asbestos is a known carcinogen. The EPA has determined that asbestos is a human carcinogen. Despite the ongoing debate concerning health effects resulting from the different asbestos fiber types, ATSDR considers all the different mineral forms of asbestos to be known human cancer-causing substances with a prolonged latency period of between 10 and 40 years between exposure and the onset of disease. The International Agency for Research on Cancer (IARC) has determined that asbestos is carcinogenic to humans.

See Chapter 2 for more information on how asbestos can affect your health.

1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO ASBESTOS?

The most common test used to determine if you have been exposed to asbestos is a chest x-ray. The x-ray cannot detect the asbestos fibers themselves, but can detect early signs of lung disease caused by asbestos. While other substances besides asbestos can sometimes

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/27

produce similar changes in the lungs, this test is usually reliable for detecting asbestos-related effects. Other tests, such as gallium-67 lung scanning and high-resolution computed tomography (CAT scan), are also useful in detecting changes in the lungs.

It is possible to test for the presence of asbestos fibers in urine, feces, or mucus. Tests can also be made for the presence of asbestos in material rinsed out of the lung. However, this test can cause some discomfort. Low levels of asbestos fibers are found in these materials for nearly all people. Higher-than-average levels can show that you have been exposed to asbestos, but it is not yet possible to use the results of this test to estimate how much asbestos you have been exposed to, or to predict whether you are likely to suffer any health effects.

See Chapters 2 and 6 for more information about how asbestos can be measured in people and in the environment.

1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government has taken a number of steps to protect citizens from exposure to asbestos. First, on July 12, 1989, the EPA established a ban on new uses of asbestos. Uses established before this date are still allowable. Second, EPA has established regulations that require school systems to inspect for asbestos and, if damaged asbestos is found, to eliminate or reduce the exposure, either by removing the asbestos or by covering it up so it cannot get into the air. In addition, EPA provides guidance and support for reducing asbestos exposure in other public buildings. Third, EPA regulates the release of asbestos from factories and during building demolition or renovation to prevent asbestos from getting into the environment. The EPA also regulates the disposal of waste asbestos materials or products, requiring these to be placed only in approved locations. Fourth, EPA has proposed a limit of 7 MFL on the concentration of long fibers that may be present in drinking water. Fifth, the Food and Drug Administration (FDA) regulates the use of asbestos in the preparation of drugs and restricts the use of asbestos in food-packaging materials. The National Institute for Occupational Safety and Health (NIOSH) has recommended that inhalation exposures not

Digitized by Google

exceed 100,000 f/m^3. However, the Occupational Safety and Health Administration (OSHA) has established an enforceable limit of 100,000 f/m^3 on the average 8-hour daily concentration of asbestos allowed in air in the workplace.

See Chapter 7 for more information about regulations and guidelines to protect people from exposure to asbestos.

1.8 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department or:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, Mailstop E-29
Atlanta, Georgia 30333
(404) 639-6000

This agency can also provide you with information on the location of occupational and environmental health clinics. These clinics specialize in the recognition, evaluation, and treatment of illness resulting from exposure to hazardous substances.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/29

2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of asbestos. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

It is important to recognize that asbestos is not a single substance, but is the generic name for a family of six related polysilicate fibrous minerals of which one (chrysotile) belongs to the serpentine family and five (actinolite, amosite, anthophyllite, crocidolite, tremolite) belong to the amphibole family. These minerals differ from each other in physical and chemical properties, and each mineral can exist in a wide range of fiber sizes. These differences between fiber type and, more importantly, fiber size (length and diameter) are believed to be important determinants of the health risks posed by asbestos.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure — inhalation, oral, and dermal; and then by health effect — death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods — acute (14 days or less), intermediate (15 - 364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/30

those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of asbestos are indicated in Tables 2-1, 2-2, and 2-3 and Figures 2-1, 2-2, and 2-3. Because cancer effects could occur at lower exposure levels, the figures also show a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

A User's Guide has been provided at the end of this profile (see Appendix A). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

2.2.1 Inhalation Exposure

Units of Exposure. Consideration and comparison of quantitative data on asbestos inhalation studies are complicated by the fact that a number of different methods have been used to measure asbestos

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/31

levels in air. Currently, the standard method for measuring asbestos concentrations in workplace air employs phase contrast microscopy (PCM). A particle visible under PCM is counted as a fiber if it is ≥5 micrometers (μm) long and has a length/thickness ratio of ≥3:1. However, the method cannot detect fibers thinner than about 0.3 μm and cannot distinguish between asbestos fibers and other fibers (NIOSH 1987). Nevertheless, because currently available risk factors for asbestos are expressed in terms of PCM fibers, all air concentration data in this section are expressed in terms of PCM fibers/mL (f/mL) unless otherwise noted. It should be noted, however, that analytical methods have improved substantially since early asbestos studies were performed, with an increase in numbers of fibers detected (Rickards 1994).

When data on airborne levels are available only in terms of mass/volume (e.g., mg/m^3), it is difficult to convert these to units of PCM fibers/mL, because the ratio between mass and fiber number depends on fiber type and size distribution and because of the measuring technique employed. For the purposes of making rough calculations when a more accurate conversion factor is not available, it is assumed that a concentration of 1 mg/m^3 in air is equal to 33 PCM f/mL (EPA 1986a).

Older occupational studies measured dust exposure in units of million particles per cubic foot (mppcf). This method did not distinguish fibrous from nonfibrous particles and used relatively low magnification, so only the largest fibers were detectable. When a more accurate value is not available, it is assumed that a concentration of 1 mppcf is equal to 3 PCM f/mL (BOHS 1968).

Overview of Health Effects. Studies in humans and animals indicate that inhalation of asbestos fibers may lead to fibrotic lung disease (asbestosis), pleural plaques and thickening, and cancer of the lung, the pleura, and the peritoneum; it may also increase the risk of some extrathoracic cancers. Significant effects on other tissues have not been detected. A number of researchers have found that the occurrence of asbestosis and lung cancer correlates with cumulative exposure (that is, the product of concentration [PCM fibers/mL] multiplied by years of exposure). Therefore, human exposures are expressed below as PCM f-yr/mL. Animal data are provided in terms of exposure level (PCM f/mL) and duration, and the cumulative exposure can be found simply by calculating the product. However, due to differences in clearance rates and lifespan as well as other differences, cumulative doses in animals are not expected to be directly comparable to cumulative doses in humans. Studies which provide reliable dose-response information on the inhalation effects of asbestos in humans are

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/32

summarized in Table 2-1 and Figure 2-1, and data in animals are summarized in Table 2-2 and Figure 2-2. The findings are discussed below.

2.2.1.1 Death

No studies were located in which acute- or intermediate-duration inhalation exposure to asbestos led to lethality in humans or animals. Inhalation exposure to asbestos can lead to death or a shortened lifespan from asbestosis or cancer, as discussed in Sections 2.2.1.2 and 2.2.1.8, respectively.

2.2.1.2 Systemic Effects

No studies were located regarding hematological, musculoskeletal, hepatic, renal, endocrine, dermal, ocular, body weight, metabolic, or other systemic effects in humans or animals after inhalation exposure to asbestos. The systemic effects observed after inhalation exposure are discussed below. The highest NOAEL values and all LOAEL values from each reliable study for systemic effects are summarized in Tables 2-1 and 2-2, and plotted in Figures 2-1 and 2-2.

Respiratory Effects. Numerous studies in humans have established that inhalation exposure to asbestos fibers can lead to a characteristic pneumoconiosis termed asbestosis. The main clinical symptom of this disease is shortness of breath, often accompanied by rales or cough (Churg 1986; Enarson et al. 1988; Finkelstein 1986). In severe cases, impairment of respiratory function may ultimately result in death, and asbestosis has led to excess mortality in a number of groups of asbestos workers (Armstrong et al. 1988; deKlerk et al. 1991; McDonald et al. 1983; Peto et al. 1985; Selikoff et al. 1979).

Available evidence indicates that all asbestos fiber types are fibrogenic (Bignon and Jaurand 1983; Davis 1972; EPA 1986a). Most studies in humans have involved exposure to chrysotile (Cullen and Baloyi 1991; Dement et al. 1983; McDonald et al. 1983, 1984; Nicholson et al. 1979), but asbestosis has also been noted in populations exposed mainly to amosite (Seidman et al. 1979), crocidolite (Armstrong et al. 1988; deKlerk et al. 1991; Luo et al. 1992; Sluis-Cremer 1991; Wignall and Fox 1982), and anthophyllite (Meurman et al. 1974; Sluis-Cremer 1991). A number of studies have indicated that long fibers (e.g., 5 μm or more) have a higher fibrogenic activity, while short fibers

Digitized by Google

TABLE 2-1. Levels of Significant Exposure to Asbestos - Inhalation - Human Studies

Key to[a] figure	Species/ strain	Exposure/ duration/ frequency	System	NOAEL (f-yr/mL)	LOAEL Less serious (f-yr/mL)	LOAEL Serious (f-yr/mL)	Reference/ chemical form[b]
INTERMEDIATE EXPOSURE							
Systemic							
1	Human	6 mo aver. (occup)	Resp			25.1 M (increased incidence of parenchymal and pleural radiological abnormalities)	Ehrlich et al. 1992 AM
CHRONIC EXPOSURE							
Systemic							
2	Human	<1 mo- >5 yr (occup)	Resp			6 M (asbestosis and other respiratory diseases)	Armstrong et al. 1988 CR
3	Human	>10 yr (occup)	Resp	20 M	43 M (crepitations)	72 M (asbestosis)	Berry et al. 1979 CH CR
4	Human	10+ yr (occup)	Resp			25 M (asbestosis)	BOHS 1983 CH
5	Human	1.1-2.7 yr (occup)	Resp			71 M (asbestosis)	de Klerk et al. 1991 CR
6	Human	10-30 yr (occup)	Resp			68 M (asbestosis, fibrosis)	Dement et al. 1983 CH
7	Human	15 yr (occup)	Resp			75 M (cough, apnea)	Enarson et al. 1988 CH
8	Human	>9 yr (occup)	Resp			100 M (asbestosis)	Finkelstein 1983 CH CR

Digitized by Google
Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/34

TABLE 2-1. Levels of Significant Exposure to Asbestos - Inhalation - Human Studies (continued)

Key to[a] figure	Species/ strain	Exposure/ duration/ frequency	System	NOAEL (f-yr/mL)	LOAEL Less serious (f-yr/mL)	LOAEL Serious (f-yr/mL)	Reference/ chemical form[b]
9	Human	0.1-39 yr (occup)	Resp			17 (fibrosis)	Green et al. 1986 CH CR
10	Human	3-51 yr (occup)	Resp			300 M (asbestosis)	Henderson and Enterline 1979 CH CR AM
11	Human	3.8 yr aver. (occup)	Resp			105 M (asbestosis)	Hughes et al. 1987 CH CR AM
12	Human	1-20 yr (occup)	Resp			50 M (parenchymal abnormalities)	Irwig et al. 1979 CR AM
13	Human	5-31 yr (occup)	Resp		9 (chronic laryngitis)		Kambic et al. 1989 AM CH CR
14	Human	1-20 yr (occup)	Resp			90 M (asbestosis)	McDonald et al. 1980 CH
15	Human	1-20 yr (occup)	Resp			90 M (asbestosis)	McDonald et al. 1983 CH
16	Human	20+ yr (occup)	Resp			300 M (asbestosis)	Nicholson et al. 1979 CH
17	Human	>5 yr (occup)	Resp			115 M (asbestosis)	Peto et al. 1985 CH CR

Toxicological Profile for Asbestos (1995)
ACL Doc 10942 · Page 35 of 233
Digitized by Google
Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/35

TABLE 2-1. Levels of Significant Exposure to Asbestos - Inhalation - Human Studies (continued)

Key to[a] figure	Species/ strain	Exposure/ duration/ frequency	System	NOAEL (f-yr/mL)	LOAEL Less serious (f-yr/mL)	LOAEL Serious (f-yr/mL)	Reference/ chemical form[b]
18	Human	<15 - >45 yr	Resp	1.5 M		3.5 M (slight asbestosis)	Sluis-Cremer 1991 AN CR
19	Human	15 yr aver. (occup)	Resp			20 M (pulmonary fibrosis)	Wollmer et al. 1987 CH
	Cancer						
20	Human	>20 yr (occup)				2.3 M (CEL: mesothelioma)	Albin et al. 1990a CH
21	Human	16.5 yr (occup)				33 M (CEL: mesothelioma)	Albin et al. 1990b CH CR AM TR
22	Human	1-20 yr (occup)				400 M (CEL: lung cancer, mesothelioma)	Amandus and Wheeler 1987 TR AC
23	Human	>1 mo-<5yr (occup)				6 (CEL: cancer of the trachea, bronchus and lung, mesothelioma, stomach cancer)	Armstrong et al. 1988 CR
24	Human	1.2-1.9 yr (occup)				64.6 M (CEL: cancer of the trachea, bronchus and lung; mesothelioma)	de Klerk et al. 1989 CR
25	Human	450-726 d (occup)				49 M (CEL: lung cancer)	de Klerk et al. 1991 CR

Digitized by Google
Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/36

TABLE 2-1. Levels of Significant Exposure to Asbestos - Inhalation - Human Studies (continued)

Key to[a] figure	Species/ strain	Exposure/ duration/ frequency	System	NOAEL (f-yr/mL)	LOAEL Less serious (f-yr/mL)	LOAEL Serious (f-yr/mL)	Reference/ chemical form[b]
26	Human	10-30 yr (occup)				14 M (CEL: lung cancer)	Dement et al. 1983 CH
27	Human	(occup)				180 M (CEL: lung cancer, gastrointestinal cancer, mesothelioma)	Enterline et al. 1987 CH CR AM
28	Human	>9 yr (occup)				44 M (CEL: lung cancer, mesothelioma)	Finkelstein 1983 CH CR
29	Human	3-51 yr (occup)				180 M (CEL: lung cancer, mesothelioma)	Henderson and Enterline 1979 CH CR AM
30	Human	3.8 yr aver. (occup)				40 M (CEL: lung cancer, mesothelioma)	Hughes et al. 1987 CH CR AM
31	Human	1-20 yr (occup)				45 M (CEL: lung cancer)	McDonald et al. 1982 CH AM CR
32	Human	1-20 yr (occup)				90 M (CEL: lung cancer)	McDonald et al. 1983 CH
33	Human	1-20 yr (occup)				180 M (CEL: lung cancer)	McDonald et al. 1984 CH
34	Human	>2 yr (occup)				10 (CEL: lung cancer, gastrointestinal cancer and mesothelioma)	Newhouse and Berry 1979 CR CH AM

Toxicological Profile for Asbestos (1995)
ACL Doc 10942 · Page 37 of 233
Digitized by Google
Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/37

TABLE 2-1. Levels of Significant Exposure to Asbestos - Inhalation - Human Studies (continued)

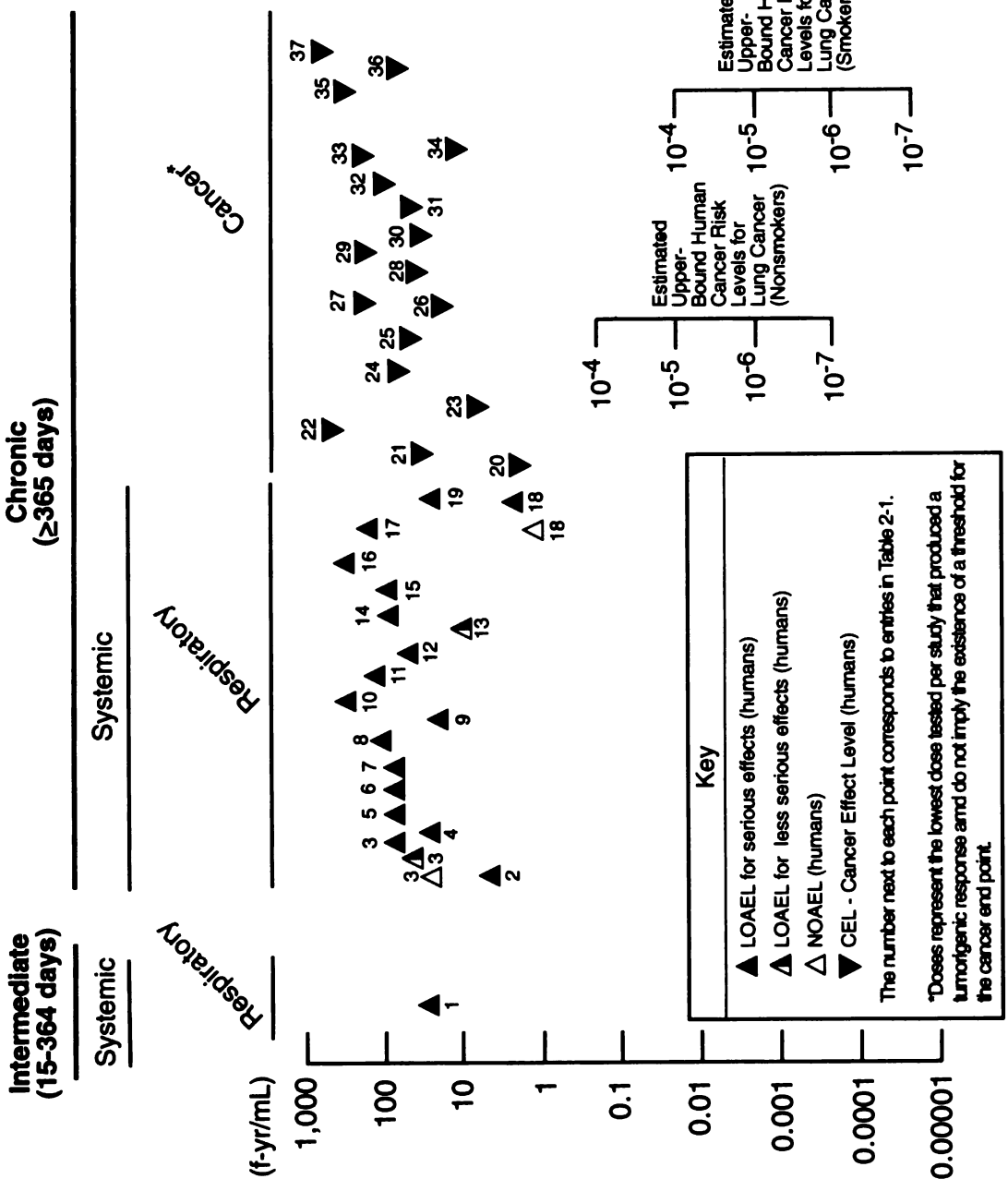
Key to [a] figure	Species/ strain	Exposure/ duration/ frequency	System	NOAEL (f-yr/mL)	LOAEL Less serious (f-yr/mL)	LOAEL Serious (f-yr/mL)	Reference/ chemical form [b]
35	Human	20+ yr (occup)				300 M (CEL: lung cancer, mesothelioma)	Nicholson et al. 1979 CH
36	Human	>5 yr (occup)				72 M (CEL: lung cancer, mesothelioma)	Peto et al. 1985 CH CR
37	Human	<2 - >10 yr (occup)				450 M (CEL: lung cancer, mesothelioma)	Weill et al. 1979 CH CR AM

[a]The number corresponds to entries in Figure 2-1.
[b]The forms of asbestos listed below represent those which predominated in the workplace air; other forms may have been present as well.

AC = actinolite; AM = amosite; aver. = average; CEL = cancer effect level; CH = chrysotile; CR = crocidolite; d = day(s); F = female; f-yr/mL = fiber-years per milliliter; LOAEL = lowest-observed-adverse-effect-level; M = male; mo = month(s); NOAEL = no-observed-adverse-effect-level; (occup) = occupational; Resp = respiratory; TR = tremolite; yr = year(s)

Toxicological Profile for Asbestos (1995)
ACL Doc 10942 · Page 38 of 233
Digitized by Google
Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/38

Figure 2-1. Levels of Significant Exposure to Asbestos – Inhalation (Human Studies)



Digitized by Google

TABLE 2-2. Levels of Significant Exposure to Asbestos - Inhalation - Animal Studies

Key to figure[a]	Species/ strain	Exposure/ duration/ frequency	System	NOAEL (PCM f/mL)	LOAEL Less serious (PCM f/mL)	LOAEL Serious (PCM f/mL)	Reference/ chemical form
ACUTE EXPOSURE							
Systemic							
1	Mouse B10.D2/nSn	5 hr	Resp			132 M (fibrosis)	McGavran et al. 1989 CH
INTERMEDIATE EXPOSURE							
Systemic							
2	Rat PVG	15 wk 5 d/wk 7 hr/d	Resp			330 M (diffuse fibrosis)	Donaldson et al. 1988 CH
CHRONIC EXPOSURE							
Systemic							
3	Rat Wistar	1 yr 1-5 d/wk 7 hr/d	Resp			70 M (fibrosis)	Davis et al. 1980a CH
4	Rat Wistar	1 yr 1-5 d/wk 7 hr/d	Resp			330 M (fibrosis)	Davis et al. 1980a AM
5	Rat NS	12 mo	Resp			330 (fibrosis)	Davis et al. 1980b AM CH
6	Rat Wistar	12 mo 5 d/wk 7 hr/d	Resp			1600 M (fibrosis)	Davis et al. 1985 TR
7	Rat Wistar	12 mo 5 d/wk 7 hr/d	Resp			2060 M (fibrosis)	Davis et al. 1986a AM-L

Toxicological Profile for Asbestos (1995)
ACL Doc 10942 · Page 40 of 233
Digitized by Google
Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/40

TABLE 2-2. Levels of Significant Exposure to Asbestos - Inhalation - Animal Studies (continued)

Key to[a] figure	Species/ strain	Exposure/ duration/ frequency	System	NOAEL (PCM f/mL)	LOAEL Less serious (PCM f/mL)	LOAEL Serious (PCM f/mL)		Reference/ chemical form
8	Rat CD	2 yr 4 d/wk 4 hr/d	Resp			54	(fibrosis)	Reeves et al. 1974 CH
9	Rat CD	2 yr 4 d/wk 4 hr/d	Resp			1105	(fibrosis)	Reeves et al. 1974 CR
10	Rat NS	2 yr 4 d/wk 4 hr/d	Resp			860	(fibrosis)	Reeves et al. 1974 AM
11	Rat Wistar	24 mo 5 d/wk 7 hr/d	Resp			350	(fibrosis)	Wagner et al. 1974 AM AN CR CH
12	Rat Wistar	12 mo 5 d/wk 7.5 hr/d	Resp			430	(fibrosis)	Wagner et al. 1980a CH
	Cancer							
13	Monkey Baboon	4 yr 5 d/wk 6 hr/d				1110 M	(CEL: mesothelioma)	Goldstein and Coetzee 1990 AM
14	Monkey Baboon	4 yr 5 d/wk 6 hr/d				1130	(CEL: mesothelioma)	Goldstein and Coetzee 1990 CH CR
15	Rat Wistar	1 yr 5 d/wk 7 hr/d				1170	(CEL: lung adenoma, adenocarcinoma, and mesothelioma)	Davis and Jones 1988 CH-S
16	Rat Wistar	1 yr 1-5 d/wk 7 hr/d				330 M	(CEL: lung carcinomas, adenocarcinomas)	Davis et al. 1980a AM

Digitized by Google
Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/41

TABLE 2-2. Levels of Significant Exposure to Asbestos - Inhalation - Animal Studies (continued)

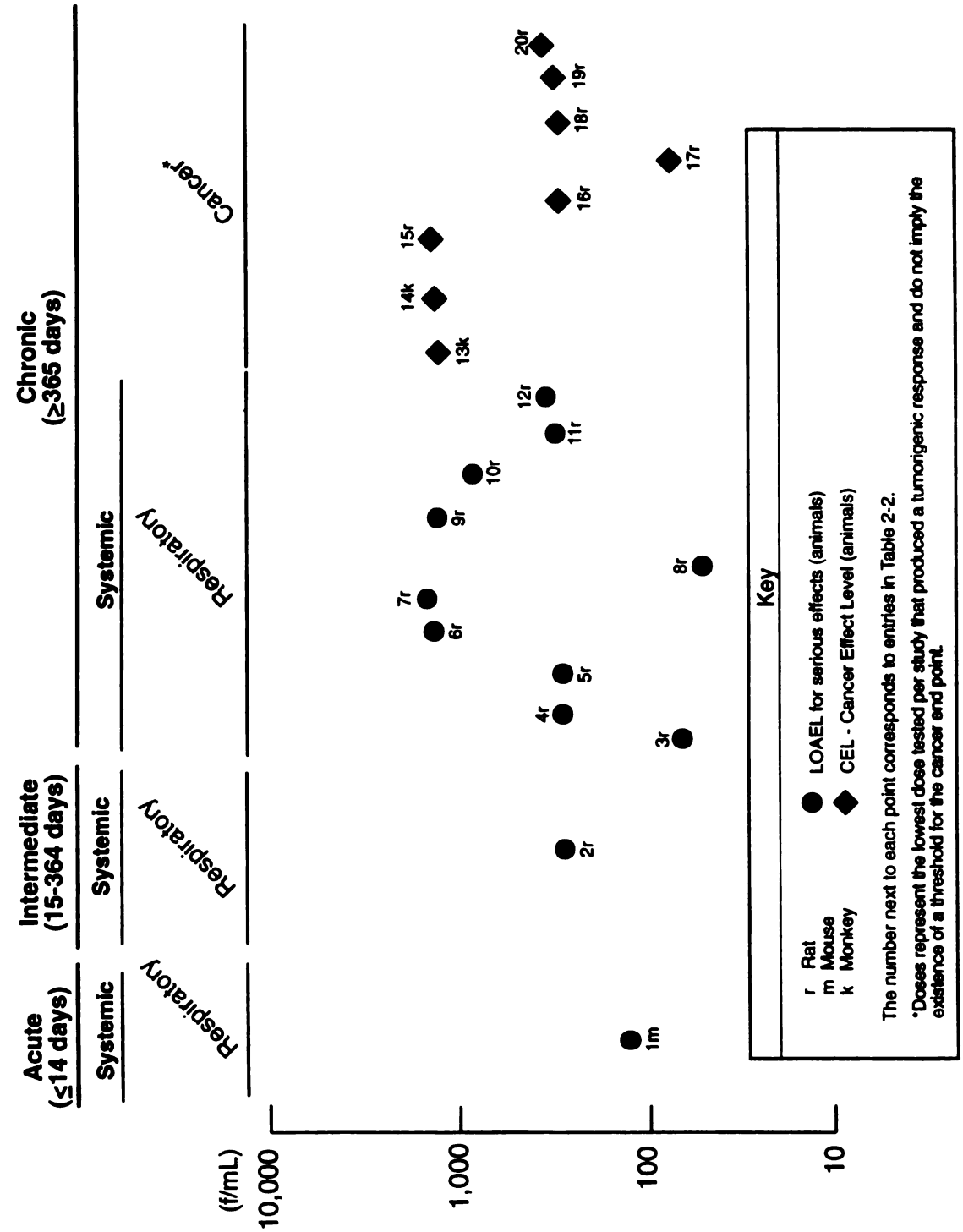
Key to[a] figure	Species/ strain	Exposure/ duration/ frequency	System	NOAEL (PCM f/mL)	LOAEL Less serious (PCM f/mL)	LOAEL Serious (PCM f/mL)	Reference/ chemical form
17	Rat Wistar	1 yr 1-5 d/wk 7 hr/d				70 M (CEL: lung adenomas, adenocarcinomas, and squamous carcinomas)	Davis et al. 1980a CH
18	Rat NS	12 mo				330 (CEL: lung adenomas and carcinomas)	Davis et al. 1980b AM CH
19	Rat Wistar	24 mo 5 d/wk 7 hr/d				350 (CEL: lung adenoma, adenocarcinoma, squamous carcinoma, and mesothelioma)	Wagner et al. 1974 AM AN CR CH
20	Rat Wistar	12 mo 5 d/wk 7.5 hr/d				430 (CEL: lung adenoma, adenocarcinoma, squamous carcinoma, and mesothelioma)	Wagner et al. 1980 CH

[a]The number corresponds to entries in Figure 2-2.

AM = amosite; AN = anthophyllite; CEL = cancer effect level; CH = chrysotile; CR = crocidolite; d = day(s); F = female; PCM f/mL = phase contrast microscopy fibers per milliliter; hr = hour(s); L = long; LOAEL = lowest-observed-adverse-effect-level; M = male; mo = month(s); NOAEL = no-observed-adverse-effect-level; NS = not specified; Resp = respiratory; S = short; TR = tremolite; wk = weeks(s); yr = year(s)

Toxicological Profile for Asbestos (1995)
ACL Doc 10942 · Page 42 of 233
Digitized by Google
Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/42

Figure 2-2. Levels of Significant Exposure to Asbestos – Inhalation (Animal Studies)



Digitized by Google

have a lower fibrogenic activity (Adamson and Bowden 1987a, 1987b; Davis et al. 1986a; Davis and Jones 1988; Platek et al. 1985). This may be related to the inability of macrophages to engulf and remove fibers that are significantly larger than themselves (Bignon and Jaurand 1983).

As shown in Table 2-1 and Figure 2-1, cumulative exposures of 17–75 f-yr/mL have been found to result in signs of fibrotic lung lesions in humans (Berry et al. 1979; deKlerk et al. 1991; Enarson et al. 1988; Ehrlich et al. 1992; Green et al. 1986; Irwig et al. 1979; BOHS 1983; Wollmer et al. 1987). Although most of these studies involved chronic exposure to asbestos, a single study reported an increased incidence of radiological abnormalities indicative of pulmonary fibrosis in amosite workers exposed for a median duration of 6 months (Ehrlich et al. 1992). Death from asbestosis or the presence of asbestosis at death has been reported in humans with cumulative exposures of 3.5–300 f-yr/mL (Armstrong et al. 1988; Dement et al. 1983; Finkelstein 1983; Henderson and Enterline 1979; Hughes et al. 1987; McDonald et al. 1980, 1983; Nicholson et al. 1979; Peto et al. 1985; Sluis-Cremer 1991). Asbestosis might occur at even lower cumulative exposures (Dement et al. 1983), but there were too few cases to establish this with certainty.

An important aspect of the pathobiology of asbestosis is that because asbestos fibers (particularly amphiboles) are very resistant to breakdown in the lung, the inflammatory response triggered by the fibers is ongoing, even after exposure has ceased (Finkelstein 1986; Wagner et al. 1974). Consequently, because fibers are retained in the lung, the severity of pathological lesions and clinical symptoms tends to progress with time. For this reason, EPA (1986a) has suggested that a cumulative exposures of 10 f-yr/mL might be an appropriate estimate of the threshold for minimal functional impairment in exposed workers. This corresponds to a concentration of 0.02 f/mL for an individual exposed continuously for 50 years. However, more recent studies suggest that effects may occur at cumulative exposures <10 f-yr/mL (Armstrong et al. 1988; Sluis-Cremer 1991).

Inhalation of asbestos fibers can lead not only to injury to the lung parenchyma, but also to a number of changes in the pleura (Boutin et al. 1989; Churg 1986; Ehrlich et al. 1992; Jones et al. 1988b). The most common lesions are pleural plaques. These are generally oval areas of acellular collagen deposits, usually located on the inferior and posterior surfaces of the pleura. Diffuse thickening and fibrosis of the pleura may also occur, as may pleural effusions. The incidence of pleural abnormalities (usually detected by x-ray examination) is often quite high (20% to 60%) in people employed in asbestos-related occupations for subchronic (Ehrlich et al. 1992) and chronic-durations (Anton-Culver

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/44

et al. 1989; Baker et al. 1985; Bresnitz et al. 1993; Gibbs 1979; Hsaio et al. 1993; Jarvholm et al. 1986; Ohlson et al. 1985; Ren et al. 1991; Viallat and Boutin 1980). Pleural abnormalities are also common in household contacts and family members of asbestos workers (where exposure is presumably due to asbestos carried home on the workclothes) (Anderson et al. 1976, 1979), and in people who live in regions with high asbestos levels in the soil (Boutin et al. 1989; Churg and DePaoli 1988; Jarvholm et al. 1986; Luo et al. 1992; Rey et al. 1993). An elevated incidence of pleural abnormalities (3.7%) was noted in long-time (70 years) residents of an area with elevated levels of asbestos in soil (Boutin et al. 1989). Cumulative exposure to asbestos in these residents was estimated to be 0.12 f-yr/mL. The incidence of pleural abnormalities (specifically, pleural thickening) in members of the general population of the United States was found to be 2.3% in males, and 0.2% in females, most of which is probably due to occupational exposure to asbestos (Rogan et al. 1987). The health significance of asbestos-induced pleural abnormalities is not precisely defined, but most researchers consider pleural plaques to be essentially benign (Becklake 1976; Jones et al. 1988b; Ohlson et al. 1984, 1985). However, diffuse pleural thickening can lead to decreased ventilatory capacity, probably because of the restrictive effect of pleural fibrosis (Baker et al. 1985; Britton 1982; Churg 1986; Jarvholm and Larsson 1988; Jones et al. 1988b; McGavin and Sheers 1984; Miller et al. 1992; Rom and Travis 1992; Schwartz et al. 1990). Human data suggest that in some cases, the pulmonary impairment from pleural thickening can be very severe, even causing death (Miller et al. 1983).

Asbestos exposure may also produce adverse effects in the upper airways. A higher incidence of laryngitis was noted in workers chronically exposed to asbestos (Kambic et al. 1989; Parnes 1990). A dose-dependent increase was noted for the incidence of chronic laryngitis in workers exposed to <9 f-yr/mL (7.5%), 18 f-yr/mL (14%), and 27 f-yr/mL (33.6%) (Kambic et al. 1989). Although this effect has not been reported by a large number of studies, it is consistent with the idea of asbestos acting as an irritant on the laryngeal mucosa.

Fibrosis has been produced in animals by inhalation or by intratracheal exposure to chrysotile (Chang et al. 1988; Davis et al. 1980a, 1980b; Donaldson et al. 1988a; Green et al. 1986; McGavran et al. 1989; Wagner et al. 1980a), amosite (Davis et al. 1986a; Reeves et al. 1971, 1974; Webster et al. 1993), anthophyllite (Wagner et al. 1974), crocidolite (Reeves et al. 1971, 1974; Wagner et al. 1974), and tremolite (Davis et al. 1985; Green et al. 1986). As shown in Table 2-2 and Figure 2-2 fibrosis has been noted in rodents after exposure to 132 f/mL for 5 hours (McGavran et al. 1989), exposure to

Digitized by Google

330 f/mL for 7 hours/day, 5 days/week for 15 weeks (Donaldson et al. 1988a), and chronic exposure to 54–2,060 f/mL (Davis et al. 1980a, 1980b, 1985, 1986a; Reeves et al. 1974; Wagner et al. 1974, 1980a). Studies in animals indicate that asbestosis stems from the inflammatory response triggered in the lung by the deposition of asbestos fibers (Davis 1970). Fibers deposited in the ciliated portion of the airway are removed by mucociliary transport (see Section 2.3.4) and do not appear to injure the lung. However, fibers deposited in the terminal bronchioles and alveoli are not cleared as rapidly, and these can stimulate an influx of macrophages (Chang et al. 1988) which then release a variety of inflammatory mediators (chemoattractants, lysosomal enzymes, activated oxygen species, growth factors, etc.) (Davis 1972; Hansen and Mossman 1987; Kagan 1988; Miller et al. 1978; Schwartz et al. 1993). This is thought to be responsible for the gradual loss of some epithelial cells and the deposition of collagen by fibroblasts (Davis et al. 1986c; Davis and Jones 1988). In animals, histological signs of tissue injury can be detected at the site of deposited fibers within a few days, although in humans, measurable abnormalities of lung function do not usually appear for a number of years (Dement et al. 1983; Hughes et al. 1987; Kagan 1988; Schwartz et al. 1993).

Cardiovascular Effects. No studies were located regarding a direct effect upon the cardiovascular system in humans after inhalation exposure to asbestos. However, increased ($p<0.01$) mortality from cardiovascular disease in workers exposed to asbestos has been reported (Doll 1955). Fibrosis of the lung can lead to increased resistance to blood flow through the pulmonary capillary bed, leading in turn to pulmonary hypertension and compensatory hypertrophy of the right heart (Selikoff and Lee 1978). This condition is known as cor pulmonale. Cor pulmonale may be detected by standard clinical and radiological tests of cardiac function and by changes in the electrocardiogram (Kokkola and Huuskonen 1979), although this is not a very sensitive test (Selikoff and Lee 1978). Cor pulmonale is usually associated with severe cases of asbestosis (Lemen et al. 1980), although pulmonary hypertension has been reported in some cases prior to measurable decreases in respiratory function (Tomasini and Chiappino 1981). Limited data from case reports suggest that constrictive pericarditis due to fibrous thickening may result from asbestos exposure (Davies et al. 1991).

No studies were located regarding cardiovascular effects in animals after inhalation exposure to asbestos.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/46

Gastrointestinal Effects. The majority of asbestos fibers which are deposited in the lung during inhalation exposure are transported by mucociliary action to the pharynx, where they are swallowed (see Section 2.3). Consequently, the gastrointestinal epithelium is also directly exposed to fibers. While there is some evidence that inhalation exposure to asbestos may increase the risk of gastrointestinal cancer in humans (see Section 2.2.1.8), no information was located to indicate that any nonneoplastic effects occur in the gastrointestinal system after inhalation exposure.

No studies were located regarding gastrointestinal effects in animals after inhalation exposure to asbestos.

2.2.1.3 Immunological and Lymphoreticular Effects

A number of studies have investigated the status of the immune system in humans who have been exposed to asbestos. Although there is some variability, most studies indicate that cell-mediated immunity (measured by tests of dermal sensitization *in vivo* and lymphocyte responsiveness and function *in vitro*) is depressed in workers who have radiological evidence of asbestosis (DeShazo et al. 1988; Gaumer et al. 1981; Kagan et al. 1977; Lange et al. 1986). Alterations in lymphocyte (Sprince et al. 1991, 1992) and leukocyte (Hurbankova and Kaiglova 1993) distribution have been noted in asbestos-exposed workers. Increased numbers of lymphocytes and $CD4^+$ were reported in men with occupational exposure to asbestos (Rom and Travis 1992), although numbers of total circulating lymphocytes were similar in asbestos workers compared to controls in another study (Al Jarad et al. 1992). Mediastinal lymph node enlargement has been reported in asbestosis patients (Sampson and Hansell 1992). Increased levels of IgA and IgG have been reported in asbestos-exposed individuals (Hurbankova and Kaiglova 1993; Nigam et al. 1993), and concentrations of autoantibodies (rheumatoid factor, antinuclear antibodies) tend to be abnormally high in asbestos-exposed workers (Anton-Culver et al. 1988; Pernis et al. 1965; Warwick et al. 1973; Zerva et al. 1989). In some cases, increased autoantibodies can lead to rheumatoid arthritis (Caplan's Syndrome), although this is more common in coal miners and workers with other pneumoconioses than in workers with asbestosis (Constantinidis 1977; Greaves 1979). Immunological abnormalities are usually mild or absent in asbestos-exposed workers who have not developed clinical signs of asbestosis (DeShazo et al. 1988; Kagan 1988; Selikoff and Lee 1978; Warwick et al. 1973). Although the biological significance of these immunological changes is difficult to judge, they are of special concern because depressed immune

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/47

function might be a factor in the etiology of asbestos-induced cancer (Lew et al. 1986). Exposures to asbestos associated with immunological effects generally have not been quantified.

No studies were located regarding immunological or lymphoreticular effects in animals after inhalation exposure to asbestos.

No studies were located regarding the following effects in humans or animals after inhalation exposure to asbestos:

2.2.1.4 Neurological Effects

2.2.1.5 Reproductive Effects

2.2.1.6 Developmental Effects

2.2.1.7 Genotoxic Effects

Studies of exposed asbestos workers and mesothelioma patients suggest that asbestos is genotoxic. The number of chromosomal aberrations and the rate of sister chromatid exchange were significantly elevated in the peripheral blood lymphocytes of asbestos workers compared to a control population (Fatma et al. 1991). The mean sister chromatid exchange rate was significantly increased ($p=0.002$) in nonsmoking asbestos insulators compared to a control population (Rom et al. 1983). The increase in sister chromatid exchange rate was not statistically significant in smoking asbestos insulators, and for the whole group (smokers and nonsmokers) the increase approaches statistical significance ($p=0.056$). An increased incidence of DNA double-strand breaks was noted in the leukocytes of asbestos workers compared to controls (Marczynski et al. 1994). Several studies have reported either chromosomal aberrations in the pleural effusion of mesothelioma patients (Hansteen et al. 1993) or significant correlations between specific chromosomal abnormalities and lung burden of asbestos in mesothelioma patients (Pelin-Enlund et al. 1990; Tammilehto et al. 1992; Tiainen et al. 1989). However, it is uncertain as to whether these chromosomal abnormalities were responsible for the development of mesothelioma, or whether the abnormalities are a result of the disease. Increases ($p<0.01$) in the excretion of the DNA adduct 8-hydroxydeoxyguanosine, a marker of DNA damage, have been observed in the urine of Polish asbestos workers (Tagesson et al. 1993). Other genotoxicity studies are discussed in Section 2.4.

Digitized by Google

2.2.1.8 Cancer

A voluminous body of evidence establishes that inhalation exposure to asbestos increases the risk of lung cancer and mesothelioma in humans and animals. Some evidence suggests that inhalation exposure to asbestos increases risk of cancer at other sites as well (especially the gastrointestinal tract). Each of these carcinogenic effects are discussed separately below. All CEL values from each reliable study for cancer are summarized in Tables 2-1 and 2-2, and plotted in Figures 2-1 and 2-2.

Lung Cancer. Evidence for the role of asbestos in human lung cancer is derived primarily from studies of the cause of death of occupationally-exposed workers. For example, the causes of death in a very large cohort of insulation workers (17,800 men) in the United States and Canada have been studied (Selikoff et al. 1979. Between 1967 and 1976, there were 2,271 deaths in this group, of which 486 were attributable to lung cancer. This is 4.6 times the number of lung cancer deaths that would have been expected in this group based on the lung cancer rates in the average male population of the United States. Similar findings have been reported in a very large number of analogous studies under a wide variety of occupational circumstances. In a review, a statistically significant ($p<0.05$) increase in lung cancer death rates had been reported in 32 of 41 recent studies (EPA 1986a). Lung cancer has been reported in household contacts and family members of asbestos workers, where exposure is presumably due to asbestos carried home on the workclothes (Magnani et al. 1993).

There is little doubt that all types of asbestos can cause lung cancer. For example, statistically significant increases in lung cancer mortality have been reported in workers exposed primarily to chrysotile (Dement et al. 1983; Huilan and Zhiming 1993; McDonald et al. 1980, 1983, 1984; Nicholson et al. 1979), amosite (Seidman et al. 1979), crocidolite (Armstrong et al. 1988; deKlerk et al. 1989, 1991; Wignall and Fox 1982), anthophyllite (Meurman et al. 1974, 1994), and tremolite (Amandus and Wheeler 1987; Kleinfeld et al. 1974; McDonald et al. 1986) or to multiple fiber types (Enterline et al. 1987; Henderson and Enterline 1979; Hughes et al. 1987; McDonald et al. 1982; Newhouse and Berry 1979; Peto et al. 1985; Weill et al. 1979).

As with most carcinogenic agents, there is a substantial latency period (10–40 years in humans) between the onset of exposure to asbestos and the occurrence of lung cancer (Dement et al. 1983; Huilan and Zhiming 1993; McDonald et al. 1983; Nicholson et al. 1979; Selikoff et al. 1979; Sluis-Cremer 1991). After sufficient time (e.g., 20 years), the risk of lung cancer in exposed workers is

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/49

generally observed to increase in proportion to the cumulative exposure (f-yr/mL). Most researchers have found that the chances that asbestos exposure will lead to lung cancer depends not only on the cumulative dose of asbestos, but also on the underlying risk of lung cancer due to other factors (Enterline et al. 1987; EPA 1986a; McDonald et al. 1982, 1983; Peto et al. 1985). For example, asbestos exposure results in a larger increase in lung cancer risk in smokers than nonsmokers, possibly because smokers have a higher underlying risk of lung cancer than nonsmokers. Alternatively, the larger increase in lung cancer risk in smokers may be due to a synergism between tobacco smoke and asbestos fibers. (See Section 2.7 for additional discussion of the interaction between smoking and asbestos). Figure 2-1 displays the levels of asbestos exposure that are estimated by EPA (1986a) to be associated with excess lifetime lung cancer risks of 10^{-4} to 10^{-7} for smokers and nonsmokers. For smokers, cumulative exposures of 0.035, 0.0035, 0.00035, and 0.000035 f-yr/mL represent excess lung cancer risks of 10^{-4}, 10^{-5}, 10^{-6}, and 10^{-7}, respectively. For nonsmokers, cumulative exposures of 0.35, 0.035, 0.0035, and 0.00035 f-yr/mL represent excess lung cancer risks of 10^{-4}, 10^{-5}, 10^{-6}, and 10^{-7}, respectively. Appendix D provides further details on the derivation of these risk estimates. While these values are considered to be the best available for assessing risk from environmental exposures to airborne asbestos, the range of uncertainty is probably a factor of 2.5–10 (EPA 1986a).

Although a number of studies seem to suggest that not all asbestos fibers types are equally likely to lead to lung cancer, the evidence is equivocal. Some of this variation in potency between fibers may be due to differences between mineral types with respect to surface properties such as surface charge density (Bonneau et al. 1986; Davis et al. 1988), iron content (Lund and Aust 1992), and durability (Lippmann 1990), but the bulk of the available data indicate that fiber size is the most important determinant of carcinogenic potential (see Section 2.3.5).

Some epidemiological studies have detected little or no increase in lung cancer risk until the cumulative dose of asbestos exceeds 25–100 f-yr/mL (Berry and Newhouse 1983; Hughes and Weill 1980; McDonald et al. 1980; Weill et al. 1979), and this has led to the proposal that there may be a dose threshold for asbestos-induced lung cancer (Browne 1986a, 1986b). However, a number of other studies indicate that lung cancer risk is linearly related to cumulative dose without any obvious threshold (Dement et al. 1983; Finkelstein 1983; Henderson and Enterline 1979; Hughes et al. 1987; McDonald et al. 1983; Seidman et al. 1979). In general, dose-response data from epidemiological studies lack the statistical power to detect small effects at low doses, so it is not possible to conclude from such data that a hazardous chemical does (or does not) have a threshold dose. Consequently, it

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/50

seems most appropriate at present to continue to assume that there is no threshold for asbestos-induced lung cancer. Possible areas of additional research on this subject are discussed in Section 2.9.3.

Studies in animals have reported increased incidence of lung cancer following chronic inhalation exposure to chrysotile (Davis and Jones 1988; Gross et al. 1967; Reeves et al. 1974; Wagner et al. 1974, 1980a), amosite (Davis et al. 1980a, 1980b, 1986a; Reeves et al. 1974), crocidolite (Reeves et al. 1971, 1974; Wagner et al. 1974), anthophyllite (Wagner et al. 1974) and tremolite (Davis et al. 1985). Exposure levels that have resulted in increased lung tumor frequency in animals range from 70 to 1,170 PCM f/mL. In general, tumors were characterized as adenomas, adenocarcinomas, and squamous cell carcinomas. There is some evidence from animal studies that mineral-fiber lung tumors arise from fibrotic areas of the lung (Davis and Cowie 1990).

Mesothelioma. Mesotheliomas are tumors arising from the thin membranes that line the chest (thoracic) and abdominal cavities and surround internal organs. Mesotheliomas are relatively rare in the general population (approximately 2 per million) (Enterline and Henderson 1987), but are often observed in populations of asbestos workers. For example, in the mortality study of insulation workers, there were 175 deaths attributable to mesotheliomas, 63 arising from the pleural membrane and 112 arising in the peritoneum (Selikoff et al. 1979). Mesothelioma has been reported in household contacts and family members of asbestos workers, where exposure is presumably due to asbestos carried home on the workclothes (Bianchi et al. 1993b; Magnani et al. 1993). Mesotheliomas are often difficult to diagnose, so use of death certificate information may lead to an underestimate (Selikoff et al. 1979) or an overestimate (Bignon et al. 1979) of the true incidence of this disease.

Cases of death from mesothelioma have been reported in studies of workers or in persons exposed environmentally to each of the main types of asbestos, including predominantly chrysotile (Albin et al. 1990a, 1990b; McDonald et al. 1980, 1993; Selcuk et al. 1992; Tulchinsky et al. 1992), amosite (Seidman et al. 1979), crocidolite (Armstrong et al. 1988; deKlerk et al. 1989; Jones et al. 1980a), and tremolite (Kleinfeld et al. 1974; Sahin et al. 1993; Selcuk et al. 1992). Although these findings suggest that all asbestos types can cause mesothelioma, there are several studies which suggest that amphiboles (tremolite, amosite, and especially crocidolite) may be more potent than chrysotile (Berry and Newhouse 1983; Churg 1986; Churg and Wright 1989; Henderson and Enterline 1979; Hughes et al. 1987; Jones et al. 1980a; Newhouse and Sullivan 1989; Rogers et al. 1991; Sluis-Cremer et al. 1992; Weill et al. 1979). For example, a group of workers in a friction materials plant that used

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/51

mainly chrysotile, but where crocidolite had also been used on two occasions has been studied (Berry and Newhouse 1983). In a case-control analysis, it was found the workers dying from mesothelioma (11 cases) were 8-times more likely to have been exposed to crocidolite than workers dying from other causes. In another approach, the chrysotile and amphibole content of lungs from persons dying from mesothelioma was examined, and it was found that mesotheliomas occurred in amphibole workers with much lower fiber burdens than observed for chrysotile workers. The authors conclude that amphiboles were two orders of magnitude more potent for inducing mesothelioma than chrysotile (Churg and Wright 1989). This has led to the hypothesis that many cases of mesothelioma in chrysotile-exposed workers are really due to the presence of amphibole contamination (Churg 1988; McDonald et al. 1989). However, it is difficult to draw strong inferences regarding relative potency of different mineral types from lung burden data, because amphiboles are more stable in lung tissue than chrysotile (see Sections 2.3.3.1 and 2.5). Based on an analysis of the ratio of excess deaths from mesothelioma to excess deaths from lung cancer in a number of studies, EPA concluded that crocidolite could be 2- to 4-times more potent for mesothelioma than chrysotile, but that this difference was generally overshadowed by differences in fiber size distribution and differences between cohorts (EPA 1986a).

Several studies (Newhouse and Berry 1976, 1979; Nicholson et al. 1982; Peto et al. 1982) have indicated that risk of mesothelioma from a given level of exposure to asbestos depends primarily upon the time elapsed since exposure (latency), with risk increasing exponentially with time after a lag period of about 10 years. In contrast to the situation for lung cancer, the effect of asbestos on mesothelioma risk does not appear to be increased by smoking (Berry et al. 1985; Hammond et al. 1979; Selikoff et al. 1980). By extrapolating from epidemiological studies in asbestos workers, EPA (1986a) estimated that continuous lifetime exposure to air containing 0.0001 f/mL of asbestos would result in about 2–3 cases of mesothelioma per 100,000 persons. The corresponding cumulative lifetime exposures associated with excess risks of 10^{-4} to 10^{-7} are shown in Figure 2-1. Cumulative exposure levels of 0.031, 0.0031, 0.00031, and 0.000031 f-yr/mL represent excess mesothelioma risks of 10^{-4}, 10^{-5}, 10^{-6}, and 10^{-7}, respectively. Appendix D provides further details on the derivation of this risk estimate.

Animal studies also indicate that inhalation exposure to asbestos produces mesotheliomas. Mesotheliomas have been observed in rats exposed to 350–1,170 f/mL for 1 year (Wagner et al. 1974, 1980a; Davis and Jones 1988) and in baboons exposed to either 1,110–1,220 f/mL for 4 years (Goldstein and Coetzee 1990) or 1,100–1,200 f/mL for up to 898 days (Webster et al. 1993).

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/52

Incidences of mesothelioma ranged from 0.7–42% in these studies. Higher incidence of mesothelioma have been observed in animals after intrapleural administration (see Section 2.4), presumably due to a greater number of fibers reaching the target tissue, as this method of administration circumvents the natural defense mechanisms of the body. However, intrapleural administration is not a route of exposure experienced by humans.

Cancer at Extrathoracic Sites. Mortality studies of asbestos workers have often revealed small increases in the incidence of death from cancer at one or more extrathoracic sites, mostly in tissues of the gastrointestinal system. For example, a total of 99 deaths from cancers of the esophagus, stomach, colon or rectum were observed in a cohort of 17,800 insulation workers, while only 59.4 deaths of this sort were expected (Selikoff et al. 1979). Similarly, 26 deaths from gastrointestinal cancer were observed in a group of 2,500 asbestos textile workers, where only 17.1 were expected (McDonald et al. 1983). In this study, there was an approximately linear increase in gastrointestinal cancer death rate as a function of cumulative exposure to asbestos. Similar increases in gastrointestinal cancer rates in asbestos workers have been reported (Armstrong et al. 1988; Enterline et al. 1987; Gerhardsson de Verdier et al. 1992; Jakobsson et al. 1994; Neugut et al. 1991; Newhouse and Berry 1979; Raffn et al. 1989; Seidman et al. 1979, 1986). Some studies have also noted excess deaths from, or reported cases of, cancers at other sites such as the kidney (Enterline et al. 1987; Selikoff et al. 1979; Smith et al. 1989), brain (Kishimoto et al. 1992), and bladder (Bravo et al. 1988). Several epidemiological studies have also reported an increased risk of laryngeal cancer in workers exposed to asbestos (Muscat and Wynder 1991; Parnes 1990; Raffn et al. 1989; Smith et al. 1990). One case report was located in which a reproductive effects was noted in humans. Malignant mesothelioma of the tunica vaginalis testis was diagnosed in a former railway wagon cleaner who had been exposed to asbestos in the insulating panels (Serio et al. 1992). However, the etiology of this tumor was not definitive. In contrast, a number of other epidemiological studies have not detected statistically significant associations between increased risk of extrathoracic cancers and asbestos exposure (Acheson et al. 1982; deKlerk et al. 1989; Hughes et al. 1987; McDonald et al. 1984; Meurman et al. 1974; Molinini et al. 1992; Nicholson et al. 1979; Wignall and Fox 1982; Wortley et al. 1992).

2.2.2 Oral Exposure

Units of Exposure. The principal way that humans are exposed to asbestos by the oral route is through ingestion of asbestos-contaminated drinking water (see Chapter 5). As discussed in Section

Digitized by Google

5.4.2, most asbestos fibers in water are chrysotile and are <5 μm in length. The concentration of asbestos in water is generally determined by transmission electron microscopy (TEM), and the results are expressed as millions of TEM fibers per liter (MFL). Since it is very difficult to convert from MFL to other units of dose, human exposure to asbestos via drinking water is reported below simply in terms of exposure level (MFL). In contrast, animal studies usually describe oral exposure in terms of mass (mg/day), and often it is not possible to convert accurately from this dose to units of exposure equivalent to those used for humans. Consequently, animal doses are reported below in units of mg/kg/day, and information on fiber dimensions is included when available.

Overview of Oral Health Effects. Studies in humans and in animals indicate that ingestion of asbestos causes little or no risk of noncarcinogenic injury. However, there is some evidence that acute oral exposure may induce precursor lesions of colon cancer and that chronic oral exposure may lead to an increased incidence risk of gastrointestinal tumors. Studies which provide quantitative data on the effects of ingested asbestos are summarized in Table 2-3 and Figure 2-3, and the data are discussed below.

2.2.2.1 Death

No studies were located regarding death in humans or animals after acute or intermediate oral exposure to asbestos. Feeding studies in rats and hamsters indicate that ingestion of high amounts (1% in the diet, equivalent to doses of 500–800 mg/kg/day) of chrysotile, amosite, crocidolite, or tremolite does not cause premature lethality, even when exposure occurs for a lifetime (NTP 1983, 1985, 1988, 1990a, 1990b, 1990c).

2.2.2.2 Systemic Effects

No studies were located regarding the respiratory, cardiovascular, hematological, musculoskeletal, hepatic, renal, endocrine, dermal, ocular, metabolic, or other systemic effects in humans after oral exposure to asbestos. Studies in rats and hamsters exposed to high doses (1% in the diet) of chrysotile, amosite, crocidolite, or tremolite have not detected histological or clinical evidence of injury to any systemic tissues (NTP 1983, 1985, 1988, 1990a, 1990b, 1990c), with the possible exception of mild effects on the gastrointestinal tract (see below). These findings are consistent with the concept that very few asbestos fibers cross from the gastrointestinal lumen into the blood (see

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/54

Section 2.3.1), and that the risk of noncarcinogenic injury to tissues such as lung, heart, muscle, liver, kidney, skin, or eyes is negligible. The highest NOAEL values and all LOAEL values from reliable studies for systemic effects are summarized in Table 2-3 and plotted in Figure 2-3.

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after oral exposure to asbestos. Because most ingested asbestos fibers are not absorbed into the body following oral exposure (see Section 2.3.1), the tissue most directly exposed to ingested asbestos is the gastrointestinal epithelium. A few studies in rats have described some histological or biochemical alterations in cells of the gastrointestinal tract after chronic exposure to oral doses of 20–140 mg/kg/day of chrysotile (Delahunty and Hollander 1987; Jacobs et al. 1978a, 1978b). Increased numbers of aberrant crypt foci, putative precursors of colon cancer, were induced in rats that were administered by gavage either a single dose (70 mg/kg/day) of chrysotile, a single dose (40 mg/kg/day) of crocidolite, or three doses (33 mg/kg/day) of crocidolite, although no dose response was noted in the single-dose of crocidolite regimen (Corpet et al. 1993). Mice that were administered either a single dose (100 mg/kg) of chrysotile or three doses (50 mg/kg/day) of crocidolite did not show increases in aberrant crypt foci (Corpet et al. 1993). However, no excess nonneoplastic lesions of the gastrointestinal epithelium have been detected in a number of other animal feeding studies (Bolton et al. 1982a; Donham et al. 1980; Gross et al. 1974), including an extensive series of lifetime studies in rats and Syrian hamsters in which such effects were carefully investigated (NTP 1983, 1985, 1988, 1990a, 1990b, 1990c). Thus, the weight of evidence indicates that asbestos ingestion does not cause any significant noncarcinogenic effects in the gastrointestinal system.

Body Weight Effects. A single study reported a 15–37% decreased body weight gain in rats exposed to 500 mg/kg/day amosite (NTP 1990b). Changes in food consumption do not explain the decreased body weight gain since treated rats had slightly higher food intakes than controls. Effects on body weight gain have generally not been observed in other studies (Gross et al. 1974; NTP 1983, 1985, 1988, 1990a, 1990c). The significance of this finding, therefore, is uncertain.

2.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological or lymphoreticular effects in humans or animals after oral exposure to asbestos.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/55

TABLE 2-3. Levels of Significant Exposure to Asbestos - Oral

Key to figure[a]	Species/ strain	Exposure/ duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference/ chemical form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
INTERMEDIATE EXPOSURE							
Reproductive							
1	Rat F344/N	2-12 wk (F)		500			NTP 1985, 1988, 1990b, 1990c CH CR TR AM
2	Hamster Syrian	3-6 wk (F)		830			NTP 1983, 1990a CH AM
Developmental							
3	Rat F344/N	2-12 wk (F)		500			NTP 1985, 1988, 1990b, 1990c CH CR TR AM
4	Mouse CD-1	15 d Gd1-15 (W)		33 F			Schneider and Maurer 1977 CH
5	Hamster Syrian	3-6 wk (F)		830			NTP 1983, 1990a CH AM
CHRONIC EXPOSURE							
Systemic							
6	Rat Wistar	25 mo (F)	Gastro	100 M			Bolton et al. 1982a AM CR CH
7	Rat Sprague-Dawley	1.5 yr (W)	Gastro		20M (altered permeability of the intestines)		Delahunty and Hollander 1987 CH

Toxicological Profile for Asbestos (1995)
ACL Doc 10942 · Page 56 of 233
Digitized by Google
Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/56

TABLE 2-3. Levels of Significant Exposure to Asbestos - Oral (continued)

Key to[a] figure	Species/ strain	Exposure/ duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference/ chemical form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
8	Rat NS	21 mo (F)	Resp	2500 M			Gross et al. 1974 CH
			Cardio	2500 M			
			Gastro	2500 M			
			Hemato	2500 M			
			Musc/skel	2500 M			
			Hepatic	2500 M			
			Renal	2500 M			
			Dermal	2500 M			
9	Rat MRC Hooded	15 mo (F)	Gastro		140M (increased DNA synthesis)		Jacobs et al. 1978b CH
10	Rat F344/N	lifetime (F)	Resp	500			NTP 1985, 1988, 1990b, 1990c CH CR TR AM
			Cardio	500			
			Gastro	500			
			Hemato	500			
			Musc/skel	500			
			Hepatic	500			
			Renal	500			
			Endocr	500			
			Dermal	500			
			Bd Wt	500			

Toxicological Profile for Asbestos (1995)
ACL Doc 10942 · Page 57 of 233
Digitized by Google
Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/57

TABLE 2-3. Levels of Significant Exposure to Asbestos - Oral (continued)

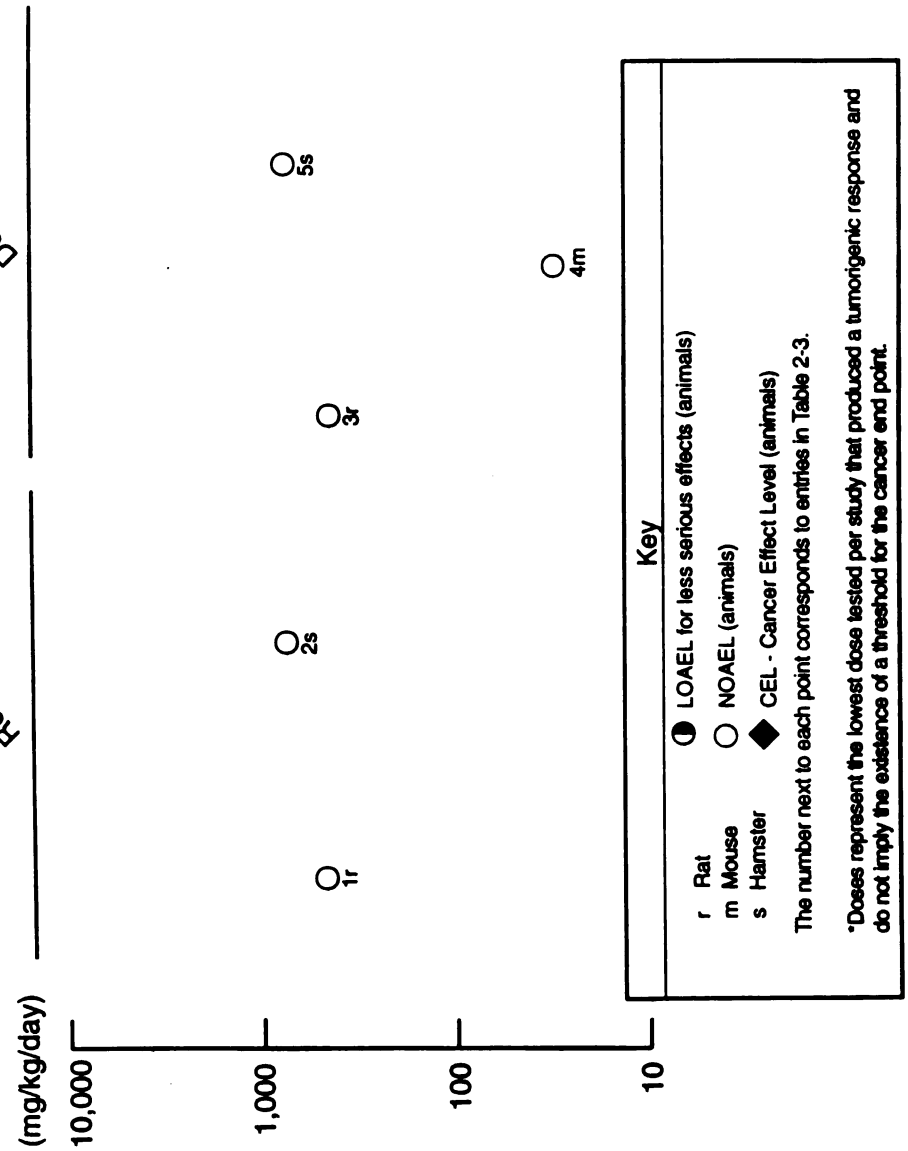
Key to[a] figure	Species/ strain	Exposure/ duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference/ chemical form
11	Hamster Syrian	lifetime (F)	Resp	830			NTP 1983, 1990a CH AM
			Cardio	830			
			Gastro	830			
			Hemato	830			
			Musc/skel	830			
			Hepatic	830			
			Renal	830			
			Endocr	830			
			Dermal	830			
			Bd Wt	830			
	Neurological						
12	Rat F344/N	lifetime (F)		500			NTP 1985, 1988, 1990b, 1990c CH CR TR AM
13	Hamster Syrian	lifetime (F)		830			NTP 1983, 1990a CH AM
	Cancer						
14	Rat F344/N	lifetime (F)				500 M (CEL: intestinal polyps)	NTP 1985 CH-I

[a]The number corresponds to entries in figure 2-3.

AM = amosite; Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; CH = chrysotile; CR = crocidolite; d = day(s); DNA = deoxyribonucleic acid; Endocr = endocrine; (F) = food; F = female; Gastro = gastrointestinal; Gd = gestation day; Hemato = hematological; I = intermediate; LOAEL = lowest-observed-adverse-effect-level; M = male; mg/kg/day = milligrams per kilogram per day; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect-level; NS = not specified; Resp = respiratory; TR = tremolite; (W) = water; wk = week(s); yr = year(s)

Toxicological Profile for Asbestos (1995)
ACL Doc 10942 · Page 58 of 233
Digitized by Google
Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/58

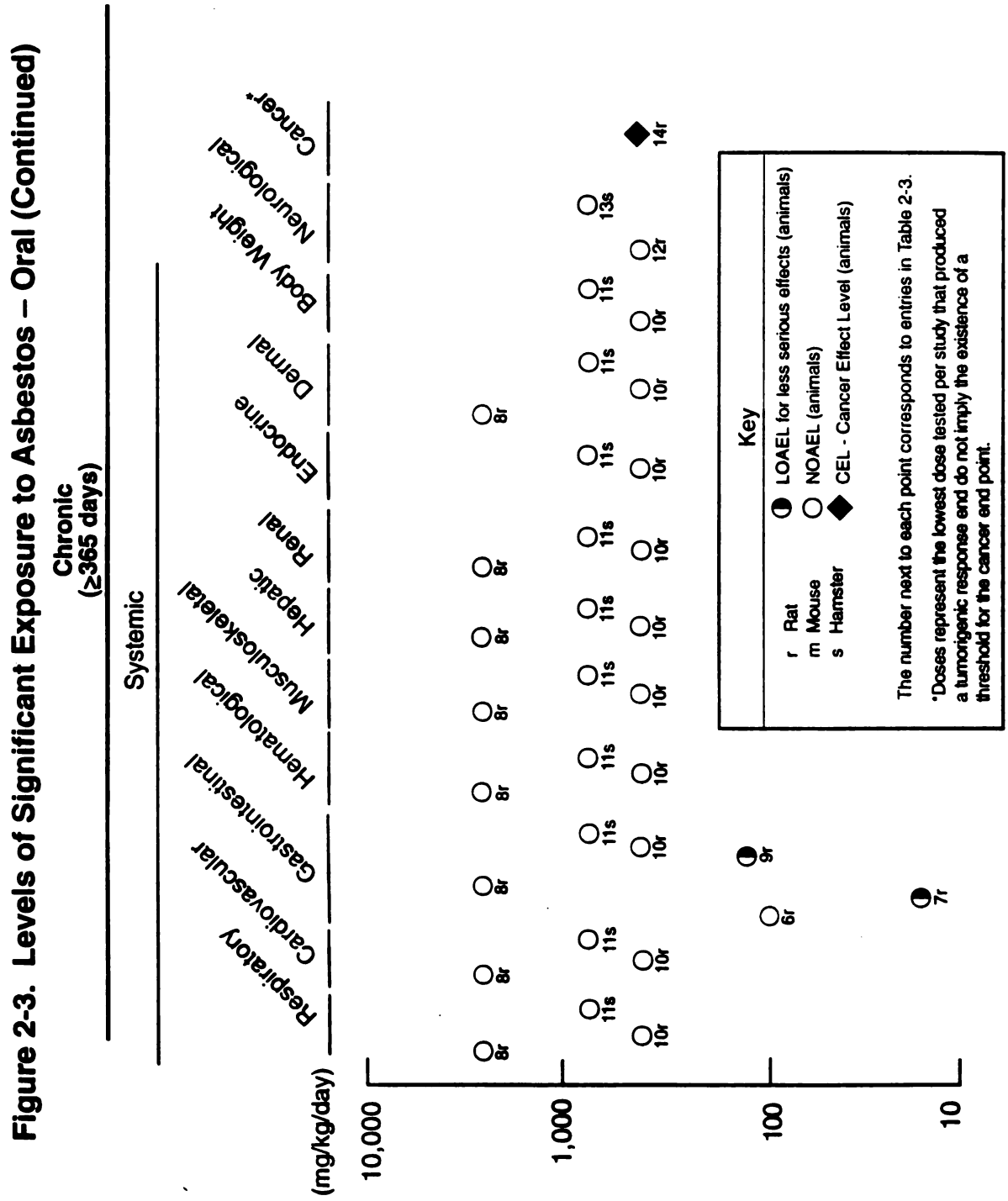
Figure 2-3. Levels of Significant Exposure to Asbestos – Oral



Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/59

Figure 2-3. Levels of Significant Exposure to Asbestos – Oral (Continued)



Digitized by Google

2.2.2.4 Neurological Effects

No studies were located to indicate that ingestion of asbestos leads to neurological effects in humans. No histological or clinical evidence of neurological injury was detected in rats or hamsters chronically exposed to high doses (500 and 830 mg/kg/day, respectively) of chrysotile, amosite, crocidolite, or tremolite in the diet (NTP 1983, 1985, 1988, 1990a, 1990b, 1990c). No clinical signs of neurological damage was noted after acute exposure of rats and mice to crocidolite (160 and 50 mg/kg/day, respectively) or to chrysotile (70 and 100 mg/kg/day, respectively) (Corpet et al. 1993).

2.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to asbestos. In animals, no histopathological changes in reproductive organs or effects on fertility were observed in rats or Syrian hamsters exposed to chrysotile, amosite, crocidolite, or tremolite (500 and 830 mg/kg/day, respectively) in the diet during breeding, gestation, and lactation (NTP 1983, 1985, 1988, 1990a, 1990b, 1990c). The highest NOAEL values from reliable studies for reproductive effects are summarized in Table 2-3 and plotted in Figure 2-3.

2.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans after oral exposure to asbestos. Although detailed studies were not performed, no teratogenic effects were noted in the offspring of rats or hamsters exposed to chrysotile, amosite, crocidolite, or tremolite (500 and 830 mg/kg/day, respectively) during gestation (NTP 1983, 1985, 1988, 1990b, 1990c). A slight reduction in pup birth weight was noted in some cases (NTP 1985, 1990a), but it seems unlikely that this was the result of any direct effect on the fetus. No teratogenic effects in mice given doses up to 33 mg/kg/day of chrysotile during gestation (Schneider and Maurer 1977). The highest NOAEL values from reliable studies for developmental effects are summarized in Table 2-3 and plotted in Figure 2-3.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/61

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after oral exposure to asbestos. Genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

As discussed in Section 2.2.1.8, a number of epidemiological studies of workers exposed to asbestos fibers in workplace air suggest that workers may have increased risk of gastrointestinal cancers. It is usually assumed that any effect of asbestos on the gastrointestinal tract after inhalation exposure is most likely the result of mucociliary transport of fibers from the lung to the stomach (see Section 2.3.4). Because of these findings, a number of researchers have investigated the carcinogenic risk (especially the risk of gastrointestinal cancer) in humans and animals when exposure to asbestos occurs by the oral route.

Human Studies. A number of epidemiological studies have been conducted to determine if human cancer incidence is higher than expected in geographical areas where asbestos levels in drinking water are elevated (usually in the range of 1–300 MFL) (Andersen et al. 1993; Conforti et al. 1981; Howe et al. 1989; Kanarek et al. 1980; Levy et al. 1976; Polissar et al. 1982, 1984; Sigurdson et al. 1981; Toft et al. 1981; Wigle 1977). Most of these studies have detected increases, some of which were statistically significant, in cancer death or incidence rates at one or more tissue sites (mostly gastrointestinal) in populations exposed to elevated levels of asbestos in their drinking water. However, the magnitudes of the increases in cancer incidence are usually rather small, may be related to other risk factors such as smoking, and there is relatively little consistency in the observed increases, either within studies (i.e., between sexes) or between studies.

The basis of these inconsistent findings is not certain. On one hand, it seems likely that at least some of the apparent associations are random or are due to occupational exposures (Polissar et al. 1982, 1984; Toft et al. 1981; Wigle 1977). On the other hand, failure of some studies to detect effects may be due to lack of statistical power, stemming from limitations regarding study design, exposure level and duration, latency since exposure, population size and mobility, population density, exposure to other risk factors, differences in sensitivity between sexes and groups, differences in asbestos fiber types and size, and numerous other possible confounding factors. In a review of data from eight

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/62

independent epidemiological studies it was concluded that the number of positive findings for neoplasms of the esophagus, stomach, pancreas, and prostate were unlikely to have been caused by chance alone (Marsh 1983). In a more recent review, it was noted that there were relatively consistent findings for increased stomach and pancreatic cancer among the studies (Kanarek 1989). However, none of the studies provides a basis for identification of an oral exposure level that may be definitely stated as having caused increased death from cancer.

Animal Data. Early animal studies on gastrointestinal cancer from ingested asbestos were mostly negative (Cunningham et al. 1977; Gross et al. 1974), although some studies yielded increases in tumor frequency that were not statistically significant (Bolton et al. 1982a; Donham et al. 1980; Ward et al. 1980). More recently, a series of large scale, lifetime feeding studies have been performed by the National Toxicology Program (NTP). These studies have also yielded mostly negative results, although some suggestive increases in tumor frequencies did occur (Table 2-4). An increased incidence of benign adenomatous polyps of the large intestine was observed in male rats exposed to 500 mg/kg/day intermediate range chrysotile (65% of all fibers over 10 μm) in the diet (NTP 1985). These tumors were not observed either in female rats or in Syrian hamsters exposed to the same diet. Aberrant crypt foci, putative precursors of colon cancer, were induced in rats given acute doses of chrysotile (70 mg/kg/day) or crocidolite (33 mg/kg/day) by gavage (Corpet et al. 1993). Overall, however, the data were interpreted as providing "some evidence" of carcinogenicity for intermediate range chrysotile fibers. No tumorigenicity was noted for short-range chrysotile (NTP 1985).

Quantitative Risk Estimate. None of the available epidemiological studies of cancer risk in humans exposed to asbestos in drinking water are suitable for estimating quantitative dose-response relationships. However, both EPA and National Academy of Sciences (NAS) have sought to estimate risk of gastrointestinal cancer after oral exposure by extrapolating dose-response data from occupational studies (EPA 1980; NAS 1983). As noted before, this approach rests on the assumption that the observed excess gastrointestinal cancer risk in the occupational studies is due to the swallowing of fibers that have been deposited in the lung. These calculations indicate that lifetime ingestion of water containing 1.0 MFL would produce an excess gastrointestinal cancer risk of about $3x10^{-5}$ to $1x10^{-4}$ (EPA 1980; NAS 1983). It should be noted that this approach requires a number of assumptions, and that the risk estimates should be considered to be only approximate. It is also important to note that if these risk estimates are correct, then the expected relative risk of gastrointestinal cancer in populations consuming drinking water at concentrations of 1–200 MFL

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/63

TABLE 2-4. Summary of NTP Lifetime Asbestos Feeding Studies

Asbestos type	Species	Median length (μm)	Size distribution	Carcinogenic effects	Comments	Conclusion	Reference
Amosite	Rat	4.37	74% > 6 μm	Increased C-cell carcinoma (males)	Not considered treatment related	Not carcinogenic	NTP 1990b
				Increased leukemia (males)	Questionable biological and statistical significance		
	Syrian hamster	4.37	74% > 6 μm	None		Did not cause a carcinogenic response	NTP 1983
Crocidolite	Rat	10	73% > 8 μm	None		Did not cause a carcinogenic response	NTP 1988
Tremolite	Rat	No data	22% > 5 μm	None		Did not cause a carcinogenic response	NTP 1990c
Chrysotile (short range)	Rat	0.66	30% > 4.5 μm	None		No evidence of carcinogenicity	NTP 1985
Chrysotile (intermediate range)	Rat	0.82	60% > 5.4 μm	Benign intestinal polyps (males)	Not significant based on concurrent controls; highly significant based on historical controls	Some evidence of carcinogenicity	NTP 1985
				Clitoral gland neoplasm (females)	Not significant compared to historical controls	No evidence of carcinogenicity	
Chrysotile (short range)	Syrian hamster	0.66	30% > 4.5 μm	Adrenal cortical adenomas (males)	Not significant compared to historical controls	Not carcinogenic	NTP 1990a
Chrysotile (intermediate range)	Syrian hamster	0.82	60% > 5.4 μm	Adrenal cortical adenomas (males and females)		Not carcinogenic	

Toxicological Profile for Asbestos (1995)
ACL Doc 10942 · Page 64 of 233
Digitized by Google
Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/64

would be quite low, and would likely not be consistently detectable in epidemiological studies (NAS 1983).

Another quantitative estimate of gastrointestinal cancer risk has been calculated based on the incidence of benign intestinal polyps in male rats exposed to 500 mg/kg/day chrysotile (65% >10 μm long) in the diet (EPA 1985a). This calculation indicates the lifetime excess risk from ingesting water containing 1.0 MFL would be about $1.4x10^{-7}$.

Figure 2-4 summarizes the risk estimates of NAS (1983) and EPA (1985a). It should be noted that these estimates differ by several orders of magnitude. Based on extrapolation from human inhalation studies, exposure levels of 1.1, 0.11, 0.011, and 0.0011 MFL in drinking water represent excess gastrointestinal cancer risks of 10^{-4}, 10^{-5}, 10^{-6}, and 10^{-7}, respectively. Based on animal data, exposure levels of 710, 71, 7.1, and 0.71 MFL in drinking water represent excess gastrointestinal cancer risks of 10^{-4}, 10^{-5}, 10^{-6}, and 10^{-7}, respectively. There are many possible reasons for this substantial difference, including uncertainty in each model's assumptions or conversion factors, differences in fiber potency (due to differences in type and/or length), and inherent differences between humans and rats. Appendix D provides further details on the derivation of these risk estimates.

2.2.3 Dermal Exposure

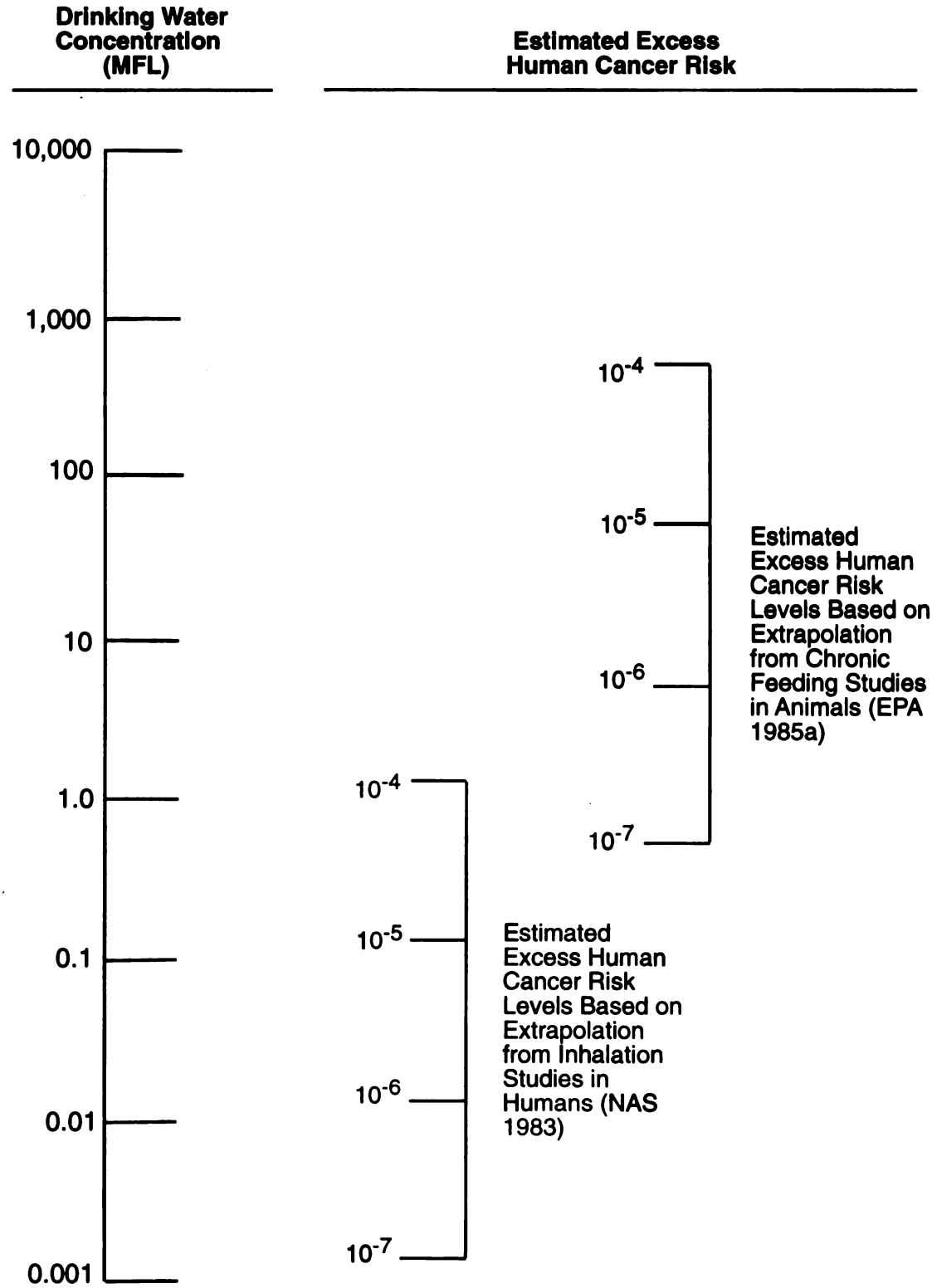
The only adverse health effect that has been reported after dermal contact with asbestos is the formation of small "warts" or corns. No quantitative dose-response data are available, but in a group of workers installing amosite insulation in ships, nearly 60% of the people had one or more of these lesions, mostly on the hands (Alden and Howell 1944). All of the workers with lesions reported an original pricking sensation and the feeling of a small splinter-like foreign body. This strongly indicates that the lesions are associated with penetration of the skin by a macroscopic spicule, although histological examination of the corns did not reveal the presence of a fiber. The corns develop within about 10 days and are painful at first. They later become highly cornified and do not appear to be of pathological concern (Alden and Howell 1944; Dupre et al. 1984; Selikoff and Lee 1978).

No studies were located regarding the following health effects in humans or animals after dermal exposure to asbestos.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/65

FIGURE 2-4. Summary of Calculated Gastrointestinal Cancer Risks from Ingestion of Asbestos



Digitized by Google

2.2.3.1 Death

2.2.3.2 Systemic Effects

2.2.3.3 Immunological and Lymphoreticular Effects

2.2.3.4 Neurological Effects

2.2.3.5 Reproductive Effects

2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

No studies were located regarding carcinogenic effects in humans or animals after dermal exposure to asbestos.

2.3 TOXICOKINETICS

Overview

Asbestos fibers may enter the body after inhalation or oral exposures. It is unlikely that any appreciable uptake of asbestos will occur after dermal exposure. The deposition and fate of the fiber in the lungs is largely dependent on its size and shape. Fibers which are deposited in the lung may be removed from the lung by mucociliary clearance or by macrophages, or they may be retained in the lung. Very few of the fibers are likely to move through the lungs and be distributed to other tissues. Longer fibers that are retained in the lung may undergo a number of processes including translocation, dissolution, fragmentation, splitting or protein encapsulation. Long fibers that reside in the lung can become encapsulated in protein, forming what is often referred to as an "asbestos body" (the term "ferruginous body" is used when the nature of the core fiber is not known). These bodies are golden brown in appearance, owing to the presence of iron. The protein coat is rich in ferritin (an iron storage protein) possibly arising from macrophages and giant cells. The formation of asbestos bodies

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/67

may represent an attempt of macrophages to digest long fibers extracellularly (Koerten et al. 1990a, 1990b). Fibers which are retained in the lung or mesothelium for long periods of time are capable of producing chronic inflammation and fibrotic and tumorigenic effects. These effects may be mediated by direct interactions between the fiber and key cellular macromolecules, or they may be mediated by the production of reactive oxygen species and other cellular factors originating from alveolar macrophages. Fibers which enter the gastrointestinal tract, either by ingestion or mucociliary transport from the lungs, are mostly excreted in the feces, although a small fraction of the fibers may become lodged in cells or penetrate the gastrointestinal lining and enter other tissues.

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

When asbestos fibers are inhaled, many are deposited on the epithelial surface of the respiratory tree. The number of fibers that are deposited, and the location within the airway where deposition occurs, is a function of the aerodynamic properties of the fibers. In humans, the fibers in the upper airway consist mainly of relatively thick fibers (greater than about 3 μm), with thinner fibers being carried deeper into the airways (Timbrell 1982). In rats, about 30–40% of typical fibers of chrysotile, amosite, and crocidolite, are retained, with most of these (about 60%) being deposited in the upper airways (nose, throat, and trachea) (Evans et al. 1973; Morgan et al. 1975). The median length for these fibers was 1–2 μm, while the median diameter was 0.2–0.4 μm. After intratracheal administration of chrysotile and asbestos fibers in hamsters, chrysotile fibers were found to be primarily located near air duct bifurcations, while amosite fibers tended to be more distributed over the bronchial surface (Kimizuka et al. 1992). Many of these smaller fibers deposit preferentially at bifurcations in the terminal bronchioles (Brody 1986; Evans et al. 1973), with the number of fibers deposited at each location decreasing in proportion to the preceding airway path length and the number of preceding branch points (Pinkerton et al. 1986).

2.3.1.2 Oral Exposure

Animal studies indicate that most asbestos fibers which are ingested are not absorbed across the gastrointestinal tract (Gross et al. 1974). However, electron micrographic studies indicate that some fibers penetrate into the gastrointestinal epithelium (Storeygard and Brown 1977; Westlake et al.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/68

1965). In addition, some fibers pass through the gastrointestinal wall and reach blood, lymph, urine and other tissues (Carter and Taylor 1980; Cunningham and Pontefract 1973; Cunningham et al. 1977; Hallenbeck and Patel-Mandlik 1979; Patel-Mandlik and Millette 1983; Sebastien et al. 1980b; Weinzweig and Richards 1983). The mechanism by which asbestos fibers pass through the gastrointestinal wall is not known with certainty, but it has been noted that a wide variety of μm-sized particles (e.g., starch granules, cellulose particles, pollen) can cross the gut by passing between (not through) the cells of the epithelial layer in a process termed persorption, and it seems likely that this may account for uptake of asbestos fibers as well (Volkheimer 1974). Available data are not sufficient to make a precise estimate of the fraction of ingested fibers which pass through the gastrointestinal wall, but there is agreement that it is a very small amount (Sebastien et al. 1980b; Weinzweig and Richards 1983). Several researchers have found that the average length of fibers in extra-gastrointestinal tissues or fluids is shorter than the average length of the fibers ingested (Cunningham et al. 1977; Patel-Mandlik and Millette 1983; Weinzweig and Richards 1983), suggesting that short fibers pass through the gastrointestinal epithelium more easily than long fibers.

2.3.1.3 Dermal Exposure

As discussed above (see Section 2.2.3), asbestos fibers can penetrate into the skin, producing asbestos warts. No studies were located which indicate that asbestos fibers can pass through the skin into the blood.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

As noted above, only a tiny fraction of inhaled fibers penetrate through the epithelial layer of the lungs. No quantitative studies were located regarding the distribution of these fibers in the rest of the body after inhalation exposure, but some appear to be retained in the pleura, with others passing into the lymph (Hillerdal 1980; Holt 1983; Rudd 1989). Those fibers that enter the lymph are presumably able to reach other tissues of the body. This is supported by the finding that people with high levels of asbestos fibers in the lung (measured as asbestos bodies) also had asbestos bodies in kidney, heart, liver, spleen, adrenals, pancreas, brain, prostate, and thyroid tissues (Auerbach et al. 1980). Dogs exposed by nose-only inhalation to neutron-activated crocidolite were found to have small amounts of

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/69

radioactivity in blood, liver, head, and gastrointestinal tract (Griffis et al. 1983). However, it is also possible that fibers originally deposited in the lungs may reach other tissues following mucocillary transport of fibers to the gastrointestinal tract and uptake from that tissue (see Section 2.3.1.2). Asbestos fibers have been detected in human placenta, fetal, and neonatal tissues at concentrations of up to 215,000 fibers/gram (Haque et al. 1991, 1992), suggesting that transplacental transfer can occur.

Distribution of asbestos fibers within the lung has been investigated in a number of studies. Most fibers deposited in the airways are removed from the lung by mucociliary transport or by macrophages (see Section 2.3.4), but a small fraction remain in the lung for long periods (Jones et al. 1988a). In addition, some fibers appear to pass from the lung to the pleura, although the precise mechanism of transport is not known (Hillerdal 1980; Rudd 1989; Viallat et al. 1986). In humans, the presence of asbestos fibers in the pleura after inhalation exposure has been demonstrated by a number of researchers (Jones et al. 1980b; Roggli and Longo 1991; Sebastien et al. 1980a; Stephens et al. 1987). Available data are not sufficient to estimate the fraction of deposited asbestos fibers which penetrate the lung in this way, but it is probably quite small.

Intracellularly, asbestos fibers tend to be located near the nucleus. *In vitro* studies have indicated that during endocytosis, asbestos fibers were observed to be transported along the microtubule network to the perinuclear region (Cole et al. 1991; Malorni et al. 1990). The proximity of asbestos fibers to the nucleus may be an important factor regarding their genotoxicity and carcinogenicity.

2.3.2.2 Oral Exposure

Asbestos fibers have been detected in blood (Weinzweig and Richards 1983) and lymph (Sebastien et al. 1980b) of rats exposed to oral doses of asbestos, suggesting that fibers penetrating the gut might be carried to tissues throughout the body. In support of this, asbestos fibers have been detected in lung, kidney, liver, brain, heart, and spleen of rats that had been exposed to asbestos in the diet (Pontefract and Cunningham 1973; Cunningham et al. 1977). Highest levels of fibers were found in the omentum (a fold of the peritoneum connecting abdominal viscera to the stomach), supporting the idea that the fibers were emanating from the gastrointestinal tract. Although the diet fed to the animals was prepared using corn oil, to minimize asbestos fiber inhalation, the possibility that some fiber inhalation took place cannot be eliminated (Cunningham et al. 1977).

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/70

2.3.2.3 Dermal Exposure

No studies were located regarding distribution of asbestos fibers after dermal exposure. It is generally considered that dermal uptake of asbestos is not significant.

2.3.2.4 Other Exposure

The distribution of asbestos fibers has been investigated in a number of studies after exposure via intratracheal or intravenous injection. The translocation of chrysolite fibers from the lung to the pleura and mesothelium has been observed in rats exposed by intratracheal injection (Fasske 1988; Viallat et al. 1986). Following intravenous injection of chrysotile fibers into pregnant rats, fibers were detected at higher levels in fetus of exposed dams (Cunningham and Pontefract 1974), suggesting that placental transfer can occur. These observations support those made in humans and animals after inhalation exposure to asbestos.

2.3.3 Metabolism

2.3.3.1 Inhalation Exposure

Asbestos fibers are not metabolized in the normal sense of the word, and amphibole fibers which are retained in the lung do not appear to undergo any major changes (Bellmann et al. 1987; Carter and Taylor 1980; Roggli et al. 1987a). However, chrysotile fibers appear to undergo some type of breakdown or alteration in the lung. This conclusion is based primarily on measurements of asbestos levels in the lung as a function of exposure duration. While amphibole levels tend to rise linearly, chrysotile levels reach a steady-state concentration within several months (Wagner et al. 1974). These data from animal studies are supported by a number of human studies in which the ratio of amphibole to chrysotile concentration in lung tissue was much higher than expected based on the composition of the inhaled fibers (Jones et al. 1980a, 1980b; Pooley 1976; Stephens et al. 1987; Wagner et al. 1982a, 1982b, 1986).

The basis of this apparent loss of chrysotile fibers is not clear, but it may be related to a slow dissolution of the fibers in tissue fluids or in macrophages (Fasske 1988; Jaurand et al. 1984), or to a separation of the fibers into much finer component fibrils (Bellmann et al. 1987; Coin et al. 1992;

Digitized by Google

Cook et al. 1982; Roggli et al. 1987a). In the latter case, the apparent loss of fibers could be an artifact due to the inability of normal methods for fiber isolation and quantification in tissues to detect very fine fibrils. Recently, loss of chrysotile has been reported to be related to the fragmentation of long fibers, resulting in the formation of smaller fibers (Churg et al. 1989a, 1989b). There appears to be preferential clearance of short chrysotile fibers compared to long ones (Coin et al. 1992). Long fibers that reside in the lung can form asbestos bodies. The formation of asbestos bodies might represent an attempt by macrophages to digest these fibers extracellularly (Koerten et al. 1990a, 1990b).

2.3.3.2 Oral Exposure

No studies were located regarding any changes in asbestos fibers in the gastrointestinal tract per se. However, chrysotile fibers incubated in simulated gastric juice underwent leaching of magnesium ion from the silica framework, with a resultant change in net fiber charge from positive to negative (Seshan 1983), and chrysotile fibers with altered appearance and x-ray diffraction patterns were detected in the urine of animals (Hallenbeck and Patel-Mandlik 1979; Patel-Mandlik and Millette 1983). These observations, although limited, suggest that chrysotile fibers undergo some metal ion exchange and alterations in gross structure in biological fluids after oral exposure. Asbestos bodies have been detected is tissues such as the colon (Ehrlich et al. 1992), suggesting that this process may occur in extrapulmonary tissues as well.

2.3.3.3 Dermal Exposure

No studies were located regarding any changes in asbestos fiber composition or structure after dermal exposure.

2.3.3.4 Other Exposure

As stated above, asbestos fibers are not metabolized in the true sense of the word, however a number of animal studies indicate that chrysotile fibers are physically altered in the lung after intratracheal injection. Following phagocytosis, chrysotile fibers were observed to decrease in size, become transparent, and in some cases break into fragments (Fasske 1988). Longitudinal splitting, resulting in a greater number of thinner fibers was noted for actinolite and amosite (Cook et al. 1982), and

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/72

fragmentation, resulting in shorter fibers was observed for chrysotile (Churg et al. 1989a, 1989b). These changes in fiber shape and size may directly impact fiber clearance and toxicity in the lung.

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

The principal pathway by which fibers are removed from the lung is mucociliary transport. This is mediated by ciliated epithelial cells which produce and move the layer of mucus coating the epithelial tissue upwards toward the throat, where it is swallowed. Fibers deposited in this mucus layer are swallowed into the alimentary canal and most are ultimately excreted in the feces (Cunningham et al. 1976; Evans et al. 1973; Griffis et al. 1983; Morgan et al. 1978). However, a small number of fibers may penetrate through the epithelial layers of the lung and/or the gastrointestinal tract and are transferred to the blood and eventually to the kidney, where some of them may be excreted in the urine (Finn and Hallenbeck 1984). In addition, some fibers are not cleared from the lung, leading to a gradual accumulation with time (Jones et al. 1988a; Wagner et al. 1974).

Clearance of fibers from the upper airways generally occurs within a few hours (Bolton et al. 1983; Evans et al. 1973). However, clearance from the lower airways is slower, with half-times ranging up to 160 days (Bellmann et al. 1987; Coin et al. 1992; Evans et al. 1973; Morgan et al. 1978). This slow clearance is mediated largely by macrophages, which engulf fibers in the bronchioles and alveoli (which are not ciliated), and carry them to the ciliated portion of the airway for transport upward (Holt 1974). Macrophages may also translocate some fibers from the lung to the pleura (Holt 1983). The clearance of chrysolite fibers from the lungs is dependent on fiber length. Long fibers (in excess of 5 or 10 μm) are cleared from the lower airways more slowly than short fibers (Bellmann et al. 1987; Davis et al. 1986a, 1988; Morgan et al. 1978; Roggli et al. 1987a), probably because long fibers cannot be easily engulfed and moved by a single macrophage (Morgan et al. 1978). Fibers less than 1 μm in length were cleared from the lung with a half-life of less than 10 days whereas fibers longer than 16 μm were cleared with a half-life of greater than 100 days (Coin et al. 1992). The preferential clearance of chrysotile over amphiboles may be attributed to fragmentation of long fibers, resulting in the formation of shorter fibers which are more readily engulfed and moved by a single macrophage.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/73

2.3.4.2 Oral Exposure

Nearly all asbestos fibers which are ingested are excreted in the feces. This is essentially complete within 48 hours following a single oral dose (Gross et al. 1974). Small numbers of fibers may also be excreted in the urine (Boatman et al. 1983; Hallenbeck and Patel-Mandlik 1979), but this accounts for only a very small fraction of the ingested dose (Cook and Olson 1979).

2.3.4.3 Dermal Exposure

No studies were located regarding excretion of asbestos fibers after dermal exposure. It is generally considered that dermal exposure does not result in uptake of asbestos.

2.3.4.4 Other Exposure

Similar to observations made in inhalation studies, studies in which animals are exposed by intratracheal injection indicate that chrysotile fibers are preferentially cleared from the lung over amphiboles (Churg et al. 1989a, 1989b; Sebastien et al. 1990). The enhanced clearance was generally attributed to fragmentation of fibers, rather than dissolution. The resulting fibers are shorter and more readily engulfed and moved by alveolar macrophages.

2.3.5 Mechanisms of Action

Fibers which persist within the lung or the mesothelium are capable of producing fibrogenic and tumorigenic effects in these tissues. Although the precise mechanisms by which asbestos fibers cause toxicity have not been determined, data are available which indicate both direct binding and cell-mediated pathways may be involved. In addition, the physical-chemical nature of the fiber appears to be an important determinant of toxicity. Each of these topics is discussed below.

Direct-Binding Mechanism. Asbestos fibers can adsorb to a variety of cellular macromolecules (proteins, membranes, RNA, DNA). In rat lung microsomes, chrysotile fibers were found to bind to cytochrome P-450, thereby decreasing mono-oxygenase activity (Khan et al. 1992; Rahman et al. 1990). Chrysotile and crocidolite fibers were found to bind to artificial lipid membranes, thereby increasing membrane rigidity (Gendek and Brody 1990). This effect was also noted in erythrocytes,

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/74

and may be responsible in part for the hemolytic activity of asbestos fibers. The interaction between asbestos fibers and cell membranes was mediated in part by surface charge (positively charged chrysotile fibers can become associated with negatively charged membrane constituents), and also fiber binding to fibronectin (Brown et al. 1991). The integrity of cultured human lung epithelial cells was found to be compromised by chrysotile, resulting in increases in epithelial permeability that occurred in the absence of cell death and inflammatory cells (Peterson et al. 1993). The coulombic forces between the asbestos fiber and macromolecules (DNA, RNA and protein) may induce conformational changes (Chang et al. 1990), and these changes could affect protein function and chromosomal fidelity. Surface charge density may be an important factor in fiber potency, as well (Bonneau et al. 1986; Davis et al. 1988). Asbestos fibers were observed to be translocated near the nucleus where they can interact with the cytoskeleton and interfere with chromosome segregation (Malorni et al. 1990). Deletion of chromosome arms (particularly the short arm of chromosome 3) has been noted in human mesothelioma cells, and interference with chromosome segregation may account for this (Barrett et al. 1989). Additional evidence supporting the importance of fiber surfaces comes from studies in which the fiber surfaces have been altered. Modification of asbestos fiber surfaces with certain dyes, alkyl groups, or phosphate was found to decrease their hemolytic and cytotoxic activity (Awadalla et al. 1990; Brown et al. 1990, 1991; Habashi et al. 1991). These data suggest that direct interactions between asbestos fibers and key cellular molecules may be responsible at least, in part, for asbestos-related health effects.

Active Oxygen Mechanism. In response to the asbestos fibers, alveolar macrophages produce reactive oxygen species in an attempt to digest the fiber. The reactive oxygen species include hydrogen peroxide and superoxide (Cantin et al. 1988; Hansen and Mossman 1987; Nyberg and Klockars 1991; Roney and Holian 1989). These reactive oxygen species are relatively mild oxidants. However, they can spontaneously react with each other, producing hydroxyl radicals which are much more potent oxidants. This reaction is often referred to as the Haber-Weiss or Fenton reaction (Garcia et al. 1988; Weitzman and Graceffa 1984; West 1985). The Haber-Weiss reaction is greatly enhanced in the presence of redox-active metals such as iron. Numerous *in vitro* studies have linked the production of reactive oxygen species to asbestos-induced lipid peroxidation (Fontecave et al. 1990; Goodglick et al. 1989; Yano 1988), cytotoxicity (Garcia et al. 1988; Goodglick and Kane 1990; Iguchi and Kojo 1989; Kennedy et al. 1989; Shatos et al. 1987), and cell proliferation (Marsh and Mossman 1991), genotoxicity (Korkina et al. 1992; Lund and Aust 1991a, 1992). *In vitro* studies have also shown that these effects of asbestos are diminished by the addition of catalase and superoxide

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/75

dismutase (enzymes which catalyze the decomposition of reactive oxygen species) or free radical scavengers (ascorbic acid, bemitil, mannitol, salicylate, 5,5'-dimethyl-1-pyroline N-oxide, rutin, vitamin E) (Garcia et al. 1988; Goodglick et al. 1989; Goodglick and Kane 1990; Iguchi and Kojo 1989; Korkina et al. 1992; Lund and Aust 1992; Yano 1988). Cell membrane lipids have been shown to be peroxidized, resulting in membrane permeability in rat lung fibroblasts cultured with asbestos (Iguchi et al. 1993). Additional evidence supporting the involvement of reactive oxygen species in asbestos toxicity comes from *in vivo* studies. Activities of superoxide dismutase, glutathione peroxidase and catalase were significantly elevated in rats exposed to crocidolite by inhalation (Janssen et al. 1992). Levels of superoxide dismutase and plasma malondialdehyde (an indicator of lipid peroxidation) were significantly elevated in asbestos workers compared to controls (Kamal et al. 1989, 1992). Lipid peroxidation was noted in cells and fluid from bronchoalveolar lavage of rats after inhalation exposure to crocidolite (Petruska et al. 1991); endogenous peroxidase activity was noted in macrophages from pleural lavage of mice after intraperitoneal injection of crocidolite (Branchaud et al. 1993). Interestingly, uptake of asbestos fibers into epithelial cells is increased by reactive oxygen species (Hobson et al. 1990). Overall, the data collectively indicate that the production of reactive oxygen species is likely to be an important component of the mechanism of asbestos-induced toxicity.

Other Cell-Mediated Mechanisms. In addition to the release of active oxygen species, alveolar macrophages and other cells, including pleural mesothelial and lung cells, release a number of factors such as leukotrienes (Dubois et al. 1989; Garcia et al. 1989; Hayes et al. 1990), prostaglandins (Bissonnette et al. 1989, 1990; Garcia et al. 1988), interleukins (Boylan et al. 1992; Griffith et al. 1994; Perkins et al. 1993), and growth factors (Bermudez et al. 1990; Guillemin et al. 1991; Walker et al. 1992a) in response to asbestos exposure. These factors are mediators of a number of cellular reactions including inflammation, macrophage recruitment and cell proliferation that can result in a gradual loss of some epithelial cells and the deposition of collagen by fibroblasts (Davis et al. 1986c; Davis and Jones 1988). These data suggest that the effects of asbestos exposure may be mediated by stimulation of the autocrine (same cell) and paracrine (different cell) systems.

Role of Fiber Properties. A number of physical and chemical properties such as fiber size, durability, and iron content are important determinants of asbestos toxicity. The dependence of toxicity on these fiber properties is discussed below.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/76

Fiber size. The size (length and diameter) of an asbestos fiber appears to be one of the most important determinants of its toxicity. Fiber size dictates its respirability, deposition, and clearance from the lung. In general, only fibers less than 3 μm thick are capable of reaching lower airways (Timbrell 1982). Fibers longer than approximately 5–10 μm are generally cleared more slowly than fibers shorter than 5 μm (Bellmann et al. 1987; Morgan et al. 1978; Roggli et al. 1987a). The maximum fiber length that can be engulfed by a single macrophage is approximately 16–17 μm (Coin et al. 1992; Lippmann 1990). Asbestos-associated diseases are associated with fibers of different sizes. The strongest evidence for this conclusion comes from studies in animals, where chronic inhalation exposure to dust clouds rich in long fibers (those in excess of 5 μm) produces higher incidence of lung cancer than exposure to dust clouds rich in short fibers (mostly less than 5 μm) (Davis et al. 1986a; Davis and Jones 1988). Asbestosis is associated with fibers longer than 2 μm, mesothelioma with fibers longer than 5 μm, and lung cancer with fibers longer than 10 μm (Lippmann 1990). The dose-response relationships for the production of mesothelioma in rats intraperitoneally injected with amosite, chrysotile, and crocidolite was similar when doses were expressed in terms of the number of long (>4–8 μm), thin (<0.25 μm) fibers (Davis et al. 1991a; Stanton et al. 1981). In general, fiber width must be less than 0.1 μm for mesothelioma, but can be larger for asbestosis and lung cancer. Ultimately, the size of the fiber determines its residence time in the lung. Longer fibers remain in the lung or mesothelium, whereas shorter fibers are cleared, therefore the mechanism of action for long fibers is on-going.

Interestingly, Churg et al. (1989a, 1990) reported that fibrosis in asbestos workers exposed primarily to tremolite and chrysotile, or amosite was positively correlated with lung burden, but was negatively correlated with fiber size. An explanation for these observations is not readily apparent, but the data suggest that short fibers may be more important to some aspects of asbestos-mediated toxicity than previously thought. One possible explanation for this observation is that fiber size is also related to fiber surface area. As mentioned above, fiber surface properties are important to toxicity. Smaller thinner fibers have a greater surface area per unit mass than larger thicker fibers, thereby allowing for greater interaction with cell macromolecules. In addition, increased surface area may be important to providing more catalytically active iron sites (see below) for hydroxyl radical formation from reactive oxygen species.

Fiber durability. Numerous studies have indicated that some asbestos fibers, particularly chrysotile fibers, undergo fragmentation (latitudinal breakage) and/or splitting (longitudinal breakage) (Bellmann

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/77

et al. 1987; Churg et al. 1989a, 1989b; Coin et al. 1992; Cook et al. 1982; Fasske 1988; Roggli et al. 1987a). The importance of fiber size and surface area with respect to toxicity is discussed above. Both fragmentation and splitting serve to increase the number of fibers and fiber surface area, therefore toxicity of the resulting fibers is likely to increase as well. However, fiber fragmentation results in shorter fibers which are more readily cleared from the lungs by alveolar macrophages, whereas fiber splitting is likely to result in no change in fiber clearance. Clearly, the process of fiber splitting results in increased short-term and long-term toxicity. However, in the case of fiber fragmentation, whereas the short-term toxicity may be increased, the long-term toxicity is reduced. Differences in fiber durability may account for the differences observed in fiber potency between chrysotile and amphiboles.

Iron content. Iron is a redox-active metal and can catalyze the formation of hydroxyl radicals from superoxide and hydrogen peroxide (Haber-Weiss reaction). Evidence supporting the importance of iron in asbestos-induced toxicity include the success of iron chelators (deferoxamine) in inhibiting the production of reactive oxygen species and subsequent toxicity (Goodglick et al. 1989; Lund and Aust 1991b; Mahmood et al. 1993). Deferoxamine has also been shown to decrease the ability of asbestos fibers to induce DNA single-strand breaks (Chao and Aust 1994). Silicate fibers capable of producing pneumoniotic changes were also able to serve as Haber-Weiss catalysts, whereas silicate fibers that were nonpneumoniotic lacked this activity (Kennedy et al. 1989).

There are several possible sources of iron in the lung which may contribute to asbestos toxicity. One source of iron is the fiber itself. Crocidolite and amosite asbestos may contain levels of 26–36% iron by weight (Lund and Aust 1991a). A second source of iron is as a contaminant of asbestos. Iron containing minerals such as pyrite, magnetite, nemalite, and iron ore often occur as contaminants of asbestos and can be deposited in the lung along with asbestos fibers (Fontecave et al. 1990). A third possible source of iron is from within the exposed animal. Ferritin (an iron-containing protein) is present in macrophages and giant cells. Iron metabolism was found to be altered in these cells by the presence of poorly digestible fibers (Koerten et al. 1990a). Iron is also a component of the protein-coat covering asbestos bodies (Koerten et al. 1990a, 1990b). The extent to which each of these sources of iron contribute to the catalysis of hydroxyl radical formation *in vivo* is uncertain and warrants further investigation.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/78

2.4 RELEVANCE TO PUBLIC HEALTH

The general public may encounter low levels of asbestos by oral, inhalation, or dermal routes of exposure. Although some studies have indicated that oral exposure to asbestos may be linked to the development of gastrointestinal cancer, the majority of the data indicate that the inhalation of asbestos is the principal route of exposure of health concern to the general public. It is unlikely that dermal exposure to asbestos is of health concern to the general public. Studies in humans and animals indicate that inhalation exposure to asbestos fibers may lead to the development of pulmonary disease including asbestosis and/or lung cancer and mesothelioma of the pericardium or peritoneum. In general, noncancer effects to other tissues have not been detected, however, the development of extrathoracic cancers in some worker populations may be related to asbestos exposure. The toxicity of asbestos is dependent on exposure intensity, exposure duration, and a number of other factors regarding the physical and chemical properties of the fiber. Some fibers can be retained in the lung and pleura for long periods of time, therefore inhalation exposure to asbestos is generally regarded as cumulative. Asbestos-related lung disease (malignant and nonmalignant) has been reported to occur in humans following cumulative exposures of 2.3-450 f-yr/mL. Although asbestos-related effects have been primarily reported after chronic exposures to asbestos in an occupational setting, these effects have been described following relatively brief occupational exposures, as well. Exposures of this magnitude are usually not encountered by the general public.

Minimal Risk Levels for Asbestos

Inhalation MRLs. No MRLs were derived for inhalation exposure to asbestos for any duration. Although some studies have reported NOAEL values for asbestosis in humans occupationally exposed to asbestos for chronic durations (Berry et al. 1979; Sluis-Cremer 1991), these studies do not define the threshold exposure level with confidence. Data regarding the adverse health effects associated with acute- or intermediate-duration exposure to asbestos are lacking or are too limited to support the derivation of an MRL.

Oral MRLs. No MRLs were derived for oral exposure to asbestos for any duration. Studies in humans and animals indicate that significant adverse noncancer health effects are not likely to occur following ingestion of asbestos, and the oral route of exposure is generally not considered to be of public health concern for noncancer effects.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/79

Death. Exposure to asbestos, either by inhalation or ingestion, has not been observed to result in acute or short-term lethality in humans or animals. However, delayed mortality may occur as the result of asbestosis or cancer. These effects are discussed below.

Systemic Effects

Respiratory Effects. Deposition of asbestos fibers in the lung can lead to substantial fibrotic injury and may even cause death. This disease, termed asbestosis, results from a prolonged inflammatory response stimulated by the presence of the fibers in the lung. Alveolar macrophages, which normally phagocytize foreign bodies deposited in the lungs, seek to engulf the asbestos fibers and remove them. While short fibers may be cleared in this way, long fibers cannot be removed, and this results in an ongoing focal inflammatory response. With time, epithelial cells are lost and are replaced with fibrous tissue, resulting in a progressive loss of lung compliance and respiratory function. This can also result in increased resistance to blood flow through the lungs, leading to pulmonary hypertension and compensatory hypertrophy of the right heart (a condition termed cor pulmonale).

The level of asbestos exposure needed to cause asbestosis is not known precisely, but most human studies indicate that effects are likely to be minimal or absent following workplace exposures of 10 f-yr/mL or less (Berry et al. 1979; BOHS 1983; EPA 1986a; Wollmer et al. 1987). However, asbestosis has been noted in some studies of asbestos workers following cumulative exposures of 3.5–6 f-yr/mL (Armstrong et al. 1988; Sluis-Cremer 1991). An exposure of 10 f-yr/mL corresponds to 50 years of workplace exposure to an average asbestos concentration of 0.2 f/mL. Exposures at 10- to 100-times this level or even higher were at one time common in the workplace, and many asbestos workers have developed asbestosis. However, as discussed in Section 5.4.1, levels of asbestos in ambient air and in the indoor air of homes and schools are usually much lower than this, so asbestosis is unlikely to be of concern for most people in the general population (Hallenbeck 1988).

Another tissue that may be affected in humans exposed to asbestos in air is the pleura. The most common effect is formation of thickened fibrous areas called plaques, but diffuse thickening and fibrosis may also occur, as may areas of pleural effusions. An increased incidence of pleural plaques has been noted at relatively low cumulative exposures (approximately 0.12 f-yr/mL) (Boutin et al. 1989). Localized pleural plaques are not thought to be of significant health concern, although diffuse pleural thickening and circumscribed pleural plaques are associated with impairment of respiratory

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/80

function (Swartz et al. 1990). This may also be due to subclinical alveolitis or interstitial fibrosis not detected by routine chest radiograms. These plaques are normally very mild, but may be severe in a few cases (Churg 1986; Jarvholm et al. 1986; Miller et al. 1983).

A few studies have also reported an increased incidence of laryngitis in workers exposed to asbestos (Kambic et al. 1989; Parnes 1990). These data suggest that the upper airways may also be affected by asbestos exposure.

Cardiovascular Effects. As discussed above, fibrotic changes in the lung can lead to pulmonary hypertension and compensatory hypertrophy of the right heart (cor pulmonale). Constrictive pericarditis due to fibrosis has also been reported after asbestos exposure in several case reports (Davies et al. 1991).

Gastrointestinal Effects. A few studies suggest that fibers in the gastrointestinal tract may cause some histological or biochemical changes (Corpet et al. 1993; Delahunty and Hollander 1987; Jacobs et al. 1978a), but most studies indicate that there are no significant noncarcinogenic effects (NTP 1983, 1985, 1988, 1990a, 1990b, 1990c).

Dermal Effects. Dermal contact with asbestos fibers may result in the formation of warts or corns. However, this effect does not appear to be of pathological concern. Dermal/ocular effects are generally not associated with inhalation or oral exposure to asbestos.

Body Weight Effects. Although decreased body weight gain was noted in a single study involving oral exposure of rats to amosite (NTP 1990b), this effect has generally not been detected in a number of studies. Therefore, it is unlikely that this effect is of significant health concern to the general public.

Immunological and Lymphoreticular Effects. Studies of workers suffering from asbestos-related diseases such as asbestosis or mesothelioma indicate that the cellular immune system in such patients can be depressed (DeShazo et al. 1988; Gaumer et al. 1981; Lange et al. 1986; Lew et al. 1986). This is an effect of particular interest and concern since impaired immune surveillance may contribute to the increased incidence of cancer in asbestos-exposed people. Moreover, interindividual variation in the immune system might be an important determinant of why some people develop cancer or

Digitized by Google

asbestosis while others, with approximately equal exposures, do not. However, it is very difficult to distinguish whether the alterations in immune function noted in such studies are the cause or the result of asbestos-induced disease. The frequency of impaired cellular immunity in exposed workers without clinically-apparent disease is generally low (DeShazo et al. 1988; Kagan 1988; Selikoff and Lee 1978), although alterations in lymphocyte distribution have been noted in some studies (Sprince et al. 1991, 1992). This could mean that the immune changes do not occur until the disease develops (i.e., the changes are the result of the disease). Alternatively, it could mean that workers with immune systems that are not impaired by asbestos do not get serious disease, while workers whose immune systems are injured by asbestos do tend to develop disease (i.e., effects on the immune system are the cause of the disease). Available data do not allow a firm distinction between these alternatives at present, but the possible immunotoxic effects of asbestos are of clear concern.

Neurological Effects. Studies of humans and animals exposed to asbestos either by inhalation or by ingestion have not provided evidence that the nervous system is impaired by asbestos. Detailed studies have not been performed to search for subtle (preclinical) effects that might occur, but it is difficult to envision a mechanism that could lead to serious neurological injury.

Reproductive Effects. Studies have not been performed to determine if asbestos exposure can cause adverse reproductive effects in humans, but no injury to reproductive tissues and no impairment of fertility was detected in rats and Syrian hamsters exposed to high concentrations of asbestos in the diet preceding and during gestation (NTP 1983, 1985, 1988, 1990a, 1990b, 1990c). As noted earlier, it does not seem likely that a sufficient number of fibers could penetrate from the lungs or the gastrointestinal tract to cause any adverse effects on reproductive tissues.

Developmental Effects. Studies of possible adverse developmental effects from inhalation or oral exposure to asbestos have not been performed in humans. No obvious developmental effects were seen in a series of experiments in rats and Syrian hamsters exposed to high doses of asbestos in the diet during gestation, but such effects were not specifically investigated. Although asbestos fibers have been reported to cross the placenta (Cunningham and Pontefract 1974), the number of fibers that would be expected to reach the fetus via the maternal circulation is so low that developmental toxicity is unlikely to be of significant concern.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/82

Genotoxic Effects. The genotoxicity of asbestos has been investigated *in vivo*, as summarized in Table 2-5, and *in vitro*, as summarized in Table 2-6.

In vivo studies have reported increased frequencies of chromosomal aberrations and/or sister chromatid exchange in the peripheral blood lymphocyte of asbestos cement workers (Fatma et al. 1991; Hansteen et al. 1993; Rom et al. 1983), mesothelioma cells from patients (Pelin-Enlund et al. 1990; Tammilehto et al. 1992; Tiainen et al. 1989), leukocytes from asbestos workers (Marczynski et al. 1994), rat bone marrow cells and mesothelial cells (EPA 1988f; Fatma et al. 1992) and *Drosophila* (Osgood and Sterling 1991). Chromosomal aberrations generally included aneuploidy, partial or total chromosome loss, translocations, breaks, deletions, and rearrangements. Significant correlations were noted between lung fiber content and chromosomal abnormalities, particularly on chromosomes 1 and 4 (Tammilehto et al. 1992; Tiainen et al. 1989). Differences in fiber potency were noted for the induction of aneuploidy in drosophila (Osgood and Sterling 1991). In this assay system, chrysotile was more effective than amosite, whereas crocidolite and tremolite were relatively ineffective. Increases in the excretion of a DNA adduct, a marker of DNA damage, have been observed in the urine of asbestos workers (Tagesson et al. 1993).

Most tests for gene mutations have been negative, both in prokaryotes (Chamberlain and Tarmy 1977) and eukaryotes (Kelsey et al. 1986; Kenne et al. 1986; Reiss et al. 1982). However, a recent study reported an increased frequency of mutations in human-hamster hybrid cells exposed to chrysotile (Hei et al. 1992). These mutations consisted primarily of large deletions, which may not be detected as easily in other assay systems. Marginal evidence for weak mutagenicity of chrysotile, crocidolite, and amosite in Chinese hamster ovary (CHO) cells was reported by Huang (1979).

A large number of studies indicate that asbestos fibers can cause chromosomal aberrations in Chinese hamster ovary (CHO) and Syrian hamster embryo (SHE) cells. The aberrations include aneuploidy (usually polyploidy), fragmentation, breaks, rearrangements, gaps, dicentrics, inversions, and rings (Kelsey et al. 1986; Lavappa et al. 1975; Oshimura et al. 1986; Palekar et al. 1987; Sincock 1977; Sincock et al. 1982; Sincock and Seabright 1975). Aneuploidy was also induced in rat mesothelial cells *in vitro* using crocidolite (Yegles et al. 1993). Chromosomal aberrations have been produced by chrysotile in three studies using human cells (Korkina et al. 1992; Olofsson and Mark 1989; Valerio et al. 1980), but not in another (Sincock et al. 1982). The mechanism by which these clastogenic

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/83

TABLE 2-5. Genotoxicity of Asbestos *in Vivo*

Species (test system)	End point	Results	Reference	Form
Mammalian cells:				
Human blood leukocytes	Chromosomal aberration	+	Marczynski et al. 1944	NS
Human blood lymphocytes	Chromosomal aberration	+	Fatma et al. 1991	NS
Human blood lymphocytes	Sister chromatid exchange	(+)	Rom et al. 1983	NS
Human mesothelioma cells	Chromosomal aberration	+	Hansteen et al. 1993	NS
Human mesothelioma cells	Chromosomal aberration	+	Tiainen et al. 1989	CR,AM,AN
Human mesothelioma cells	Chromosomal aberration	+	Tammilehto et al. 1992	CR,AM,AN
Human mesothelioma cells	Chromosomal aberration	+	Pelin–Enlund et al. 1990	NS
Rat bone marrow cells	Chromosomal aberration	+	Fatma et al. 1992	CH
Rat mesothelioma cells	Chromosomal aberration	+	Palekar et al. 1988a	CH
Nonmammalian cells:				
Drosophila	Chromosomal aberration	+	Osgood and Sterling 1991	AM,CH
Drosophila	Chromosomal aberration	–	Osgood and Sterling 1991	CR,TR

+ = positive result; (+) = weakly positive; – = negative result; AM = amosite; AN = anthophyllite; CH = chrysotile; CR = crocidolite; NS = not specified; TR = tremolite

Toxicological Profile for Asbestos (1995)
ACL Doc 10942 · Page 84 of 233
Digitized by Google
Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/84

TABLE 2-6. Genotoxicity of Asbestos *in Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Form
Prokaryotic organisms:					
Salmonella typhimurium	Gene mutation	No data	–	Chamberlain and Tarmy 1977	CR,CH, AM,AN
Escherichia coli CP2	Gene mutation	No data	–	Chamberlain and Tarmy 1977	AN
Mammalian cells:					
Human-hamster hybrid cells	Gene mutation	No data	+	Hei et al. 1992	CH
Chinese hamster CHO cells	Gene mutation	No data	–	Kenne et al. 1986	CR
Chinese hamster CCL 39 cells	Gene mutation	No data	(+)	Huang 1979	CR,CH,AM
Rat liver epithelial cells	Gene mutation	No data	–	Reiss et al. 1982	CR,CH,AM
Human TK6 cells	Gene mutation	No data	–	Kelsey et al. 1986	CR
Chinese hamster CHO–K1 cells	Chromosomal aberrations	No data	+	Sincock 1977	CR,CH, AM,AN
Chinese hamster CHO–K1 cells	Chromosomal aberrations	No data	+	Sincock and Seabright 1975	CR
Chinese hamster CHO cells	Chromosomal aberrations	No data	+	Kenne et al. 1986	CR
Chinese hamster CHO cells	Chromosomal aberrations	No data	+	Kelsey et al. 1986	CR
Chinese hamster CHO cells	Chromosomal aberrations	No data	+	Sincock et al. 1982	CH
Chinese hamster V79 cells	Chromosomal aberrations	No data	+	Palekar et al. 1987, 1988a	CR,CH
Syrian hamster cells	Chromosomal aberrations	No data	+	Lavappa et al. 1975	CH
Syrian hamster cells	Chromosomal aberrations	No data	+	Oshimura et al. 1986	CH

Toxicological Profile for Asbestos (1995)
ACL Doc 10942 · Page 85 of 233
Digitized by Google
Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/85

TABLE 2-6. Genotoxicity of Asbestos *in Vitro* (*continued*)

Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Form
Human mesothelial cells	Chromosomal aberrations	No data	+	Olofsson and Mark 1989	CR,CH,AM
Human lymphocytes	Chromosomal aberrations	No data	+	Valerio et al. 1980	CH
Human fibroblasts	Chromosomal aberrations	No data	–	Sincock et al. 1982	CH
Human lymphoblastoid cells	Chromosomal aberrations	No data	–	Sincock et al. 1982	CH
Human blood lymphocytes	Chromosomal aberrations	No data	+	Korkina et al. 1992	CH
Human lymphocytes	Chromosomal aberrations	No data	+	Emerit et al. 1991	CH
Human fibroblasts	Sister chromatid exchange	No data	–	Casey 1983	NS
Human lymphoblastoid cells	Sister chromatid exchange	No data	–	Casey 1983	NS
Chinese hamster CHO cells	Sister chromatid exchange	No data	–	Kelsey et al. 1986	CR
Chinese hamster CHO cells	Sister chromatid exchange	No data	–	Casey 1983	NS
Chinese hamster CHO cells	Sister chromatid exchange	No data	+	Livingston et al. 1980	CR,CH,AM
Chinese hamster CHO cells	Sister chromatid exchange	No data	+	Babu et al. 1980	CH
Chinese hamster V79–4 cells	Sister chromatid exchange	No data	–	Price-Jones et al. 1980	CR
Chinese hamster V79 cells	Sister chromatid exchange	No data	-	Lu et al. 1979	CH
Chinese hamster V79 cells	Micronucleus assay	No data	+	Lu et al. 1979	CH
Rat mesothelial cells	Sister chromatid exchange	No data	–	Kaplan et al. 1980	NS
Rat embryo cells	DNA strand breakage	No data	+	Libbus et al. 1989	CR
Rat mesothelial cells	Unscheduled DNA synthesis	No data	+	Dong et al. 1944	CH,CR
Rat mesothelial cells	Aneuploidy	No data	+	Yegles et al. 1993	CR

Toxicological Profile for Asbestos (1995)
ACL Doc 10942 · Page 86 of 233
Digitized by Google
Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/86

TABLE 2-6. Genotoxicity of Asbestos *in Vitro* (*continued*)

Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Form
Hamster tracheal epithelial	DNA strand breakage	No data	–	Mossman et al. 1983b	CR,CH
Human bronchial cells	DNA strand breakage	No data	–	Lechner et al. 1983	CR,CH,AM
Human fibroblasts	DNA strand breakage	No data	–	Hart et al. 1979	NS
Calf thymus DNA	DNA damage	No data	+	Adachi et al. 1992a	CR,CH,AM
Syrian hamster embryo cells	Cell transformation	No data	+	Hesterberg and Barrett 1984	CH,CR
Syrian hamster embryo cells	Cell transformation	No data	–	DiPaolo et al. 1983	AM,AN, CH,CR
Mouse fibroblasts	Cell transformation	No data	–	Brown et al. 1983	CR,AM

– = negative result; + = positive result; (+) = weakly positive result; AM = amosite; AN = anthophyllite; CH = chrysotile; CHO = Chinese hamster ovary; CR = crocidolite; DNA = deoxyribonucleic acid; NS = not specified

Toxicological Profile for Asbestos (1995)
ACL Doc 10942 · Page 87 of 233
Digitized by Google
Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/87

effects occur may be related to physical interference with chromosome segregation by the asbestos fiber during the mitotic process (Barrett et al. 1989; Malorni et al. 1990; Palekar et al. 1987).

Results of tests for other genotoxic effects (increased sister chromatid exchange, DNA strand breaks, DNA hydrolysis, cell transformations) have been largely negative (Brown et al. 1983; Casey 1983; DiPaolo et al. 1983; EPA 1979a; Kelsey et al. 1986; Lechner et al. 1983; Lu et al. 1994; Mahmood et al. 1993; Mossman et al. 1983b; Price-Jones et al. 1980), although positive results have been noted in a few cases (Babu et al. 1980; Hesterberg and Barrett 1984; Livingston et al. 1980). For example, Adachi et al. (1992a) reported DNA damage as indicated by the formation of 8-hydroxy-2'-deoxyguanosine when fibers were incubated with calf thymus DNA and hydrogen peroxide. DNA strand breaks were noted in rat embryo cells exposed to crocidolite (Osgood and Sterling 1991). Blood cultures of individuals exposed to ultrafiltrates of media from human lymphocyte cultures that were treated with chrysotile showed increased ($p<0.001$) chromosomal aberrations (Emerit et al. 1991). Thus it appeared that a clastogenic agent was produced in treated cultures. These effects are equivocal, however, as there was no dose response. Chrysotile induced increased ($p<0.01$) numbers of cells with micronuclei and increased numbers of cells with two or more nuclei in Chinese hamster lung (V79) cells (Lu et al. 1994). Increases in unscheduled DNA synthesis have been reported using rat pleural mesothelial cells after exposure to crocidolite and chrysotile (Dong et al. 1994). Of special interest, the cell transformation reported by Hesterberg and Barrett (1984) was abolished when the fibers were milled to a short length.

These observations, especially the findings of cytogenotoxicity, are consistent with the greater observed carcinogenic potential of long asbestos fibers, and support possible mechanisms by which asbestos might be acting.

Cancer. There is no doubt that inhalation of asbestos can lead to increased risk of lung cancer and mesothelioma. This has been conclusively demonstrated in numerous studies of occupationally exposed workers, and has been confirmed in a number of animal experiments. For lung cancer, the magnitude of the risk appears to be a complex function of a number of parameters, most important of which are: (1) the level and the duration of exposure; (2) the time since exposure occurred; (3) the age at which exposure occurred; (4) the tobacco-smoking history of the exposed person; and (5) the type and size distribution of the asbestos fibers.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/88

The last parameter is of special practical importance, since the variability in potency between fibers means that cancer risk from asbestos exposure may vary widely from location to location. Some of this variation may be attributable to differences between the mineral types, but fiber size (length and thickness) appear to be of prime importance. There is strong evidence from inhalation studies (Davis et al. 1980a; Davis and Jones 1988), intrathoracic and intraperitoneal dosing studies (Bolton et al. 1982b; Davis et al. 1985, 1986a; Davis and Jones 1988; Jaurand et al. 1987; Stanton et al. 1981; Wagner et al. 1973, 1980a), and *in vitro* studies (Hesterberg and Barrett 1984), that long fibers are more carcinogenic than short fibers. However, this should not be construed to mean that shorter fibers are totally without carcinogenic potency. The relation between fiber size and carcinogenicity may vary between lung cancer and mesothelioma (Lippmann 1990), but this is not yet clear.

There is some evidence from animal studies that asbestos-induced lung cancer stems from regions in the lung with advanced fibrosis (asbestosis) (Davis and Cowie 1990); although lung cancer with chrysotile was also produced at fiber concentrations which did not lead to fibrosis (Reeves et al. 1974). Possibly, if a threshold exists for asbestosis, it is plausible a threshold might also exist for lung cancer. However, this is uncertain and warrants further investigation.

Because of the large number of variables, it is difficult to make reliable predictions of the magnitude of the cancer risk that may result from exposures of the general population to asbestos levels that are likely to be encountered outside the workplace. Although there is considerable uncertainty in the estimates, EPA calculated that lifetime exposure to asbestos dust containing 0.0001 fiber greater than 5 μm in length per mL of air could result in about 2–4 excess cancer deaths (lung cancer plus mesothelioma) per 100,000 people (EPA 1986a). Based on available exposure information, the Health Effects Institute estimated the lifetime cancer risk (lung cancer and mesothelioma combined) for various exposure scenarios (HEI 1991). (See Appendix D).

While lung cancer and mesothelioma are generally associated with chronic exposure to asbestos, there are several studies which indicate that short-term exposures are also of concern. For example, it has been noted that workers exposed to asbestos for only 1–12 months had an increased risk of developing lung cancer a number of years later (Seidman et al. 1979, 1986; Jones et al. 1980a). In animals, mesotheliomas developed in two rats exposed to amosite or crocidolite for only 1 day (Wagner et al. 1974). These data are not extensive enough to define the dose- or time-dependency of health risks

Digitized by Google

from short-term exposure to asbestos, but the data do indicate that short-term exposures should not be disregarded.

Asbestos exposure is also suspected of increasing the risk of cancer in the gastrointestinal tract and at other extrathoracic sites. However, this is a controversial subject. Data supporting this view have been derived mainly from three types of studies. First, workers exposed to asbestos by inhalation are noted to have small excesses in death rates from gastrointestinal cancer (Armstrong et al. 1988; Enterline et al. 1987; Neugut et al. 1991; Newhouse and Berry 1979; Raffn et al. 1989; Seidman et al. 1979, 1986). This is presumed to be due to the transfer of inhaled fibers from the lung to the gastrointestinal tract. Second, some studies suggest that populations with high levels of asbestos fibers in drinking water may have increased risk of gastrointestinal cancers (Andersen et al. 1993; Conforti et al. 1981; Howe et al. 1989; Kanarek et al. 1980; Levy et al. 1976; Polissar et al. 1982, 1984; Sigurdson et al. 1981; Toft et al. 1981; Wigle 1977). Third, one lifetime feeding study in rats indicated that intermediate length chrysotile can increase the frequency of benign intestinal tumors in male rats (NTP 1985).

However, none of these lines of evidence are entirely convincing. The excess gastrointestinal mortality noted in workers and in populations exposed through drinking water were usually quite small (from an epidemiological point of view) or the follow-up period was of insufficient duration. Also, it is very difficult to determine whether the excesses are due to asbestos or to other factors (exposure to other chemicals, misdiagnosis, dietary factors, alcohol intake, etc). With regard to the one positive tumorigenicity finding in animals, this must be balanced against the fact that the tumors were both infrequent and benign, and that no significant excess of gastrointestinal tumors was noted in a number of other animal studies.

Several government office and regulatory agencies have considered the evidence regarding the overall carcinogenicity of asbestos. The Department of Health and Human Services has determined that asbestos is a known carcinogen (NTP 1991). The EPA has determined that asbestos is a human carcinogen (Group A) (IRIS 1993). In addition, the International Agency for Research on Cancer (IARC) has determined that asbestos is carcinogenic to humans (Group 1) (IARC 1987). These conclusions are based primarily on the evidence that asbestos causes thoracic tumors. A number of researchers and regulatory groups have reviewed the weight of evidence on the issue of cancer at extrathoracic sites after inhalation exposure to asbestos in the workplace, and have reached differing

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/90

conclusions. For example, some believe that the data constitute strong or substantial evidence that inhalation of asbestos in the workplace does increase risk of extrathoracic cancer (EPA 1986a, 1989c; OSHA 1986; Frumkin and Berlin 1988; Smith et al. 1989, 1990). In contrast, others feel the evidence is not adequate to reach a firm conclusion (Dupre et al. 1984; Edelman 1989; Lemen et al. 1987; Morgan et al. 1985; NRC 1984; WHO 1986), and some believe that the apparent increases in gastrointestinal cancer are probably due to other factors (misdiagnosis, diet, alcohol, disease history, etc.) and cannot be attributed to asbestos (Doll 1989; Doll and Peto 1985; Edelman 1988a; Garabrant et al. 1992; Mossman et al. 1990a). As these conflicting analyses illustrate, when epidemiological studies provide limited evidence for a small increase in cancer risk at a site, it is difficult to distinguish between two alternative interpretations: (1) the risk is real, and inconsistencies in the data are due to limitations in the sensitivity and accuracy of epidemiological studies; or (2) the risk is not real, and the apparent effects are attributable to other causes or reasons. In view of the limitations and uncertainties in the data available, it does not appear that a definitive distinction can currently be drawn between these alternatives. However, it seems only prudent to consider increased risk of gastrointestinal cancer an effect of concern. This conclusion is similar to that reached by a working group for the U.S. Department of Health and Human Services (Lemen et al. 1987).

2.5 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s), or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/91

can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to asbestos are discussed in Section 2.5.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by asbestos are discussed in Section 2.5.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, "Populations That Are Unusually Susceptible."

2.5.1 Biomarkers Used to Identify or Quantify Exposure to Asbestos

At present, there are no routine methods used to identify or quantify exposure to asbestos in living persons except for measuring asbestos fiber concentrations in air or water. Chest x-rays are useful in identifying early signs of asbestos-related lung effects after inhalation exposure, but asbestos fibers are far too small to be seen by this approach. Another approach is to collect a sample of cells from the lung by bronchoalveolar lavage, and to examine the cells (mainly macrophages) for the presence of asbestos fibers or asbestos bodies (Barbers and Abraham 1989; De Vuyst et al. 1982; Johnson et al. 1988). This method is minimally invasive, and offers a convenient means for confirming that asbestos exposure has occurred. However, it is not possible to use the data to quantify exposure or predict any likely health effects.

Asbestos fibers can also be measured in urine (see Section 6.1), and limited data indicate that above average exposures in the workplace (Finn and Hallenbeck 1984) and through drinking water (Cook

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/92

and Olson 1979) can be detected by this means. However, only a tiny fraction of inhaled or ingested fibers are excreted in the urine, and the quantitative relationship between exposure and urinary fiber concentration appears quite variable. Moreover, urinary levels presumably are mainly a reflection only of recent exposures. Thus, urinary analysis for fibers has not been established or validated as a reliable means of biomonitoring for chronic asbestos exposure.

Most studies rely on analysis of tissue samples taken at autopsy to quantify asbestos exposure. These studies indicate, as might be anticipated, that lung burdens of asbestos are generally higher in persons with asbestos-related disease than in persons without disease. However, the quantitative relationship between lung burden and disease is difficult to define, due to differences between studies in level and duration of exposure, type of asbestos, and latency since exposure. This variability is compounded by differences between laboratories in the methods used to measure tissue burdens (Gylseth et al. 1985). For example, asbestosis was not clinically significant in naval dockyard workers at lung burdens up to around $25x10^6$ fibers per gram dry lung tissue (f/g) (measured by electron microscopy), but that severe lung disease was common in workers with levels of $50x10^6$ to $350x10^6$ f/g (Wagner et al. 1986). In contrast, within the lung of a single person, fibrosis was minimal in regions where fiber burdens ranged from 100 to $200x10^6$ f/g dry lung tissue (Gylseth and Skaug 1986).

The high fiber content in lung of workers with asbestosis is usually due almost entirely to an increase in amphibole content (crocidolite and amosite), while chrysotile levels are often not much different from persons without apparent disease (Wagner et al. 1982b). This observation is sometimes taken to indicate that it is the amphiboles which are the principal cause of the asbestosis. For example, the lung burden of asbestos was compared in people with asbestosis who had either been exposed in the chrysotile industry (low amphibole exposure) or in the shipyard and insulation industry (higher amphibole exposure) (Churg and Wright 1989). The mean tissue burden was 330 f/g in asbestosis cases who had been exposed to chrysotile, but was only 30 f/g in asbestosis cases from the shipyard and insulation industries. While this suggests that amphiboles may be more potent than chrysotile in inducing asbestosis, interpretation of this data is complicated by the preferential breakdown or dissolution of chrysotile fibers in the lung, with little or no loss of amphibole fibers (see Section 2.3.3). Consequently, the relationship between asbestosis and lung burden is difficult to establish.

Similar dose-response data correlating asbestos lung burden and disease are not available for respiratory tumors, but several studies confirm that lung burdens of asbestos are higher in cancer cases

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/93

than controls. For example, the distribution of fiber levels (measured by phase contrast microscopy) was compared in a group of mesothelioma patients, and it was found that levels ranged from around $0.02x10^6$ to $20x10^6$ f/g of dried lung tissue, in comparison to controls where levels ranged from $0.005x10^6$ to $0.05x10^6$ f/g (Whitwell et al. 1977). Similarly, the asbestos tissue burden ranged from around $5x10^6$ to $60x10^6$ f/g in mesothelioma cases, but rarely exceeded $1x10^6$ f/g in controls (Berry and Newhouse 1983). As noted above, the higher tissue levels are due mostly to amphiboles rather than chrysotile (Jones et al. 1980b), but this does not necessarily imply that the amphiboles are the chief cause of the disease. Interpretation of these data is also complicated by the fact the fiber retention in lung parenchyma does not correlate well with pleural retention, with differences in both fiber level and type (Sebastien et al. 1980a).

2.5.2 Biomarkers Used to Characterize Effects Caused by Asbestos

The most common means of characterizing the effects of inhalation exposure to asbestos in living persons is the chest x-ray (e.g., Anton-Culver et al. 1989; Jones et al. 1988b). This method is capable of detecting both pleural and parenchymal abnormalities, but sensitivity and specificity are limited (Gefter and Conant 1988). In particular, x-ray changes are rarely detectable until after some degree of physiological impairment has occurred (Aberle et al. 1988a). A more sensitive method is gallium-67 lung scanning, which often can detect asbestos-induced inflammation and other lung abnormalities prior to their detection by x-ray (Bisson et al. 1987; Hayes et al. 1989; Klaas 1993). Computerized tomography (CT) and high-resolution computed tomography (HRCT) may also be superior to conventional radiological examination in some cases (Aberle et al. 1988a, 1988b; Akira et al. 1991; Al Jarad et al. 1993; Friedman et al. 1988; Gamsu et al. 1989; Klaas 1993; Oksa et al. 1994; Sluis-Cremer et al. 1984).

Examination of cells and cellular factors present in lung lavage fluid and blood serum may be used to indicate early changes associated with asbestos-induced fibrosis. A number of human studies have shown that the differential cell count (Hayes et al. 1989; Rom 1991) and levels of fibronectin (Begin et al. 1986; Rom 1991), procollagen III (Begin et al. 1986), and hyaluronic acid (Cantin et al. 1992) are elevated in the lung lavage fluid of asbestos workers as compared to nonexposed controls. A significant elevation of the amino-terminal peptide of procollagen III (PIIINP) was found in the serum of asbestos workers when compared to controls (Cavalleri et al. 1991). Also, excretion of the

Digitized by Google

oxidative DNA adduct, 8-hydroxydeoxyguanosine, has been shown to be increased ($p<0.01$) in the urine of asbestos workers and therefore might be used to indicate DNA damage (Tagesson et al. 1993).

Another approach often used for evaluating the effects of asbestos inhalation is quantitative analysis of lung function (e.g., Ernst et al. 1989; Finkelstein 1986). The specific end points of greatest value are FEV_1 (forced expiratory volume in one second) and FVC (forced vital capacity), since these are most affected by fibrotic changes in the lung. Changes in biphasic lung carbon monoxide diffusing capacity may be better suited for detecting early decreases in lung function due to asbestos exposure (Dujic et al. 1992). Most studies find that respiratory changes parallel radiological changes (e.g., Britton 1982; Cordier et al. 1987; Dujic et al. 1992), although several studies report measurable respiratory decrements in the absence of radiological changes (Weill et al. 1975; Ohlson et al. 1984).

It is important to stress that neither radiological, lung lavage, nor respiratory tests are specific for asbestos-induced lung injury. Consequently, other causes of lung injury (e.g., smoking, occupational exposures to other chemicals, lung infections) must also be considered when such changes are detected in an individual.

2.6 INTERACTIONS WITH OTHER SUBSTANCES

In epidemiological studies, an interaction between two risk factors is generally defined as a greater-than-additive risk when both risk factors are present (Steenland and Thun 1986). With respect to lung cancer, some studies indicate that the interaction between asbestos and smoking is greater than additive (DHHS 1985; Selikoff et al. 1968). The most dramatic data include an age-standardized mortality ratio of 5.17 for nonsmoking asbestos workers, 10.85 for smokers not exposed to asbestos, and 53.2 for asbestos-exposed smokers (Hammond et al. 1979). The risk from combined exposure clearly exceeds the predicted risk based on additivity (15.0), and the data suggest a multiplicative interaction. Other studies have found that smoking increases the risk of lung cancer from asbestos exposure more than predicted by additivity, but often less than predicted by a multiplicative model (McDonald et al. 1980; Saracci 1987; Selikoff et al. 1980; Thomas and Whittemore 1988).

The mechanism by which smoking and asbestos interact to increase risk of lung cancer is not known, but several hypotheses (which are not mutually exclusive) have been suggested. One possible mechanism is a smoking-induced decrease in clearance of fibers from the lung, perhaps by interference

Digitized by Google

with ciliary action or macrophage activity (Plowman 1982), leading in turn to increased penetration of the respiratory epithelium by fibers (Hobson et al. 1988; McFadden et al. 1986). In guinea pigs, clearance of short chrysotile fibers was decreased by 30% after 1 month in those co-exposed to cigarette smoke compared to animals exposed to chrysotile alone (Churg et al. 1992). Similarly, exposure of rats to ozone resulted in increased retention of asbestos fibers (Pinkerton et al. 1989). Another proposal is that asbestos fibers (either in air or in the lung) may adsorb carcinogenic substances present in smoke, thereby increasing levels of these substances in the lung (Menard et al. 1986; Mossman et al. 1983a). Asbestos fibers may also catalyze the transformation of other compounds to reactive intermediates (Graceffa and Weitzman 1987). Finally, on the assumption that cancer is a multistep process, asbestos and smoking could interact by affecting different steps in the process. An interaction of this sort between dimethylbenzanthracene and asbestos has been demonstrated in a two-stage carcinogenicity assay *in vitro* (Topping and Nettesheim 1980), with asbestos displaying effects characteristic of a promoter. Asbestos and chemical carcinogens may act synergistically to cause cell proliferation and metaplasia in cells of the lung, an event critical to tumor production (Mossman et al. 1984).

There is also good evidence that smoking increases the risk of asbestosis. For example, the death rate from asbestosis was found to be 2.8 times higher in asbestos-exposed smokers than in asbestos-exposed nonsmokers (Hammond et al. 1979; Selikoff et al. 1980). Evidence of increased frequency of clinical signs of asbestosis (rales, dyspnea, crepitations) in smoking versus nonsmoking workers has been observed (Berry et al. 1979; Lerman et al. 1986). A synergistic effect of smoking on the occurrence of parenchymal opacities in the lungs of asbestos workers (Blanc et al. 1988). On the other hand, several researchers have reported that the effects of asbestos and smoking on these signs are additive rather than synergistic (Begin et al. 1987b; Hnizdo and Sluis-Cremer 1988; Weiss 1984).

In contrast to the interactive effect of smoking on lung cancer and fibrosis, smoking does not appear to increase the risk of mesothelioma (Berry et al. 1985; Hammond et al. 1979; Selikoff et al. 1980). However, studies in humans suggest that asbestos may act as a tumor promoter in mesothelioma (Browne 1983).

Data are not available on interactive effects between asbestos and other substances after oral exposure of humans. In animals, chronic oral exposure to asbestos caused no convincing increase in tumors in animals that had been treated with a known intestinal carcinogen (dimethylhydrazine) compared to the

Digitized by Google

incidence in animals treated with dimethylhydrazine alone (NTP 1983, 1985, 1990b). However, these studies were judged to be inconclusive, since the doses of dimethylhydrazine employed gave either too few or too many gastrointestinal tumors to allow easy detection of an effect by asbestos (NTP 1983, 1990b). Gamma radiation, in combination with asbestos fibers, has been shown to synergistically enhance the oncogenic transformation of mouse embryo fibroblasts (Hei et al. 1984).

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to asbestos than will most persons exposed to the same level of asbestos in the environment. Reasons include genetic make-up, developmental stage, age, health and nutritional status (including dietary habits that may increase susceptibility, such as inconsistent diets or nutritional deficiencies), and substance exposure history (including smoking). These parameters result in decreased function of the detoxification and excretory processes (mainly hepatic, renal, and respiratory) or the pre-existing compromised function of target organs (including effects or clearance rates and any resulting end-product metabolites). For these reasons we expect the elderly with declining organ function and the youngest of the population with immature and developing organs will generally be more vulnerable to toxic substances than healthy adults. Populations who are at greater risk due to their unusually high exposure are discussed in Section 5.6, "Populations With Potentially High Exposure."

Studies of workers who are exposed to asbestos in workplace air indicate that not all people who are exposed to equal doses of asbestos are equally affected. As discussed above (Section 2.7), it is likely that one main source of this variability in susceptibility between people is smoking history or the degree of exposure to other risk factors with which asbestos interacts. Another important factor is age, with people who are exposed in their youth being more likely to develop asbestos-related disease than people exposed later in life. This is probably not because young people are inherently more susceptible to asbestos than older people, but because of the long latency period (10–40 years) typically associated with asbestosis and cancer.

2.8 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to asbestos. However, because some of the treatments discussed may be experimental and

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/97

unproven, this section should not be used as a guide for treatment of exposures to asbestos. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

2.8.1 Reducing Peak Absorption Following Exposure

No studies were located regarding the reduction of absorption in humans or animals after exposure to asbestos.

2.8.2 Reducing Body Burden

No studies were located which specifically address the reduction of body burden in humans or animals after exposure to asbestos. However, there are some approaches which may prove useful in reducing the burden of fibers in the lungs after inhalation exposure to asbestos. Lung lavage fluid is often analyzed for the presence of asbestos fibers and/or asbestos bodies. In this way, lavage of the lung may remove some fibers from the lung, however the extent to which this occurs is uncertain. In addition, longer fibers which can become lodged within the tissue and are of greater health concern would less likely be removed by this method than shorter fibers.

2.8.3 Interfering with the Mechanism of Action for Toxic Effects

Although much research has been done recently, the mechanism of action for asbestos has yet to be clearly determined. Research to date indicates the involvement of reactive oxygen species and iron in the mechanism of action for asbestos. Data supporting methods for interfering with these components of the mechanism of action for asbestos are discussed below.

Free radical scavengers may prove to be successful in interfering with the mechanism of action for asbestos. A single *in vivo* study reported a dose-dependent inhibition of lung injury, inflammation, and asbestosis in rats treated with polyethylene glycol-conjugated catalase (Mossman et al. 1990b). Numerous *in vitro* studies have indicated that free radical scavengers such as ascorbic acid, bemitil, mannitol, salicylate, 5,5'-dimethyl-1-pyroline N-oxide, rutin, vitamin E, and free-radical scavenging enzymes are successful in diminishing asbestos-induced lipid peroxidation, cytotoxicity, cell proliferation, and genotoxicity (Fontecave et al. 1990; Garcia et al. 1988; Goodglick et al. 1989;

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/98

Goodglick and Kane 1990; Iguchi and Kojo 1989; Kennedy et al. 1989; Korkina et al. 1992; Lund and Aust 1991a, 1992; Marsh and Mossman 1991; Shatos et al. 1987; Yano 1988). Currently, a number of on-going studies are investigating the efficacy of beta-carotene and retinal in preventing or diminishing asbestos-related disease in asbestos workers (see Section 2.9.3).

A number of studies have implicated iron in the production of hydroxyl radicals. Iron chelators such as deferoxamine have been successful at inhibiting the production hydroxyl radicals (Goodglick et al. 1989; Lund and Aust 1991b; Weitzman and Graceffa 1984). By binding to asbestos fibers, deferoxamine blocks their ability to participate in redox reactions that produce hydroxyl radicals. A study in mice demonstrated the binding of desferroxamine to crocidolite fibers *in vivo*, suggesting that it could be used as a possible treatment (Weitzman et al. 1988). It should be noted that other iron chelators such as citrate, EDTA, or nitriloacetate actually lead to an increased production of hydroxyl radicals (Lund and Aust 1991b, 1992). Although these chelators are successful in binding iron, they do not prevent iron from participating in the redox reaction. By mobilizing iron from the fiber, these chelators may actually make the iron more redox-active.

2.9 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of asbestos is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of asbestos.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

Digitized by Google

2.9.1 Existing Information on Health Effects of Asbestos

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to asbestos are summarized in Figure 2-5. The purpose of this figure is to illustrate the existing information concerning the health effects of asbestos. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs." A data need, as defined in ATSDR's Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

There have been a very large number of studies, both in humans and animals, focusing on the major health effects associated with inhalation exposure (asbestosis, lung cancer, and mesothelioma) and oral exposure (gastrointestinal cancer). There have also been a number of studies on immune system changes in humans exposed by inhalation, but this has not been investigated in people exposed orally. There are few formal studies focusing on other possible effects of asbestos. However, because so few fibers are able to penetrate from the lungs or the gastrointestinal tract into the body, there is little reason to believe that other effects are of major concern.

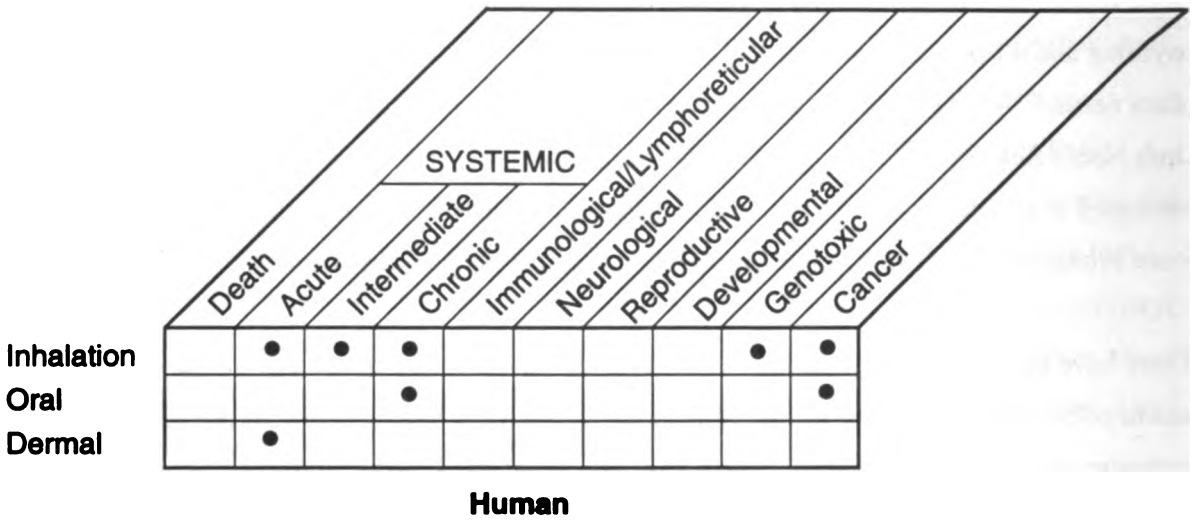
2.9.2 Identification of Data Needs

Acute-Duration Exposure. Only a few inhalation or oral studies have sought to determine the effects of single exposures to asbestos. There are no human data on noncancer effects after acute exposures, and no acute-duration MRLs have been derived. However, there is one study in animals in which a single exposure produced fibrosis of the lung (McGavran et al. 1989), and one study which suggests that a single high inhalation exposure might cause cancer (Wagner et al. 1974). This is an important point, since many people might have one or two significant exposures to asbestos during their life. Additional studies on the long-term effects of acute inhalation exposure would be valuable to determine if this is of concern, and if it is, to define the dose-response relationship for cancer, fibrosis, and other biologic outcomes. Although oral exposure to asbestos is unlikely, acute oral exposure to asbestos in rats and mice have been shown to cause aberrant crypt foci, putative precursor

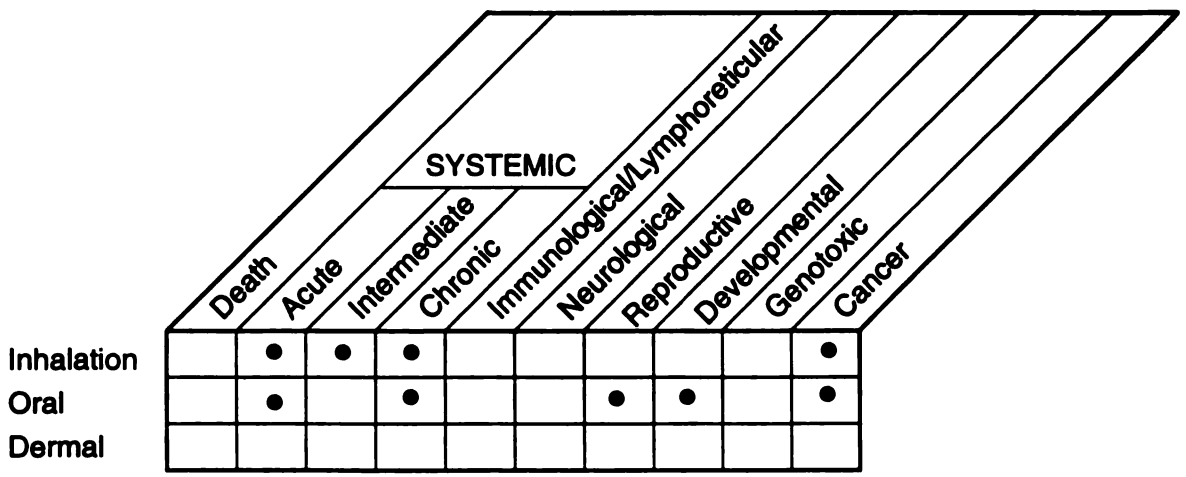
Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/100

FIGURE 2-5. Existing Information on Health Effects of Asbestos



Human



Animal

● Existing Studies

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/101

lesions of colon cancer (Corpet et al. 1993). Further studies to investigate the development of these lesions, especially after the ingestion of asbestos in drinking water, would be useful.

Intermediate-Duration Exposure. Several studies (Ehrlich et al. 1992; Jones et al. 1980a; Seidman et al. 1979, 1986) in humans suggest that workers exposed to asbestos for periods of 1–12 months may subsequently develop asbestos-associated pleural changes or lung disease. However, these studies do not provide sufficient dose-response data to derive a reliable intermediate-duration inhalation MRL. A single study in animals reported fibrosis after intermediate exposure to asbestos (Donaldson et al. 1988a). Further inhalation studies in animals to investigate the fibrogenic and carcinogenic risks from short-term exposures would be helpful in assessing the risks in humans who may only be exposed for a limited period. Several intermediate-duration oral studies in animals have been performed, and these have not revealed any evidence of noncancer effects (NTP 1983, 1985, 1988, 1990a, 1990b, 1990c; Schneider and Maurer 1977). In the absence of data to suggest that a significant noncancer risk exists after oral exposure, it does not seem that additional studies of this sort are critical.

Chronic-Duration Exposure and Cancer. There are numerous studies in animals and humans which describe the effects of chronic inhalation exposure on the lung and pleura (Armstrong et al. 1988; Boutin et al. 1989; Berry et al. 1979; deKlerk et al. 1991; McDonald et al. 1980; Sluis-Cremer 1991). These studies provide estimates of the cumulative doses that lead to asbestosis, and pleural plaques but there is considerable uncertainty in the NOAEL values. Therefore, no chronic inhalation MRL was derived. Further studies on the occurrence of noncancer effects (radiological changes, altered respiratory function) in exposed humans would be valuable in clarifying these dose and time relationships, even though the risk of cancer will typically be of chief concern after chronic inhalation exposure.

The carcinogenic effects of chronic inhalation exposure to asbestos have been amply demonstrated, both in humans (Armstrong et al. 1988; deKlerk et al. 1989; Enterline et al. 1987; McDonald et al. 1984) and animals (Davis et al. 1980a, 1980b; Davis and Jones 1988; Wagner et al. 1980a). However, a number of important issues remain to be resolved. In particular, it would be useful to know whether there are maximum and/or minimum lengths and diameters beyond which fibers lack carcinogenic effects, or whether there are continuous gradients of carcinogenicity as a function of fiber length and diameter. In this regard, additional research on the mechanism of carcinogenicity is more likely to be

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/102

useful than additional epidemiological or animal studies, since it is very difficult to prove the presence or absence of a low-dose cancer threshold by direct observation. This would include studies on the molecular and cellular mechanisms by which asbestos causes lung cancer and mesothelioma. With regard to lung cancer, asbestos appears to act mainly as a promoter, suggesting that there might be a threshold with respect to dose. If true, this would be of considerable importance, since most environmental exposures are at very low doses. The results of studies focusing on whether or not there are length, diameter, or dose thresholds could lead to important refinements in risk assessment models, which currently assume that risk is linearly related to the number of fibers greater than 5 μm in length (Davis and Jones 1988; Davis et al. 1986a).

Along these same lines, further work would be helpful in defining other fiber characteristics that are important determinants of carcinogenicity. It is suspected, for example, that crocidolite and other amphiboles are more likely to cause mesothelioma than chrysotile, but it is not certain if this is attributable to differences in fiber length alone or to differences in chemical properties (e.g., fiber morphometry, iron content, durability in biological fluids and tissues). Consequently, comparative studies of the relative carcinogenicity of different mineral preparations, carefully matched with regard to fiber size distribution, would be valuable.

Studies in animals have indicated a relationship between lung fibrosis and lung cancer (Davis and Cowie 1990). Additional animal studies which seek to determine if increased mitotic activity secondary to fibrotic injury is required for tumorigenesis might provide insight into the possibility of a threshold for lung cancer.

Another important area where further research would be valuable is the synergistic interaction between asbestos and other risk factors for lung cancer, especially smoking. Particularly helpful would be further studies on the mechanism of such interactions, since this could help improve current means of predicting the consequences of exposures to substances such as cigarette smoke.

In view of the uncertainty regarding the risk of gastrointestinal cancer following direct or indirect ingestion of asbestos, further research in this area would be of great value. Although an extensive series of lifetime feeding studies have already been performed by NTP, only two of these studies (NTP 1983, 1985) focused on the issue of fiber length in oral carcinogenicity. Further studies to investigate the role of fiber length in gastrointestinal cancer would be valuable, with special emphasis

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/103

on whether there is a minimum length below which carcinogenic risk is minimal. This would have considerable practical consequence in evaluating the potential risk to human health associated with ingestion of asbestos in drinking water. Additional epidemiological studies that include exposure both after occupational inhalation and community drinking water ingestion could also be helpful, especially if they were carefully designed to address the uncertainties and limitations in the evidence currently available.

Genotoxicity. The genotoxic effects of asbestos have been studied *in vivo* to a limited extent in humans (Fatma et al. 1991; Pelin-Enlund et al. 1990; Rom et al. 1983; Tammilehto et al. 1992; Tiainen et al. 1989) and animals (EPA 1988j; Fatma et al. 1992). These studies generally reported chromosomal aberrations with asbestos exposure. Available *in vitro* studies in eukaryotic cells indicate that asbestos is clastogenic, causing a variety of chromosomal aberrations (Kelsey et al. 1986; Kenne et al. 1986; Korkina et al. 1992; Sincock 1977; Sincock and Seabright 1975), and that asbestos may be mutagenic (Hei et al. 1992; Huang 1979). This is an observation of importance, since genotoxic effects of this sort might be involved in the carcinogenic effects of asbestos. Further studies to determine the mechanism of clastogenicity, the dependency of clastogenicity on fiber size and type, and the relative genotoxic sensitivity of different respiratory and gastrointestinal epithelial cells would be valuable.

Reproductive Toxicity. There are no studies in humans on potential reproductive effects of asbestos exposure. There is limited evidence from studies in animals that chronic ingestion of asbestos does not injure reproductive tissues, and that exposure during gestation does not reduce fertility (NTP 1983, 1985, 1988, 1990a, 1990b, 1990c). This indicates that reproductive effects are probably not of concern, and indeed there is little mechanistic basis for thinking this could occur. For these reasons, further studies on this end point do not appear critical.

Developmental Toxicity. There are no studies in humans on potential developmental effects of asbestos exposure. Although asbestos fibers have been detected in fetal tissues of humans (Haque et al. 1991, 1992), limited studies in animals have not detected any teratogenic effect in offspring of dams exposed to asbestos by the oral route. However, decreased body weight at birth and later in life were noted in some cases (NTP 1985, 1990c). It seems likely that these effects were either random or were secondary to reduced food intake by the dams, but additional studies to confirm that this is not an effect of concern would be helpful.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/104

Immunotoxicity. There are numerous studies of the immune system in workers who have been exposed to asbestos in workplace air (DeShazo et al. 1988; Kagan et al. 1977; Pernis et al. 1965; Sprince et al. 1991, 1992; Warwick et al. 1973). These studies indicate that the immune system may be depressed in individuals who have developed clinical signs of injury, such as asbestosis or cancer. However, the cause-effect relationship between the immunological changes and the asbestos-related diseases is not certain. Also, it is not known if similar effects occur after oral exposure, or if the effects are inhalation specific. Prospective studies on this subject would be very useful, both in discerning the importance of immune system injury in the etiology of asbestos-induced disease, and also to determine if immune function can be used as a possible early test of individual sensitivity to asbestos.

Neurotoxicity. There are no reliable indications in studies of humans or animals that exposure to asbestos leads to neurotoxicity. Even though tests have not been performed to search for possible subtle effects, there is little reason to suspect that this is an effect of concern, and detailed studies on this effect do not appear to be essential.

Epidemiological and Human Dosimetry Studies. There have been a very large number of epidemiological studies performed on workers exposed to relatively high concentrations of asbestos in air. Of value would be further epidemiological studies on populations with lower exposure levels, such as family members of asbestos workers, workers in buildings with asbestos-containing materials, or sailors exposed aboard ships. End points of concern would include not only cancers, but also pleural changes and respiratory function. Such studies may help estimate the magnitude of the health risks posed by current levels of asbestos inside buildings, in the ambient environment, and near waste sites.

Of special value in any ongoing or future epidemiological study, either in the workplace or in the ambient environment, is good dosimetry data, including data on the level, length and duration of exposure, and the type and size of the fibers involved. When accurate dosimetry data are not available (as is often the case), an indirect approach that can be useful is analysis of asbestos types and levels in tissue samples taken at autopsy. The main limitation of this approach is that chrysotile fibers tend to undergo breakdown or dissolution in tissues, while amphiboles tend to remain intact. Consequently, the relationship between tissue burden and exposure is not straightforward. Further investigations to

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/105

clarify the dependency of asbestos levels in tissue on the type and level of asbestos exposure would be very helpful in improving the ability to predict human cancer risk from exposure to asbestos.

Biomarkers of Exposurs and Effect

Exposure. The most relevant parameter for quantifying exposure to asbestos is the body burden of retained fibers (Gylseth et al. 1985; Wagner et al. 1986). However, there are no methods currently available for measuring tissue levels of fibers in living persons other than by biopsy. Bronchoalveolar lavage is useful for detecting the presence of asbestos fibers in respiratory macrophages, but this has not been developed as a quantitative indicator of exposure (Barbers and Abraham 1989; De Vuyst et al. 1982; Johnson et al. 1988). Fibers can also be detected in urine and feces (Cook and Olson 1979; Finn and Hallenback 1984), but these methods would likely reflect only recent exposures (within the last several days) and not the cumulative tissue burden. Efforts to develop a noninvasive method for measuring fiber levels in tissues (especially in the lung) would be particularly valuable in assessing human exposures to asbestos.

Effect. No specific and sensitive biomarkers of asbestos-induced disease are known. Chest x-rays can detect both the noncarcinogenic and carcinogenic lesions produced by asbestos in the lung and pleura, but usually not until after significant injury or change has occurred (Anton-Culver et al. 1989; Jones et al. 1988b). Similarly, spirometric tests of lung function can detect early stages of asbestos-induced disease, but only after functional decrements (Ernst et al. 1989; Finkelstein 1986). Further studies would be valuable to determine if changes such as depressed immune system function or altered levels of other biochemical parameters can be used as an indicator of risk of asbestos-induced cancer or fibrosis. Also, further efforts would be valuable to improve diagnostic methods for detecting early asbestos-related effects, such as high-resolution computed tomography to detect pleural thickening or pleural plaques (Aberle et al. 1988a, 1988b).

Absorption, Distribution, Metabolism, and Excretion. Because asbestos consists of insoluble fibers, it does not undergo absorption, distribution, metabolism or excretion in a fashion similar to most other chemicals. With respect to inhalation exposure, the toxicokinetic parameters of greatest relevance are the extent and location of fiber deposition in the airway, the rate of fiber removal from the airway by mucociliary transport, and translocation of fibers within and across the lung. A number of studies are available on the deposition and clearance of asbestos fibers from the lungs, both in

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/106

humans and animals, and these processes are fairly well understood (Bolton et al. 1983; Coin et al. 1992; Evans et al. 1973; Morgan et al. 1975; Timbrell 1982). However, additional research would be valuable to clarify the biological and mineralogical parameters which influence fiber penetration through the lungs into the pleural membrane, since this is a likely determinant of mesothelioma risk. Similar studies on the penetration of the gastrointestinal tract by fibers would also be helpful, since this might be key in extrathoracic cancer risks following oral intake. Additional studies on the long-term stability of fibers in the lung would be helpful in understanding why amphibole fibers appear to be more durable than chrysotile.

Comparative Toxicokinetics. Studies in humans and animals indicate the lung is the principal target organ after inhalation exposure. Comparative studies between humans and animals with respect to the details of where fibers are deposited, how that pattern depends on fiber dimension, and the rate of clearance from various locations in the respiratory tree, would be valuable in extrapolating animal deposition and clearance data to humans, and in identifying the best animal model for studying human health effects.

Methods for Reducing Toxic Effects. *In vitro* studies indicate an iron-catalyzed production of reactive oxygen species in the mechanism of action for asbestos (Fontecave et al. 1990; Garcia et al. 1988; Korkina et al. 1992; Shatos et al. 1987; Weitzman and Graceffa 1984). These studies also indicate that iron chelators and free radical scavengers can reduce some of the toxic effects of asbestos *in vitro* (Goodglick et al. 1989; Lund and Aust 1991b; Shatos et al. 1987). Inhibition of lung injury, inflammation, and asbestosis has been reported *in vivo* in an animal inhalation model of disease using polyethylene glycol-conjugated catalase (Mossman et al. 1990b). Additional *in vivo* studies which evaluate the efficacy of various iron chelators and free radical scavengers may lead to the development of a method for reducing the toxic effects of asbestos.

2.9.3 On-going Studies

Asbestos toxicity continues to be a matter of great concern, and a large number of studies are being performed to provide additional data on the health effects of this fiber class. Federally sponsored studies that are being carried out in humans, animals or *in vitro* are summarized in Table 2-7.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/107

TABLE 2-7. On-going Studies on the Health Effects of Asbestos

Investigator	Affiliation	Research description	Sponsor
Shapira, PM	Veterans Administration, Milwaukee, WI	Growth factor secretion in dust-induced lung disease	VA
Wiessner, JH	Veterans Administration, Milwaukee, WI	Mechanisms of pulmonary fibrosis	VA
Grammer, LC	Veterans Administration, Chicago, IL	Occupational and immunologic lung disease	VA
Auerbach, O	Veterans Administration, East Orange, NJ	Relationship of smoking and other factors to disease of the lung, heart, and other organs	VA
Bevan, DR	Virginia Polytechnic Institute, Blacksburg, VA	Interaction between benz(a)pyrene and asbestos in producing DNA damage	USDA
Rom, W	New York University Medical Center, New York, NY	Bronchoalveolar lavage in asbestosis	NCRR
Lawrence, EC	Baylor College of Medicine, Houston, TX	Asbestos effects on human alveolar function	NIH
Merrill, WW	Yale University, New Haven, CT	Epithelial surface proteins	NIH
Hunninghake, GW	Univ. of Iowa, Iowa City, IA	Bronchoalveolar lavage and interstitial lung disease	NIH
Staub, NC	San Francisco General Hospital, San Francisco, CA	Dynamics of pleural liquid and solute exchange	NIH
Bozelka, BE	Tulane Univ. School of Med., New Orleans, LA	Intrapulmonary cell mechanisms in asbestosis	NIH

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/108

TABLE 2-7. On-going Studies on the Health Effects of Asbestos (*continued*)

Investigator	Affiliation	Research description	Sponsor
Hei, TK	Columbia Univ., New York, NY	Radiation, asbestos, and mutagenesis	NIH, NIEHS
Aust, AE	Utah State Univ., Logan, UT	Role of iron in asbestos-induced DNA damage	NIH, NIEHS
Holian, A	Univ. of Texas, Health Sci. Ctr., Houston, TX	Effects of silica and asbestos on macrophage function	NIH, NIEHS
Kane, AB	Brown Univ., Providence, RI	Pathogenesis of mineral dust toxicity	NIH, NIEHS
Looney, JR	Univ. of Rochester, Rochester, NY	Alveolar macrophage immunoglobin receptors in host defenses	NIH, NIEHS
Finkelstein, JN	Univ. of Rochester Rochester, NY	Molecular and cellular response of lung cells to oxidant stress	NIH, NIEHS
Aust, AE	Utah State University, Logan, UT	Role of oxygen radicals and iron in asbestos-induced cancer	NIH, NIEHS
Boylan, AM	University of California - San Francisco, San Francisco, CA	Molecular mechanisms of asbestos and mesothelial cell interaction	NIH, NIEHS
Pinkerton, KE	Univ. of California, Davis, CA	Lung epithelium and interstitial asbestos accumulation	NIH, NIEHS
Fang, C-P	New York University Medical Center, New York, NY	Generation of fibrous aerosols in narrow size ranges	NIH, NIEHS
Haque, AK	University of Texas Medical Branch, Galveston, TX	Transplacental transfer of asbestos in humans	NIH, NIEHS
Hei, TK	Columbia University, New York, NY	The mutagenicity of mineral fibers	NIH, NIEHS

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/109

TABLE 2-7. On-going Studies on the Health Effects of Asbestos (*continued*)

Investigator	Affiliation	Research description	Sponsor
Kane, AB	Brown University, Providence, RI	Pleural dosimetry and biomarkers of response to fibers	NIH, NIEHS
Kane, AB	Brown University, Providence, RI	Pathogenesis of mesenchymal tumors induced by asbestos	NIH, NIEHS
Mossman, BT	University of Vermont, Burlington, VT	Mechanisms of cell replication in asbestos cancers	NIH, NIEHS
Schapira, RM	Medical College of Wisconsin, Milwaukee, WI	Growth factor secretion in dust-induced lung disease	NIH, NIEHS
Walker, CL	University of Texas Anderson Cancer Center, Smithville, TX	Wilms' tumor suppressor gene in mesothelioma	NIH, NIEHS
Weincke JK	Harvard University, Boston, MA	DNA adducts in human lung and blood mononuclear cells	NIH, NIEHS
Adams, DD	Duke Univ., Durham, NC	Role of macrophages in the production of reactive oxygen species	NIH, NIEHS
Meyskens, FL	UCIMC Clinical Cancer Center, Orange, CA	Chemoprevention efficacy of beta-carotene/retinal in smokers and asbestos workers	NIH, NCI
Hall, EJ	Columbia Univ., New York, NY	Asbestos fibers in cell transformation	NIH, NCI
Valanis, BG	Kaiser Foundation Hospital, Portland, OR	Chemoprevention efficacy of beta-carotene/retinal in smokers and asbestos workers	NIH, NCI
Keogh, JP	Univ. of Maryland, Baltimore, MD	Chemoprevention efficacy of beta-carotene/retinal in smokers and asbestos workers	NIH, NCI
Balmes, JR	San Francisco, CA	Chemoprevention efficacy of beta-carotene/retinal in smokers and asbestos workers	NIH, NCI

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/110

TABLE 2-7. On-going Studies on the Health Effects of Asbestos (*continued*)

Investigator	Affiliation	Research description	Sponsor
Craighead, JE	Univ. of Vermont, Burlington, VT	Experimental asbestos-induced mesothelioma	NIH, NCI
Omenn, GS	Fred Hutchinson Cancer Res. Ctr., Seattle, WA	Chemoprevention efficacy of beta-carotene/retinal in smokers and asbestos workers	NIH, NCI
McLarty, JW	Univ. of Texas Health Center, Tyler, TX	Chemoprevention efficacy of beta-carotene/retinal in smokers and asbestos workers	NIH, NCI
Ghio, AJ	Duke University, Durham, NC	The silicato-iron complex and interstitial lung injury	NHLBI
Mossman, BT	University of Vermont, Burlington, VT	Molecular biology of lung antioxidant enzyme regulation	NHLBI
Gerwin, B	NCI, NIH	*In vitro* studies of human mesothelioma	NIH, NCI

Source: CRISP (1992), FEDRIP (1994)

DNA = deoxyribonucleic acid; NCI = National Cancer Institute; NCRR = National Center for Research Resources; NHLBI = National Heart, Lung, and Blood Institute; NIEHS = National Institute of Environmental Health Sciences; NIH = National Institutes of Health; USDA = United States Department of Agriculture; VA = Veterans' Administration

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/111

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

Asbestos is a generic term for a group of six naturally occurring fibrous minerals. The basic unit of asbestos-class minerals is the silicate (SiO_4) group. This group can form a variety of polymeric structures through formation of Si-O-Si bonds. For the amphibole class of asbestos (amosite, crocidolite, tremolite, anthophyllite, actinolite), the polymeric structure consists of a linear double chain, as shown in Figure 3-1 (top). These chains crystallize into long, thin, straight fibers, which are the characteristic structure of this type of asbestos. For the serpentine class (chrysotile), the polymeric form is an extended sheet (Figure 3-1, bottom). This extended sheet tends to wrap around itself forming a tubular fiber structure. These fibers are usually curved ("serpentine"), in contrast to the straight morphometry of the amphiboles. Some of the asbestos minerals are solid solution series, since they show a range of chemical formulas as a result of ion or ionic group substitutions. Table 3-1 lists common synonyms and other pertinent identification information for asbestos (generic) and the six individual asbestos minerals.

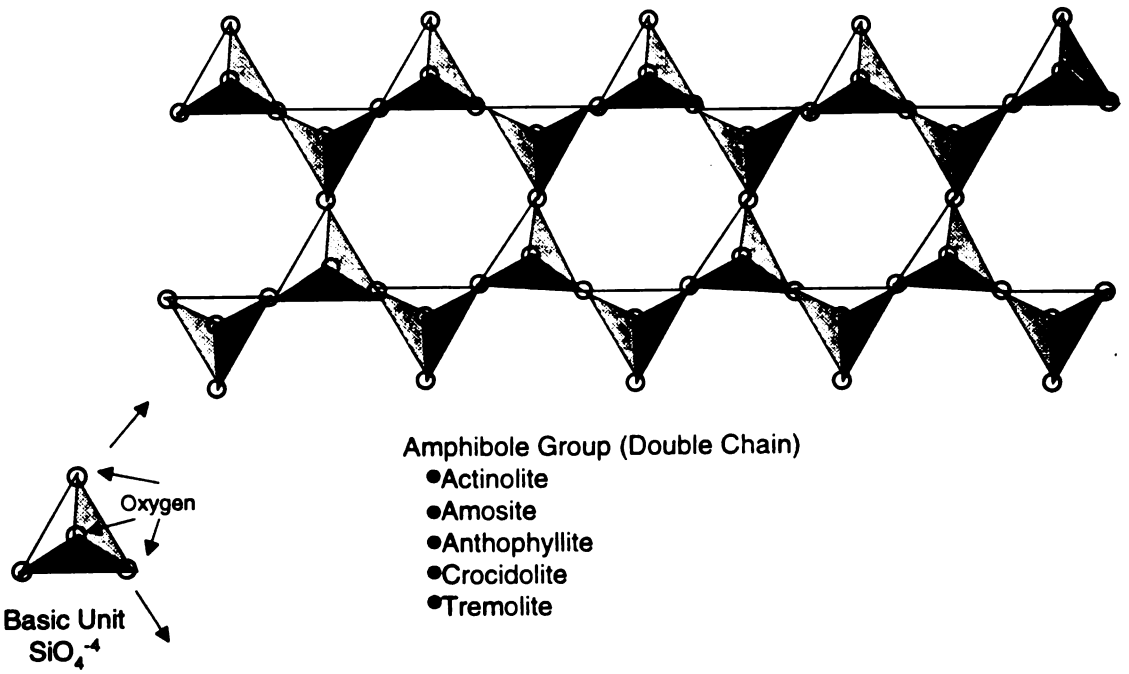
3.2 PHYSICAL AND CHEMICAL PROPERTIES

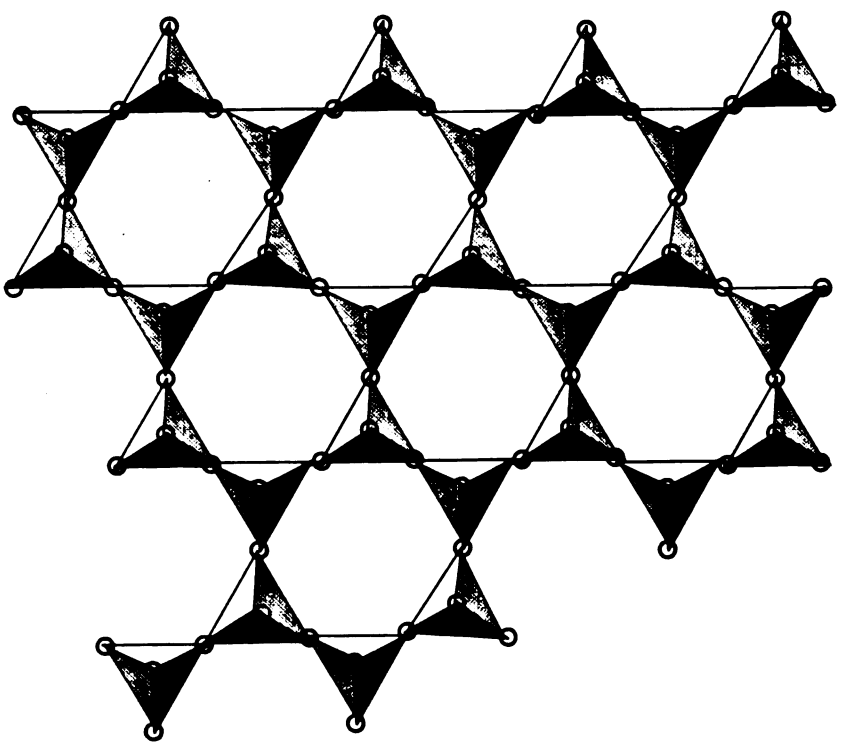
Asbestos fibers are basically chemically inert, or nearly so. They do not evaporate, dissolve, burn, or undergo significant reactions with most chemicals. Indeed, it is these properties that have made asbestos so useful. Table 3-2 summarizes the physical and chemical properties of the six asbestos minerals.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/112

FIGURE 3-1. Basic Polysilicate Structures of Asbestos*





*Adapted from Hurlbut and Klein 1977

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/113

TABLE 3-1. Chemical Identity of Asbestos

Characteristic	Asbestos	Amosite	Chrysotile	Tremolite	Actinolite	Anthophyllite	Crocidolite
Synonyms	No data	Mysorite, brown asbestos, fibrous cummingtonite/ grunerite	Serpentine asbestos; white asbestos	Silicic acid, calcium magnesium salt (8:4)	No data	Ferroantho-phyllite; azbolen asbestos	Blue asbestos
Trade name	No data	No data	Avibest; Cassiar AK; Calidria RG 144; Calidria RG 600	No data	No data	No data	No data
Chemical formula	No data	$[(Mg,Fe)_7Si_8O_{22}(OH)_2]_n$	$Mg_3Si_2O_5(OH)_4$	$[Ca_2Mg_5Si_8O_{22}(OH)_2]_n$	$[Ca_2(Mg,Fe)_5Si_8O_{22}(OH)_2]_n$	$[(Mg,Fe)_7Si_8O_{22}(OH)_2]_n$	$[NaFe_3^{2+}Fe_2^{3+}Si_8O_{22}(OH)_2]_n$
Chemical structure	See Figure 3-1						
Identification numbers:							
CAS registry	1332-21-4	12172-73-5	12001-29-5	14567-73-8	13768-00-8	17068-78-9	12001-28-4
NIOSH RTECS	CI6475000	BT6825000	GC2625000	XX2095000	AUO550000	CA8400000	GP8225000
EPA hazardous waste	No data	No data	No data	No data	No data	No data	No data
OHM/TADS	7217043	No data	No data	No data	No data	No data	No data
DOT/UN/NA/ IMCO shipping	IMCO 9.0 UN2212 UN2590	No data	IMCO 9.3 UN2590	No data	No data	No data	No data
HSDB	511	2957	2966	4212	No data	No data	No data
NCI	CO8991	No data	C61223A	CO8991	No data	No data	CO9007

Sources: EPA 1985b; HSDB 1994; IARC 1977

CAS = Chemical Abstracts Service; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances.

Toxicological Profile for Asbestos (1995)
ACL Doc 10942 · Page 114 of 233
Digitized by Google
Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/114

TABLE 3-2. Physical and Chemical Properties of Asbestos

Property	Amosite	Chrysotile	Tremolite	Actinolite	Anthophyllite	Crocidolite
Molecular weight[a]	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Color	Brown, gray, greenish	White, grey, green, yellowish	White to light green	No data	Grey, white brown-grey, green	Lavender, blue, green
Physical state	Solid	Solid	Solid	Solid	Solid	Solid
Melting point/decomposition temperature	600-900°C	800-850°C	1040°C	No data	950°C	800°C
Specific gravity	3.43	2.55	No data	No data	2.85-3.1	3.37
Solubility:						
Water	Insoluble	Insoluble	Insoluble	Insoluble	Insoluble	Insoluble
Organic solvents	Insoluble	Insoluble	Insoluble	Insoluble	Insoluble	Insoluble
Acids[b]	12.00	56.00	No data	No data	2.13	3.14
Bases[b]	6.82	1.03	No data	No data	1.77	1.20
Isoelectric point	5.2-6.0	11.8	No data	No data	No data	No data
Electrical charge at neutral pH	Negative	Positive	No data	No data	Negative	Negative
Length distribution in UICC reference samples						
% > 1 μm	46	36-44	No data	No data	46	36
% > 5 μm	6	3-6	No data	No data	5	3
% > 10 μm	1	1-3	No data	No data	1	0.7
Flammability limits	Nonflammable	Nonflammable	Nonflammable	Nonflammable	Nonflammable	Nonflammable
Conversion factors[c]						

Sources: EPA 1980, 1985b; HSDB 1994; IARC 1977; Kayser et al. 1982; NAS 1977; SRI 1982.

[a]All forms of asbestos are indefinite polymers.
[b]Percent loss in weight due to loss of counter-ions; silicate structure remains intact.
[c]See text, Section 2.2.

Toxicological Profile for Asbestos (1995)
ACL Doc 10942 · Page 115 of 233
Digitized by Google
Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/115

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

The production volume of asbestos in the United States has decreased substantially from peak production of over 299 million pounds (136,000 metric tons) in the late 1960's and early 1970's (SRI 1982) to 112 million pounds (51,000 metric tons) in 1987 and 37 million pounds (17,000 metric tons) in 1989 to an all-time low of 15,000 metric tons in 1993 (estimated) (U.S. Bureau of Mines 1994).

In the past, asbestos was produced at companies in California, Arizona, North Carolina, and Vermont but many of these companies suspended asbestos mining operations in the 1970's. In 1985, three United States companies produced asbestos fibers: Calaveras Asbestos, Ltd., Calaveras County, California; KCAC, Inc., San Benito County, California; and Vermont Asbestos Group, Orleans County, Vermont. By 1991, only two firms produced asbestos, one each in California and Vermont (U.S. Bureau of Mines 1994).

In the United States, asbestos was mainly mined in open pits. Ore is blasted or drilled from the pit, crushed, dried, and stored until milling. The milling process removes asbestos fibers from the ore by a series of crushing, fiberizing, screening, aspirating, and grading operations. More recently, an alternative method of mining was developed in order to reduce air emissions of fibers. This method uses bulldozers and scrapers (rather than blasting) to remove the ore from the pit. The ore is watered down to prevent air dispersion of the fibers, and is crushed, sized, and screened in a wet condition. After being dewatered, the fibers are pelletized, dried, and prepared for shipment either as pellets or further processed to yield open fibers (EPA 1988i).

Table 4-1 lists information on U.S. companies that reported manufacture and use of asbestos products in 1992 (TRI92 1994). The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/116

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

Table 4-1. Facilities That Manufacture or Process Asbestos

State[a]	Number of facilities	Range of maximum amounts on site in thousands of pounds[b]	Activities and uses[c]
AL	5	10-1000	2, 3, 4, 8, 9, 12, 13
AR	1	1000-10000	2, 3, 4, 7, 9
AZ	1	10-100	2, 3, 8
CA	12	0-10000	1, 2, 3, 5, 8, 12, 13
FL	4	10-1000	2, 3, 8, 9
GA	1	1-10	13
IL	3	10-1000	2, 3, 8
IN	2	10-100	2, 3, 8
KS	4	10-100	8, 12, 13
KY	3	10-1000	8, 13
LA	11	0-10000	2, 3, 8, 9, 11, 12, 13
MD	1	10-100	9
ME	1	10-100	13
NC	3	0-100	8, 9, 12
NJ	3	10-100	2, 3, 8, 9
NV	1	10-100	12, 13
NY	4	10-10000	2, 3, 8, 9, 12
OH	6	10-1000	1, 2, 3, 5, 8, 9, 13
OK	2	0-100	8, 12
OR	2	10-100	2, 3, 8, 12
PA	6	10-1000	1, 2, 3, 5, 8, 9, 13
SC	2	10-100	2, 3, 5, 8
TN	5	1-1000	1, 5, 8, 9
TX	8	10-10000	1, 2, 3, 5, 8, 12, 13
UT	1	1-10	1, 5
VA	2	10-100	1, 3, 4, 5, 9
VT	1	1000-10000	1, 4, 8, 9, 12
WA	3	10-100	2, 3, 8, 12
WV	1	10-100	11
WY	1	100-1000	2, 3, 13

Source: TRI92 1994

[a]Post office state abbreviations used
[b]Data in TRI are maximum amounts on site at each facility.
[c]Activities/Uses:

1. Produce
2. Import
3. For on-site use/processing
4. For sale/distribution
5. As a byproduct
6. As an impurity
7. As a reactant
8. As a formulation component
9. As a product component
10. For repackaging
11. As a chemical processing aid
12. As a manufacturing aid
13. Ancillary or other uses

Digitized by Google

4.2 IMPORT/EXPORT

Most asbestos used in the United States is imported. Imports from 1950 to 1974 varied from about 1,287 million pounds to 1,580 million pounds (585,000–718,000 metric tons) per year. During the late 1970's, imports began decreasing, with a sharp drop after 1980. By 1984, imports were down to 462 million pounds (210,000 metric tons), to 81 million pounds (35,000 metric tons) by 1991, and to 33,000 metric tons in 1993 (estimated). Most asbestos imported to this country comes from Canada (98%), but small amounts also are imported from South Africa (1%).

Exports of asbestos were small until the mid-1960's, when a significant increase in exports occurred. In recent years, export volumes have generally decreased from 132 million pounds (60,000 metric tons) in 1987 to 48 million pounds (22,000 metric tons) in 1991 (SRI 1982; U.S. Bureau of Mines 1992, 1994), then increased to 32,000 metric tons in 1993 (estimated), mainly as asbestos-containing finished products.

4.3 USE

It is estimated that asbestos (almost exclusively chrysotile) has been used in over 3,000 different products in the United States. The main uses have been in paper products, asbestos cement products, friction products, textiles, packings and gaskets, coatings, and asbestos-reinforced plastics. There have also been numerous other miscellaneous uses. Reported consumption of asbestos in the United States was 790 million pounds (359,000 metric tons) in 1980, 497 million pounds (226,000 metric tons) in 1984, 185 million pounds (84,000 metric tons) in 1987 and 81 million pounds (35,000 metric tons) in 1991, 33,000 metric tons in 1994 (99% of consumption was chrysotile) (SRI 1982; U.S. Bureau of Mines 1992, 1994). In 1993, 30% of the total apparent asbestos consumption was used for friction products (automobile clutch, brake, and transmission components), with 5% used for asbestos cement pipe, 50% for roofing products, 10% for packing and gaskets, and 5% for other uses (U.S. Bureau of Mines 1994). Approximately 99% of asbestos used in the United States in 1993 was chrysotile (U.S. Bureau of Mines 1994).

In October 1991, a United States federal court overturned an EPA regulation (1989f) that banned most uses of asbestos by 1997 (U.S. Bureau of Mines 1992). At present, only asbestos-containing products

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/118

that were not being manufactured, imported, or processed on July 12, 1989 remain subject to the prohibition requirements of the EPA regulation (EPA 1992a). Specific products which remain subject to the rule will be documented by EPA.

Substitutes for asbestos are constantly being developed (EPA 1989f). Nonasbestos friction materials are currently being used in disc brake pads, and substitutes are being developed for drum brake linings. Primary substitutes include semi-metallic materials for disc brakes and nonasbestos organics (e.g., fiberglass, para-aramid, mineral fibers, steel wool and fibers, and resins) for drum brakes. These and other materials are being developed as substitutes for asbestos in other products (EPA 1989f).

4.4 DISPOSAL

Currently, asbestos-containing wastes may only be deposited in landfills that are approved and regulated by the federal government. Regulations include wetting or using dust suppression agents, covering with at least 15 cm (6 inch) of nonasbestos-containing material, and deterring public areas with a fence or natural barrier (EPA 1990a). These regulations are intended to ensure that asbestos at these sites is not dispersed into the environment. No data were located on amounts of asbestos in such sites.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/119

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Although asbestos is neither volatile nor soluble, small fibers may occur in suspension in both air and water. These fibers are very stable and do not undergo significant degradation in the environment. Large fibers are removed from air and water by gravitational settling at a rate dependent upon their size, but small fibers may remain suspended for long periods of time.

Fibers in air may arise from natural sources (weathering of asbestos-containing ores), but many come from wear of automobile brakes or breakdown of asbestos-containing (mainly chrysotile) materials, such as insulation. The concentrations of fibers in outdoor air are highly variable, ranging from below 0.1 ng/m^3 ($3x10^{-6}$ PCM f/mL) in rural areas to over 100 ng/m^3 ($3x10^{-3}$ PCM f/mL) near specific industrial sources such as asbestos mines. The concentration of fibers in indoor air is also highly variable, depending on the amount and condition of asbestos-containing materials in the building. Typical concentrations range from 1 to 200 ng/m^3 ($3x10^{-5}$ to $6x10^{-3}$ PCM f/mL). For a human exposed for a lifetime (70 years), this range of exposures corresponds to cumulative doses of approximately 0.0002–0.4 PCM f-yr/mL.

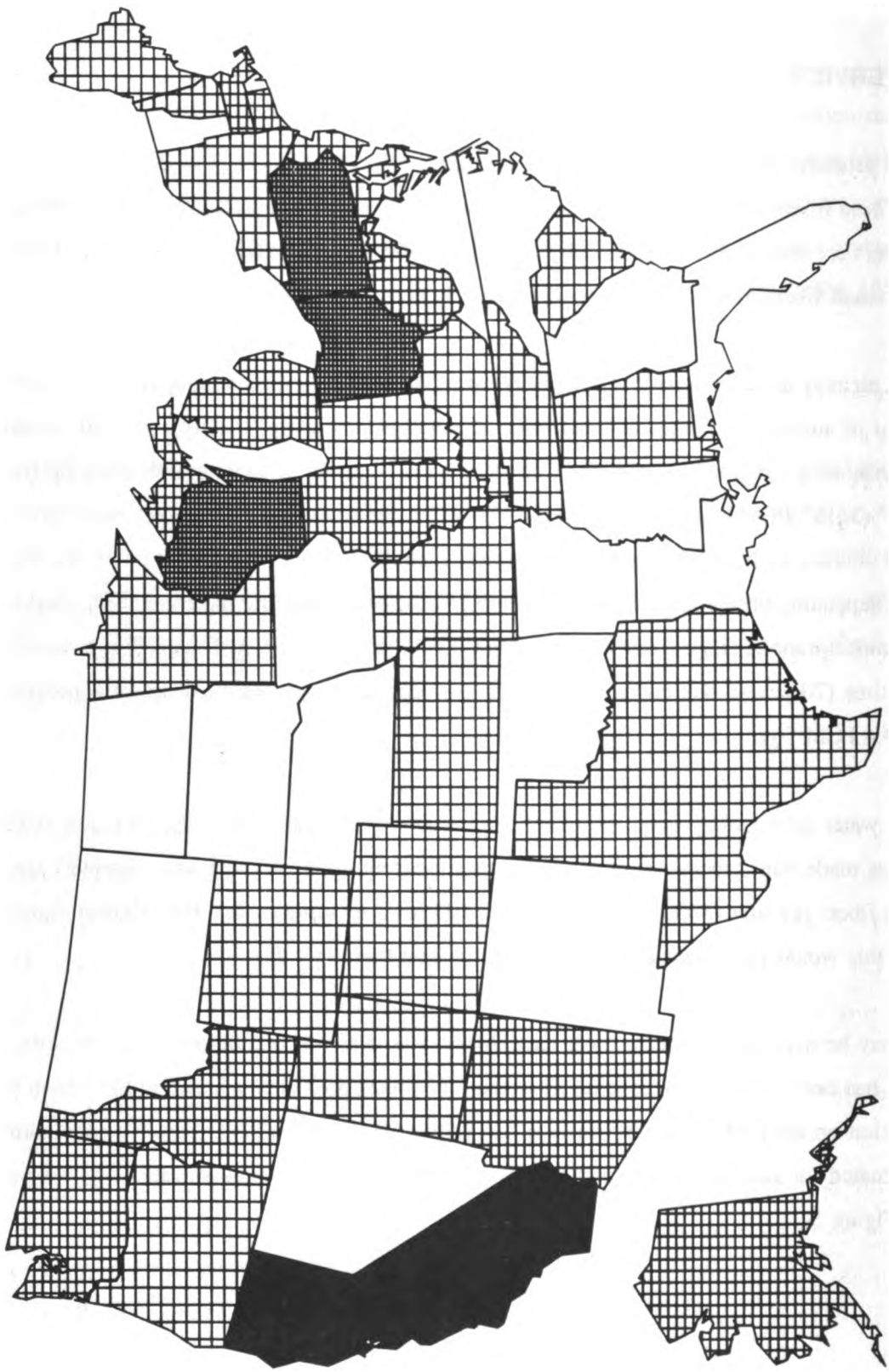
Fibers in water arise mainly by erosion from natural deposits of asbestos or by corrosion of fibers from pipes made with asbestos-containing cement. Concentrations in most water supplies are less than 1 million fibers per liter (MFL), but may exceed 100 MFL in some cases. For a human consuming 2 L/day, this would yield a dose of about 2–200 million fibers per day.

People may be exposed to asbestos near hazardous waste sites where asbestos is not properly stored. Asbestos has been identified in at least 58 of the 1,408 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HAZDAT 1994). However, the number of sites evaluated for asbestos is not known. The frequency of these sites within the United States can be seen in Figure 5-1.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/120

FIGURE 5-1. FREQUENCY OF NPL SITES WITH ASBESTOS CONTAMINATION *



Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/121

5.2 RELEASES TO THE ENVIRONMENT

5.2.1 Air

Although asbestos is not volatile, small fibers and clumps of fibers may be released to air as a dust-like suspension. One source is the erosion of natural deposits of asbestos-bearing rocks. No quantitative data were located on the amounts of asbestos released to the air from natural sources in the United States.

It is estimated that emissions from asbestos processing, including milling, manufacturing, and fabrication are about 2,240 pounds per year (EPA 1992b). This estimate assumes full compliance with the current National Emission Standards for Hazardous Air Pollutants (NESHAP) (EPA 1990a) applicable to asbestos.

As shown in Table 5-1, an estimated total of 11,264 pounds (5.1 metric tons) of asbestos, amounting to about 4.5% of the total environmental release, was discharged to the air from manufacturing and processing facilities in the United States in 1992 (TRI92 1994). The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list.

Another source of asbestos release is from clutches and brakes on cars and trucks. Release of asbestos from insulation or other building materials is discussed in Section 5.4.1, below. Estimated asbestos emissions from waste disposal from all sources were about 499,000 pounds (22.7 metric tons) per year (EPA 1990a). If all sources were in full compliance with the NESHAP for asbestos, waste disposal emissions would be reduced to 1,320 pounds (600 kg) per year (EPA 1990a).

5.2.2 Water

Asbestos is released to water from a number of sources, including erosion of natural deposits and waste piles, corrosion from asbestos-cement pipes, and disintegration of asbestos roofing materials with subsequent transport via rainwater into cisterns, sewers, etc. (Millette et al. 1980). Wastewater from asbestos-related industries may also carry significant burdens of asbestos fibers (EPA 1976).

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/122

Table 5-1. Releases to the Environment from Facilities That Manufacture or Process Asbestos

State[b]	Number of facilities	Range of reported amounts released in pounds per year[a]						
		Air	Water	Land	Underground injection	Total environment[c]	POTW transfer	Off-site waste transfer
AL	5	0-464	0	0-19000	0	0-19000	0	0-48550
AR	1	190	0	46460	0	46650	5	0
AZ	1	0	0	0	0	0	0	27
CA	12	0-359	0	0	0	0-359	0	0-303573
FL	4	0-465	0	0	0	0-465	0	0-750
GA	1	0	0	0	0	0	0	15732
IL	3	0-171	0	0	0	0-171	0	0-250
IN	2	0-250	0	0	0	0-250	0	190-4895
KS	4	0-24	0	0	0	0-24	0	0-34580
KY	3	0-53	0	0	0	0-53	0	0-185940
LA	11	0-18	0	0-170000	0	0-170000	0	0-310000
MD	1	0	0	0	0	0	0	12500
ME	1	5	0	0	0	5	0	21680
NC	3	0-171	0	0-2	0	0-171	0	2-12510
NJ	3	0-318	0	0-187	0	0-318	0	187-255
NV	1	0	0	0	0	0	0	29360
NY	4	0-250	0	0	0	0-250	0	0-197056
OH	6	0-1475	0	0	0	0-1475	0	250-296000
OK	2	0-5	0	0-250	0	0-255	0	250-122790
OR	2	0	0	0	0	0	0	0-250
PA	6	2-861	0	0	0	2-861	0-776	0-459000
SC	2	11-250	0	0	0	11-250	0	0-345
TN	5	0-540	0	0	0	0-540	0-2	0-769000
TX	8	0-252	0	0	0	0-252	0	0-1683000
UT	1	0	0	0	0	0	0	55500
VA	2	0-500	0	0	0	0-500	0	22854-331162
VT	1	500	250	0	0	750	0	0
WA	3	0-10	0	0	0	0-10	0	0-14000
WV	1	0	0	0	0	0	0	0
WY	1	0	0	0	0	0	0	28000

Source: TRI92 1994

[a]Data in TRI are maximum amounts released by each facility.
[b]Post office state abbreviations used
[c]The sum of all releases of the chemical to air, land, water, and underground injection wells by a given facility

POTW = publicly owned treatment works

Toxicological Profile for Asbestos (1995)
ACL Doc 10942 · Page 123 of 233
Digitized by Google
Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/123

The total amount of asbestos released to water has been estimated to be 110,000–220,000 pounds (50–100 metric tons) per year (NRC 1984).

As shown in Table 5-1, an estimated total of 250 pounds (0.11 metric tons) of asbestos, amounting to less than 1% of the total environmental release, was discharged to surface water from manufacturing and processing facilities in the United States in 1992 (TRI92 1994). No asbestos was reported to have been released to underground injection. The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list.

5.2.3 Soil

Soil may be contaminated with asbestos by the weathering of natural asbestos deposits, or by land-based disposal of waste asbestos materials. While disposal of waste asbestos to landfills was a common practice in the past, current regulations restrict this practice (see Chapters 4 and 7).

As shown in Table 5-1, an estimated total of 235,900 pounds (107 metric tons) of asbestos, amounting to about 95.3% of the total environmental release, was discharged to land from manufacturing and processing facilities in the United States in 1992 (TRI92 1994). The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list.

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

Asbestos fibers are nonvolatile and insoluble, so their natural tendency is to fall out of air and water and deposit in soil or sediment (EPA 1977, 1979c). However, some fibers are sufficiently small that they can remain in suspension in both air and water and be transported long distances. For example, fibers with aerodynamic diameters of 0.1–1 μm can be carried thousands of kilometers in air (Jaenicke 1980), and transport of fibers over 75 miles has been reported in the water of Lake Superior (EPA 1979c). Adsorptive interactions between the fibers and natural organic contaminants may favor coagulation and precipitation of the fibers (EPA 1979c).

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/124

5.3.2 Transformation and Degradation

5.3.2.1 Air

Asbestos fibers in air are not considered to undergo any significant transformation or degradation (EPA 1979c).

5.3.2.2 Water

Asbestos fibers in water may undergo dissolution of some of the metal ion and hydroxyl ion content, but the basic silicate structure of the fiber remains intact (Choi and Smith 1972; Morgan and Holmes 1986).

Asbestos degrades in the environment very slowly (NRC 1984). Although the estimated half-life of asbestos in aquatic systems is not known, it is expected to be quite long (NRC 1984), and asbestos may persist in the environment for a decade or more following its release (EPA 1989f).

5.3.2.3 Sediment and Soil

Asbestos fibers in soil are not known to undergo significant transformation or degradation.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

Numerous measurements have been performed to determine the concentration of asbestos fibers in both outside and inside air. These studies have reported their results in a variety of units, including ng/m^3, TEM f/mL (fibers measured by transmission electron microscopy), and PCM f/mL (fibers measured by phase contrast microscopy). The conversion factors between these units are highly variable, depending on the size and length distribution of the fibers, and no single set of factors will be accurate for all samples. With this limitation in mind, the NRC (1984) suggested that crude approximations could be achieved by assuming that one phase contrast fiber per mL is about equal to 60 transmission electron microscope fibers per mL, and that both are about equal to 30 µg/m^3. Since

Digitized by Google

the health effects data regarding inhalation exposure to asbestos is usually expressed in terms of phase contrast fibers per mL, ambient air data reported in units of ng/m^3 or TEM f/mL are converted to units of PCM f/mL using the factors suggested by NRC (1984).

Ambient outdoor air, remote from any special sources, is generally found to contain 0.001–0.1 ng/m^3 of asbestos ($3x10^{-8}$ to $3x10^{-6}$ PCM f/mL) (NRC 1984). In urban areas, most ambient air concentrations range from 0.1 to 10 ng/m^3 ($3x10^{-6}$ to $3x10^{-4}$ PCM f/mL), but may range up to 100 ng/m^3 ($3x10^{-3}$ PCM f/mL) (EPA 1991b; IARC 1977; Nicholson and Pundsack 1973; Selikoff et al. 1972). The median concentration in United States cities has been estimated to be 2.3 ng/m^3 ($7x10^{-5}$ PCM f/mL) (NRC 1984). These levels are sufficiently low that they are not likely to be of significant health concern to most people. Near industrial operations involving asbestos, levels may be as high as 50–5,000 ng/m^3 ($1.5x10^{-3}$ to $1.5x10^{-1}$ PCM f/mL) (IARC 1977). A recent analysis of monitoring data for asbestos in ambient air world-wide estimated rural and urban levels at about $1x10^{-5}$ TEM f/mL ($2x10^{-7}$ PCM f/mL) and $1x10^{-4}$ TEM f/mL ($2x10^{-6}$ PCM f/mL), respectively (HEI 1991). Higher levels were measured near source-dominated locations.

Asbestos fibers are sometimes of potential concern in indoor air, due to disturbance of asbestos from a variety of building materials such as insulation, ceiling tiles, and floor tiles (EPA 1991b). Measured indoor air values range widely, depending on the amount, type, and condition (friability) of asbestos-containing materials used in the building. In a review of indoor air monitoring data from a variety of locations, Nicholson (1987) reported that arithmetic mean concentrations ranged from 1 to 200 ng/m^3 ($3x10^{-5}$ to $6x10^{-3}$ PCM f/mL). In a recent survey performed by EPA (1988c), levels of asbestos in 94 public buildings that contained asbestos ranged from 0 to 0.2 TEM f/mL (0 to $3x10^{-3}$ PCM f/mL), with an arithmetic mean concentration of 0.006 TEM f/mL (10^{-4} PCM f/mL) (Spengler et al. 1989). Analysis of data based on air samples from 198 ACM-containing buildings indicated mean asbestos levels ranging from $4x10^{-5}$ to $2.43x10^{-3}$ TEM f/mL ($7x10^{-7}$ to $4x10^{-5}$ PCM f/mL) (HEI 1991). Asbestos concentrations in 41 schools that contained asbestos ranged from 0 to 0.1 TEM f/mL (0 to $2x10^{-3}$ PCM f/mL), with an arithmetic mean of 0.03 TEM f/mL ($5x10^{-4}$ PCM f/mL) (EPA 1988c; Spengler et al. 1989). Another study reported average airborne asbestos fibers ≥5 micron concentrations of 0.00008 TEM f/mL and 0.000022 TEM f/mL in 43 nonschool buildings and 73 school buildings, respectively (Chesson et al. 1990; HEI 1992; Spengler et al. 1989). The average of measurements taken outdoors is comparable to the measured indoor level in these studies (Spengler et al. 1989). In general, direct comparison of levels inside and outside buildings that contain asbestos

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/126

indicate that typical (nondisturbed) indoor levels are usually low, but may be higher than outside (Chesson et al. 1990).

Asbestos may also be released to indoor air from the use of asbestos-contaminated household water (Hardy et al. 1992; Webber et al. 1988). Limited studies indicate that both amphibole and chrysotile fibers can be aerosolized by portable home humidifiers (Hardy et al. 1992). The airborne asbestos concentrations in the home were directly proportional to the asbestos concentrations in the water used in the humidifiers.

5.4.2 Water

The concentration of asbestos fibers in water (expressed as million TEM fibers per liter, MFL) ranges widely. Concentrations in most areas are less than 1 MFL (EPA 1979b), but values of 1–100 MFL and occasionally higher have been detected in areas contaminated by erosion from natural asbestos deposits (EPA 1976; Kanarek et al. 1980) or from mining operations (Sigurdson et al. 1981).

Release of asbestos from asbestos-cement pipes used in drinking water distribution systems may also be significant in some cases. The amount of asbestos contributed from asbestos-cement pipe is negligible in some locations (Hallenbeck et al. 1978), but may result in concentrations of 1–300 MFL at other locations (Craun et al. 1977; Howe et al. 1989; Kanarek et al. 1981). In one reported incident, grossly deteriorated asbestos-cement pipe in the water distribution system resulted in water concentrations of asbestos up to 1,850 MFL (Webber et al. 1989). The variability in the amount of fibers coming from asbestos-cement pipe appears to depend on a number of parameters, but is mostly related to characteristics of the water such as low pH and low hardness, which influence the rate at which the water can corrode the pipe (NAS 1982). The large majority of all fibers found in water are chrysotile, and are less than 5 μm in length (Hallenbeck et al. 1978; Millette et al. 1980; Pitt 1988).

5.4.3 Sediment and Soil

No studies were located regarding the concentration of asbestos fibers that occur in soil. Asbestos was found in about 80% of a number of samples of street dirt, at concentrations ranging from 100 million to 1 billion fibers per gram (f/g) (Pitt 1988). These were primarily chrysotile fibers and most were

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/127

less than 2 μm in length. It is likely that the main source of this asbestos was release from automobile brakes.

5.4.4 Other Environmental Media

In the past, filters made from asbestos were employed in the preparation of wines, beers, and other items consumed by humans, and asbestos concentrations in these materials ranged from 1 to 10 MFL (Cunningham and Pontefract 1973). Analysis of 47 brands of sake purchased in Japan during 1983–1985 indicated that asbestos concentrations in sake ranged from less than the detection limit ($7.8x10^{-3}$ MFL) to 196 MFL (Ogino et al. 1988).

The use of asbestos filters in food or pharmaceutical preparation has been discontinued in the United States, and intake of asbestos through foods or drugs is now unlikely.

Asbestos fibers may be incorporated in sewage sludge as a result of their presence in wastewaters. Asbestos has been reported in municipal sewage sludges and sewage sludge composts from large and small cities in the United States (Manos et al. 1991, 1993; Patel-Mandlik et al. 1988). Asbestos was detected in 34 of 51 sludge ash samples at levels ranging from 1 to 10% by volume (Manos et al. 1991).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

As noted above, the concentrations of asbestos found in indoor air, outdoor air, and drinking water vary widely, and it is not possible to calculate human exposure levels accurately except on a site-by-site basis. With this limitation in mind, Table 5-2 presents some rough estimates of exposure levels for a general population living in an urban or suburban area, and for asbestos workers. The exposure levels used for the general public are intended to represent the central portion of the typical range of exposures; thus, some persons could be exposed to higher levels, while others could be exposed to less. The workplace air concentration used to estimate worker exposure (0.1 f/mL) is the same as the current workplace exposure limit. Actual workplace exposures could be higher or lower. It has been estimated that about 568,000 workers in production and services industries and 114,000 construction industries may be exposed to asbestos in the workplace (OSHA 1990). Dose of fibers transferred to

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/128

TABLE 5-2. Summary of Typical General Population and Occupational Exposures

Exposed population	Exposure medium	Typical concentration	Assumed exposure	Dose	
				Lungs[a]	GI tract[b]
General population	Ambient (outdoor) air	$1x10^{-4}$ TEM f/mL[c] ($2x10^{-6}$ PCM f/mL)	20 m^3/day, 70 years (10% of time outdoors)[d]	0.00001 f-yr/mL	0.00006 MF/day[e]
	Indoor air[f]	$2x10^{-4}$ TEM f/mL[c] ($3x10^{-6}$ PCM f/mL)	20 m^3/day, 70 years (90% of time indoors)[d]	0.0002 f-yr/mL	0.001 MF/day
	Drinking water	1.0 MFL[g]	2 L/d		2 MF/day
Asbestos worker	Workplace air	0.1 PCM f/mL[h]	40 years, 8 m^3/day, 5 days/week, 49 weeks/year[i]	1.1 f-yr/mL[j]	8.1 MF/day[e,k]

[a]Dose to lungs expressed as phase contrast microscopy (PCM) fibers
[b]Dose to GI tract expressed as transmission electron microscopy (TEM) fibers (1 PCM fiber assumed to equal 60 TEM fibers) (NRC 1984)
[c]HEI 1991
[d]Approximate value, based on EPA 1989e
[e]Assumes 30% of inhaled fibers are transferred to stomach (NAS 1983)
[f]Applies only to buildings containing asbestos building materials
[g]Millette et al. 1979; concentration expressed as TEM fibers
[h]This value is arbitrarily assumed to be one-half of the occupational exposure limit of 0.2 PCM f/mL (OSHA 1986)
[i]NAS 1983
[j]Expressed in terms of average continuous exposure (20 m^3/day, 365 days/year), rather than in terms of years of occupational exposure (8 m^3/day, 5 days/week, 49 weeks/year)
[k]Daily dose (12 million fibers/day) adjusted to account for exposure 5 days/week, 49 weeks/year (NAS 1983)

f/mL = fibers per milliliter; L/d = liters per day; MF = million fibers; MFL = million fibers per liter; PCM = phase contrast microscopy; TEM = transmission election microscopy

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/129

the gastrointestinal tract after inhalation exposure were calculated using the same assumptions as employed in similar calculations by NAS (1983).

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

The populations most likely to have high exposure to asbestos are workers who come into contact with asbestos while on the job. This includes persons involved in the mining and manufacture of asbestos products, and also people who install, service, or use these products. Although recent regulations have resulted in a marked decrease in airborne exposure levels in the workplace, the currently acceptable upper limit in workplace air (0.1 f/mL) is still considerably higher than levels found outside the workplace (usually less than 0.001 f/mL). In the past, workers may have carried asbestos home on their clothing or in their hair, resulting in exposure of family members (Anderson et al. 1979). However, this is not likely to be of concern at the present.

People who live near an asbestos-related industry or near an asbestos-containing waste site may encounter higher-than-average levels of asbestos in air. People may also receive higher-than-average exposure from a variety of asbestos-containing products, from poorly performed asbestos removal, and from living or working in a building with deteriorating asbestos insulation. Working in a building with asbestos-containing material that is in good condition has not been shown to result in significantly elevated levels of asbestos in air (HEI 1991).

Some people may also be exposed to elevated levels of asbestos in drinking water, particularly where there are widespread natural deposits of asbestos (e.g., San Francisco Bay area), disposal of asbestos-containing ore tailings (e.g., Duluth, Minnesota), or the use of asbestos-containing cement pipes in drinking water distribution systems with low pH and low hardness (Craun et al. 1977; Kanarek et al. 1981; Webber et al. 1989).

5.7 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of asbestos is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/130

research designed to determine the health effects (and techniques for developing methods to determine such health effects) of asbestos.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

5.7.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of asbestos are well characterized (see Chapter 3), and there does not appear to be a need for further research in this area.

Production, Import/Export, Use, Release, and Disposal. Asbestos is widely used by humans in a variety of products, and exposures are likely from a number of sources. Extensive data are available on current production, import, and use of asbestos (U.S. Bureau of Mines 1992). Releases to the environment may occur either to air or to soil and water, with releases to air being of greatest health concern. Waste asbestos is regulated as a hazardous substance, so disposal is permitted only in authorized waste sites. However, data are lacking on the amount of asbestos disposed in waste sites, and on the location and status of these sites.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1992, became available in May of 1994. This database is updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate. Asbestos fibers are fundamentally rather inert, and are not considered to undergo transport or degradative processes analogous to organic pollutants. Additional studies on the behavior of fibers in water (processes such as change in metal ion and hydroxyl ion composition, adsorption to organic materials, flocculation and precipitation, etc.) would be helpful in evaluating water-based transport of fibers, as well as in improving methods for removal of fibers from water.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/131

Also, studies on the stability, degradation, and alteration of fibers in soil would be useful. Transport of fibers in air is governed by processes and forces which apply to all particulate matter (EPA 1977, 1979c), and these processes are reasonably well understood.

Bioavailability from Environmental Media. Asbestos fibers are insoluble and are not absorbed in the usual sense after inhalation, oral, or dermal exposure. Most exposures occur either to fibers in air or water, so the effect of matrices such as soil or food are largely unknown. It is possible that adsorption of fibers onto other dust particles could influence the location of deposition in the lung, and might even influence the cellular response to the fibers. Research to determine if this occurs and is of biological significance would be helpful.

Food Chain Bioaccumulation. No data were located on asbestos levels in the tissues of edible organisms. However, it is not expected that either aquatic or terrestrial organisms will accumulate a significant number of fibers in their flesh. Consequently, food chain bioaccumulation or biomagnification does not appear to be of concern.

Exposure Levels in Environmental Media. There have been extensive surveys of asbestos levels in water and air (both outside air and inside air) (Chesson et al. 1990; EPA 1979b, 1991b, 1992c; HEI 1991, 1992; Howe et al. 1989; IARC 1977; Kanarek et al. 1980, 1981; NRC 1984; Spengler et al. 1989). These studies have revealed that wide ranges of asbestos levels may be encountered, indicating that human exposures can only be estimated on a site-specific basis. However, further studies on the sources of the fibers and key determinants of exposure level would be valuable. It is especially important that further studies of asbestos levels in environmental media investigate and report on the size distribution of the fibers, because this is important in evaluating the resultant risk. Few data exist on asbestos levels in soil, especially near waste sites, and more thorough and recent data on this would be helpful in assessing human intake of asbestos near such sites.

Reliable monitoring data for the levels of asbestos in contaminated media at hazardous waste sites are needed so that the information obtained on levels of asbestos in the environment can be used in combination with the known body burden of asbestos to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/132

Exposure Levels in Humans. Asbestos fibers have been detected in many tissues (especially lung and pleura) of exposed people (Berry and Newhouse 1983; Churg and Wright 1989), and low levels can also be detected in urine (Cook and Olson 1979; Finn and Hallenbeck 1984). However, most data are based on occupationally exposed populations, and human exposure levels near waste sites are not known. Studies of asbestos levels in urine or in autopsy samples from residents near waste sites known to contain asbestos would be helpful in estimating the magnitude of exposure that can result from waste sites.

This information is necessary for assessing the need to conduct health studies on these populations.

Exposure Registries. No exposure registries for asbestos were located. This substance is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

Many industries and researchers interested in studying the health effects of asbestos in exposed workers maintain registries of individuals who were exposed to asbestos on the job.

5.7.2 On-going Studies

No information was located regarding on-going studies on the stability and migration of asbestos in the environment. The EPA and many state and local agencies are continuing to make measurements of asbestos levels in air and in water in order to identify locations where significant health concerns may be warranted.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/133

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, and/or measuring, and/or monitoring asbestos, its metabolites, and other biomarkers of exposure and effect to asbestos. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

As discussed in Chapter 3, asbestos is not a single chemical entity, but is the name for a group of six hydrated fibrous polysilicates. Because the toxicity of asbestos appears to be related primarily to fiber number and size, modern analytical methods focus on providing information on these parameters as well as on total amount and mineral type. At present, the number and size distribution of fibers in a sample can only be determined by direct microscopic examination. This may be performed using either light or electron microscopy, as discussed below.

Light Microscopic Method. Currently, the standard method for the determination of airborne asbestos particles in the workplace is NIOSH method 7400, Revision #2 (replacing P&CAM and NIOSH 7400, Revision #1) (NIOSH 1987, 1989a). Asbestos particulate is collected on a 25-mm cellulose ester filter (cassette equipped with a 50-mm electrically-conductive cowl). The filter is treated to make it transparent and then analyzed by microscopy at 400 to 450x magnification, with phase-contrast illumination, using a Walton-Beckett graticule. A fiber is defined as any object whose length is greater than 5 μm and whose length to diameter ratio is 3:1 or greater. Although this method is relatively fast and inexpensive, it does not distinguish between asbestos and nonasbestos fibers, and it cannot detect fibers shorter than 5 μm or thinner than 0.25 μm. Consequently, this method is most useful for analysis of samples that are composed mainly of asbestos, and where a significant fraction of the fibers are large enough to be counted. If samples are grossly contaminated by nonasbestiform fibers, transmission electron microscopy (NIOSH Method 7402) should be used for positive

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/134

identification. If fibers are greater than 1 μm in diameter, polarized light microscopy (NIOSH method 7403) may be useful in identifying polymorphs (NIOSH 1987). Concentrations are reported as fibers/ml or fibers/cc. Recent improvements in filter preparation procedures now allow for viewing at higher magnification (1250x), resulting in a several-fold improvement in sensitivity (Pang et al. 1989). Polarized light microscopy is frequently used for determining the asbestos content of bulk samples of insulation or other building materials (EPA 1993a; NIOSH 1989c), however this approach is not used for measuring asbestos in environmental media.

Electron Microscopic Methods. Examination of a fiber sample by either scanning electron microscopy (SEM) or transmission electron microscopy (TEM) allows the detection of much smaller fibers than light microscopy, and so more thorough data can be collected on fiber length and diameter distribution. Of these two methods, TEM has greater sensitivity for small fibers, and is the most common method for measuring asbestos in ambient air or inside schools or other buildings. In addition, most modern transmission electron microscopes are equipped with instrumentation that allows examination of individual fibers by electron diffraction or energy dispersive x-ray analysis. This permits determination of the crystalline and elemental composition of the fiber. Thus, reliable distinctions can be made not only between asbestos and nonasbestos fibers, but also between different asbestos mineral classes (NIOSH 1989b). Although TEM clearly provides the most information about a fiber sample, TEM methods are relatively slow and costly compared to PCM methods.

Application of either PCM or TEM methods to the determination of asbestos fibers in biological or environmental media (air or water) requires that the fibers be separated from interfering material and collected on appropriate supports. Methods for preparing biological and environmental samples for microscopy are described below.

6.1 BIOLOGICAL MATERIALS

Asbestos fibers are particularly resistant to chemical and thermal degradation, and this property is used to advantage in the analysis of biological materials for asbestos. In most cases, the bulk of the biological material is solubilized by digesting the tissue in strong base (e.g., KOH) or a powerful oxidant (e.g., hypochlorite). The insoluble residue (including the asbestos fibers) is collected by ultracentrifugation or filtration, and may be further cleared of biological material by ashing. In some cases, biological material may be removed by ashing without prior digestion. Residual material is then

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/135

dispersed and transferred to a suitable support for microscopy. Table 6-1 summarizes several representative studies where these approaches have been applied to a variety of biological materials.

6.2 ENVIRONMENTAL SAMPLES

For the analysis of asbestos fibers in air, the sample is drawn through a filter by a vacuum pump (usually at a flow rate of around 1–2 liters per minute), and the fibers retained on the filters are examined microscopically. The sensitivity of the methods depends on the volume of air drawn through the filter, and the microscopic method employed. In the workplace, where PCM is the standard method, the theoretical detection limit for a short-term sample (15 minute) is around 0.04 PCM f/mL, but may be reduced to 0.001 f/mL using on 8-hour sample (NIOSH 1976). In practice, such low detection limits are not readily achievable, and measured values below 0.1 PCM f/mL should not usually be considered reliable (ASTM 1988). Sensitivity of TEM methods for ambient or indoor air are usually around 0.1–1 ng/m^3.

A similar approach is used for measuring asbestos in water. A known volume (generally at least one liter) is drawn through a filter, and the filter is then prepared for examination, usually by TEM. Under favorable conditions, concentrations as low as 0.01 MFL can be detected (EPA 1980b). Table 6-2 summarizes several representative methods for the analysis of asbestos in air and water.

6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of asbestos is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of asbestos.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/136

TABLE 6-1. Analytical Methods for Determining Asbestos in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Bronchoalveolar fluid	Mix with sodium hypochlorite; filter through cellulose ester membrane filter; dry	PCM	1 AB/mL	No data	Spurny 1994
Urine	Mix with hydrogen peroxide; digest for 20 hours; collect residue on filter	TEM	0.1 - 0.3 x 10^{-6} f/L	No data	Boatman et al. 1983
Urine	Filter through polycarbonate filter; ash filter; wash; collect residue on second filter	TEM	5 x 10^{3} f/mL	No data	Finn and Hallenbeck 1984
Feces	Dry, ash, dissolve residue in hydrochloric acid; filter; ash filter; transfer residue to grid	TEM	0.15 x 10^{6} f/g	85.5	Cunningham et al. 1976
Lung tissue	Dry to constant weight; digest with sodium hyroxide (90°C); ash residue; collect on nucleopore filter	TEM	0.1 x 10^{6} f/g	No data	Wagner et al. 1982a
Lung tissue	Digest wet tissue in potassium hydroxide; wash residue with water, transfer residue to slide	PCM	5,000 f/g	No data	Whitwell et al. 1977
Tissue sections	Ash on slide; transfer residue to carbon support	TEM	No data	No data	Pooley 1976

Toxicological Profile for Asbestos (1995)
ACL Doc 10942 · Page 137 of 233
Digitized by Google
Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/137

TABLE 6-1. Analytical Methods for Determining Asbestos in Biological Samples (*continued*)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Tissue specimens	Predigest in 10% potassium hydroxide; collect residue by ultra-centrifugation; ash residue; transfer to carbon grids	TEM	0.2 x 10^5 f/g	13-70	Carter and Taylor 1980

AB = asbestos body; f/g = fibers per gram; f/L; = fibers per liter; f/mL; = fibers per milliliter; PCM = phase contrast microscopy; TEM = transmission electron microscopy

Toxicological Profile for Asbestos (1995)
ACL Doc 10942 · Page 138 of 233
Digitized by Google
Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/138

TABLE 6-2. Analytical Methods for Determining Asbestos in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Pump air through filter membrane; convert to optically transparent gel	PCM	<0.5 f/mL	±35	ASTM 1988
Air	Filter	PCM	No data	No data	NIOSH 1989a
Air	Filter; mount on carbon film	TEM	<0.04 f/mL	No data	NIOSH 1989b
Water	Filter; mount on carbon film	TEM at 20,000X	0.01 MFL	100±35	Anderson and Long 1980
Water	Extract into isooctane from water containing anionic surfactant	Microscope or color spot test	0.1 MFL	No data	Melton et al. 1978
Water	Filter; mount on carbon film	TEM	No data	No data	WHO 1986
Water	Place in ultrasonic bath (15 minutes); filter; dry and collapse filter; plasma etch; mount on carbon film	TEM	No data	No data	Brackett et al. 1992

f/mL = fibers per milliliter; MFL = million fibers per liter; PCM = phase contrast microscopy; TEM = transmission electron microscopy

Toxicological Profile for Asbestos (1995)
ACL Doc 10942 - Page 139 of 233
Digitized by Google
Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/139

that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Reliable methods exist for measuring asbestos fibers in biological tissues and fluids (Boatman et al. 1983; Carter and Taylor 1980; Wagner et al. 1982a). These methods (based on microscopic examination of fibers remaining after ashing and digestion) are sufficiently sensitive to quantify fiber burden in samples from both control (background) and exposed populations. However, there is considerable variability in the details of sample preparation and this makes inter-study comparisons difficult. For this reason, it would be helpful to develop a standardized method or group of methods for analysis of asbestos in biological materials, similar to the standardized methods for asbestos in air and water. A major limitation to current methods is that lung burdens can only be measured in excised tissue samples. Consequently, it is not possible to measure lung burdens in living persons except by biopsy. Development of some noninvasive method that would permit estimation of asbestos content *in vivo* would be especially valuable.

There are no chemical analytical methods recognized for measuring asbestos-induced health effects in humans. Clinical methods (x-ray, spirometry) for evaluating effects are discussed in Section 2.5. Development of sensitive and specific chemical or biochemical tests for asbestos-induced effects would be very valuable, especially if preclinical changes could be detected.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Standardized methods have been established for measurement of asbestos in air and water, since these are the media most likely to lead to human exposure (NIOSH 1989a, 1989b; WHO 1986). These methods are sufficiently sensitive to quantify asbestos both at background levels and at levels of health concern. However, the electron microscopic techniques which give the greatest amount of useful data are also the slowest and most costly. Further efforts to reduce the time and cost per analysis would be helpful.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/140

6.3.2 On-going Studies

Given the need and financial incentives for improved, faster asbestos analysis, studies are ongoing to improve these areas. Intense activity is underway in the areas of automation and computerization, especially with transmission electron microscopy and analytical electron microscopy.

A major area of concern is the possibility that asbestos fibers carry carcinogens in smoke such as benzidine, N,N-dimethylanaline, and benzo(a)pyrene to cells. Investigations are being carried out to detect such chemical impurities on asbestos fiber surfaces by a technique known as laser microprobe mass analysis (Warner 1988).

Reliability of asbestos analysis should be improved by new regulations requiring accreditation of asbestos-testing laboratories. The National Institute of Science and Technology (formerly the National Bureau of Standards) is conducting programs for accreditation of polarized light microscopy and transmission electron microscopy laboratories.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/141

7. REGULATIONS AND ADVISORIES

Because of its potential to cause adverse health effects in exposed people, numerous regulations and advisories have been established for asbestos by various international, national and state agencies. Such regulations and advisories control asbestos in various media, such as air and water, and how it is contained, handled, disposed, etc.

Major regulations and advisories pertaining to asbestos are summarized in Table 7-1. Most states have adopted and enforce the regulations and guidelines set by national agencies. For example, with regard to emissions standards, most states follow the National Emission Standards for Hazardous Air Pollutants established by EPA (in volume 40, Part 61 of the Code of Federal Regulations) for asbestos emissions. States may establish their own standards, but they are comparable to or more stringent than the ones set forth by EPA, OSHA, etc. (CELDS 1994). In addition, states may establish regulations for asbestos when federal regulations do not exist for a particular scenario (Kaplan 1993).

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/142

TABLE 7-1. Regulations and Guidelines Applicable to Asbestos

Agency	Description	Information	References
INTERNATIONAL			
IARC	Carcinogenic classification	Group 1[a]	IARC 1987
NATIONAL			
Regulations:			
a. Air:			
EPA OAQPS	NESHAP (emissions, disposal, recordkeeping, reporting)	Yes	EPA 1990a (40 CFR 61)
OSHA	PEL TWA	0.1 fiber/cc	OSHA 1994 (29 CFR 1910, 1915, 1926)
b. Water:			
EPA OW	MCL	$7x10^6$ fibers/L[b]	EPA 1991a, 1994 (40 CFR 141.51)
EPA OWRS	General permits under NPDES	Yes	EPA 1992d (40 CFR 122, App. D, Table II)
	General pretreatment regulations for existing and new sources	Yes	EPA 1988k (40 CFR 403)
c. Food:			
FDA	Component of food packaging material	Yes	FDA 1994 (21 CFR 175)
d. Other:			
EPA OERR	Reportable quantity	1 pound	EPA 1989g (40 CFR 302.4)
EPA OTS	Prohibition of manufacture and use of certain products and phase out of use in all other products	Overturned by U.S. Federal Court, 10/91	EPA 1989f, 1992a
	Asbestos abatement projects	Yes	EPA 1986d (40 CFR 763 Subpart G)
	Worker protection rule	Yes	EPA 1986d (40 CFR 763 Subpart G)
	Asbestos containing material in schools rule	Yes	EPA 1987b (40 CFR 763)
	Toxic Chemical Release Reporting	Yes	EPA 1988b (40 CFR 372)
Guidelines:			
a. Air:			
ACGIH	TLV TWA[c,d]	Confirmed human carcinogen	ACGIH 1993
	Amosite	0.5 fibers/cc	
	Chrysotile	2 fibers/cc	
	Crocidolite	0.2 fibers/cc	
	Other forms	2 fibers/cc	

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/143

TABLE 7-1. Regulations and Guidelines Applicable to Asbestos (continued)

Agency	Description	Information	References
NATIONAL (Cont.)			
NIOSH	Recommended exposure limit (in a 400-liter air sample), 100-min TWA[c]	0.1 fiber/cc	NIOSH 1992
	Potential occupational carcinogen	Yes	NIOSH 1992
b. Water:			
EPA OW	MCLG	$7x10^{6}$ fibers/L[b]	EPA 1991a, 1994 (40 CFR 141.51)
EPA OWRS	Ambient Water Quality Criteria (Ingesting water and organisms)	$3x10^{-4}$ fibers/L	EPA 1980
c. Other:			
EPA	Carcinogen classification	Group A[e]	IRIS 1993
	Cancer unit risk (inhalation)	0.23 per fibers/mL	
STATE			
Standards or Guidelines:			
a. Air:	Acceptable ambient air concentrations		NATICH 1992
Connecticut		0.001 µg/m³ (8 hours)	
Massachusetts		0.0001 fibers/cm³ (annual)	
		0.0002 fibers/cm³ (24 hours)	
Nevada		0.00	
Nevada - Las Vegas		1,000 fibers/m³ (24 hours)	
New York		5.0 µg/m³ (1 year)	
North Carolina		$2.8x10^{-11}$ fibers/mL (annual)	
North Dakota		0.00	
Pennsylvania - Philadelphia		0.005 µg/m³ (1 year)	
		0.005 fibers/cm³ (annual)	
South Carolina		0.00 µg/m³ (24 hours)	
Texas		0.03 µg/m³ (30 minutes)	
		0.003 µg/m³ (annual)	
Vermont		0.00012 µg/m³ (annual)	
Virginia		2.0 µg/m³ (24 hours)	
Washington (S West)		0.0000042 µg/m³ (annual)	
New Mexico		0.01 µg/m³ (duration NS)	CELDS 1994
b. Water:	Drinking water quality standards		
Kansas		$7.1x10^{6}$ fibers/L[b]	FSTRAC 1990
Minnesota		$7.1x10^{6}$ fibers/L[b]	
Rhode Island		$7x10^{6}$ fibers/L[b]	
Arizona		$7x10^{6}$ fibers/L[b]	CELDS 1994
Florida		$7x10^{6}$ fibers/L[b]	
Oklahoma		$7x10^{6}$ fibers/L[b]	
Utah		$7x10^{6}$ fibers/L[b]	
Wisconsin		$7x10^{6}$ fibers/L[b]	

Digitized by Google

TABLE 7-1. Regulations and Guidelines Applicable to Asbestos (continued)

Agency	Description	Information	References
STATE (Cont.)			
	Water and fish consumption		
Alabama		$3x10^4$ fibers/L	CELDS 1994
New Jersey		$3x10^4$ fibers/L	
Oregon		$3x10^4$ fibers/L	

[a] Group 1: Sufficient evidence for carcinogenicity in animals and humans
[b] Fibers greater than 10 μm
[c] Fibers greater than 5 μm in length
[d] A change in the TLV TWA for all forms of asbestos to 0.2 fibers/cc has been proposed for a trial period of one year, at which time it may be adopted (ACGIH 1993).
[e] Group A: Human carcinogen

ACGIH = American Conference of Governmental Industrial Hygienists; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; IARC = International Agency for Research on Cancer; MCL = Maximum Contaminant Level; MCLG = Maximum Contaminant Level Goal; NESHAP = National Emission Standards of Hazardous Air Pollutants; NIOSH = National Institute for Occupational Safety and Health; NPDES = National Pollutant Discharge Elimination System; NS = not specified; OAQPS = Office of Air Quality, Planning, and Standards; OERR = Office of Emergency and Remedial Response; OSHA = Occupational Safety and Health Administration; OTS = Office of Toxic Substances; OW = Office of Drinking Water; OWRS = Office of Water Regulations and Standards; PEL = Permissible Exposure Limit; TLV = Threshold Limit Value; TWA = Time-Weighted Average

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/145

8. REFERENCES

*Aberle DR, Gamsu G, Ray CS, et al. 1988a. Asbestos-related pleural and parenchymal fibrosis: Detection with high-resolution CT. Radiology 166:729-734.

*Aberle DR, Gamsu G, Ray CS. 1988b. High resolution CT of benign asbestos-related diseases: Clinical and radiographic correlation. Am J Radiol 151:883-891.

ACGIH. 1986. Documentation of the threshold limit values and biological exposure indices. 5th ed. American Conference of Governmental Industrial Hygienists. Cincinnati, OH.

ACGIH. 1991. American Conference of Governmental Industrial Hygienists. Documentation of the threshold limit values and biological exposure indices. 6th ed. Cincinnati, OH.

ACGIH. 1992. 1992-1993 Threshold limit values for chemical substances in the work environment. American Conference of Governmental Industrial Hygienists. Cincinnati, OH.

*ACGIH. 1993. 1993-1994 Threshold Limit Values for chemical substances and physical agents and biological exposure indices. American Conference of Governmental Industrial Hygienists. Cincinnati, OH.

*Acheson ED, Gardner MJ, Pippard EC, et al. 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.

*Adachi S, Kawamura K, Yoshida S, et al. 1992a. Oxidative damage on DNA induced by asbestos and man-made fibers in vitro. Int Arch Occup Environ Health 63:553-557.

Adachi S, Kawamura K, Kimura K, et al. 1992b. Tumor incidence was not related to the thickness of visceral pleural in female syrian hamsters intratracheally administered amphibole asbestos or manmade fibers. Environ Res 58:55-65.

Adachi S, Yoshida S, Kawamura K, et al. 1994. Inductions of oxidative DNA damage and mesothelioma by crocidolite, with special reference to the presence of iron inside and outside of asbestos fiber. Carcinogenesis 15(4):753-758.

*Adamson IY, Bowden DH. 1987a. Response of mouse lung to crocidolite asbestos. 2. Pulmonary fibrosis after long fibres. J Pathol 152:109-117.

*Adamson IY, Bowden DH. 1987b. Response of mouse lung to crocidolite asbestos. 1. Minimal fibrotic reaction to short fibres. J Pathol 152:99-107.

Adamson IYR, Bowden DH. 1990. Pulmonary reaction to long and short asbestos fibers is independent of fibroblast growth factor production by Alveolar macrophages. Am J Pathol 137:523-529

---

*Cited in text

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/146

8. REFERENCES

Addison J, Browne K, Davis JM, et al. 1993. Asbestos fibers in parenteral medication. Regul Toxicol Pharmacol 18(3):371-380.

Ahrens W, Joeckel K-H, Patzak W, et al. 1991. Alcohol smoking and occupational factors in cancer of the larynx: A case-control study. Am J Ind Med 20(4):477-493.

Aisner J. 1989. Therapeutic approach to malignant mesothelioma. Chest 96(Supp 1):95S-97S

*Akira M, Yokoyama K, Yamamoto S, et al. 1991. Early asbestosis: Evaluation with high resolution CT. Thoracic Radiology 409-416.

*Albin M, Jakobsson K, Attewell R, et al. 1990a. Mortality and cancer morbidity in cohorts of asbestos cement workers and referents. Br J Ind Med 47:602-610.

*Albin M, Johansson L, Pooley FD, et al. 1990b. Mineral fibres, fibrosis, and asbestos bodies in lung tissue from deceased asbestos cement workers. Br J Ind Med 47:767-774.

*Alden HS, Howell WM. 1944. The asbestos corn. Archives of Dermatology and Syphilology. 49:312-314.

Al Jarad N, Poulakis N, Pearson MC, et al. 1991. Assessment of asbestos-induced pleural disease by computer tomography - correlation with chest radiograph and lung function. Respir Med 85:203-208.

*Al Jarad N, Macey M, Uthayakumar S, et al. 1992. Lymphocyte subsets in subjects exposed to asbestos: Changes in circulating natural killer cells. Br J Ind Med 49(11) 811-814.

*Al Jarad N, Strickland B, Bothamley G, et al. 1993. Diagnosis of asbestosis by a time expanded wave form analysis, auscultation and high resolution computed tomography: A comparative study. Thorax 48(4)347-353.

*Amandus HE, Wheeler R. 1987. The mobidity and mortality of vermiculite miners and millers exposed to tremolite-actimolite: Part II. Mortality. Am J Med 11:15-26.

*Andersen A, Glattre E, Johansen BV. 1993. Incidence of cancer among lighthouse keepers exposed to asbestos in drinking water. Am J Epidemiol 138(9):682-687.

*Anderson HA, Lilis R, Daum SM, et al. 1976. Household-contact asbestos neoplastic risk. Ann NY Acad Sci 271:311-323.

*Anderson HA, Lilis R, Daum SM, et al. 1979. Asbestosis among household contacts of asbestos factory workers. Ann NY Acad Sci 387-399.

Andrion A, Bosia S, Paoletti L, et al. 1994. Malignant peritoneal mesothelioma in a 17-year-old boy with evidence of previous exposure to chrysotile and tremolite asbestos. Hum Pathol 25(6):617-622.

*Anton-Culver H, Culver BD, Kurosaki T. 1988. Immune response in shipyard workers with x-ray abnormalities consistent with asbestos exposure. Br J Ind Med 45:464-468.

Digitized by Google

8. REFERENCES

*Anton-Culver H, Culver BD, Kurosaki T. 1989. An epidemiologic study of asbestos-related chest x-ray changes to identify work areas of high risk in a shipyard population. Appl Ind Hyg 4:110-118.

Appel JD, Fasy TM, Kohtz JD, et al. 1988. Asbestos fibers mediate transformation of monkey cells by exogenous plasmid DNA. Proc Natl Acad Sci USA 85:7670-7674.

Arden MG, Adamson IYR. 1992. Collagen synthesis and degradation during the development of asbestos-induced pulmonary fibrosis. Department of Pathology, University of Manitoba, Winnipeg, Canada. Exp Lung Res 18:9-20.

Arif JM, Khan SG, Aslam M, et al. 1992. Diminution in kerosene-mediated induction of drug metabolizing enzymes by asbestos in rat lungs. Pharmacol Toxicol 71:37-40.

*Armstrong BK, DeKlerk NH, Musk AW, et al. 1988. Mortality in miners and millers of crocidolite in Western Australia. Br J Ind Med 45:5-13.

Ashcroft T, Heppleston AG. 1973. The optical and electron microscopic determination of pulmonary asbestos fibre concentration and its relation to the human pathological reaction. J Clin Pathol 26:224-234.

*ASTM. 1988. Standard test method for airborne asbestos concentration in workplace atmosphere - method D 4240-83. In: 1988 annual book of ASTM standards. Vol 11.03. Atmospheric analysis, occupational safety and health. Philadelphia, PA: American Society for Testing and Materials, 300-308.

*ATSDR. 1989. Agency for Toxic Substances and Disease Registry. Part V. Federal Register 54:37619-37633.

*Auerbach O, Conston AS, Garfinkel L, et al. 1980. Presence of asbestos bodies in organs other than the lung. Chest 77:133-137.

*Awadalla FT, Habashi F, Page M. 1990. Reaction of chrysotile asbestos with phosphate ion in relation to toxicity. J Chem Tech Biotechnol 49:183-196.

*Babu KA, Lakkad BC, Nigam SK, et al. 1980. *In vitro* cytological and cytogenetic effects of an Indian variety of chrysotile asbestos. Environ Res 21:416-422.

*Baker EL, Dagg T, Greene RE. 1985. Respiratory illness in the construction trades. I. The signifance of asbestos-associated pleural disease among sheet metal workers. J Occup Med 27:483-489.

Balmes JR, Daponte A, Cone JE. 1991. Asbestos-related disease in custodial and building maintenance workers from a large municipal school district. Ann NY Acad Sci 540-549.

Barbers RG, Oishi J. 1987. Effects of *in vitro* asbestos exposure on natural killer and antibody-dependent cellular cytotoxicity. Environ Res 43:217-226.

*Barbers RG, Abraham JL. 1989. Asbestosis occurring after brief inhalation exposure: Usefulness of bronchoalveolar lavage in diagnosis. Br J Ind Med 46:106-110.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/148

8. REFERENCES

Baris I, Simonato L, Artivinli M, et al. 1987. 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 39:10-17.

Baris YI, Bilir N, Artvinli M, et al. 1988a. An epidemiological study in an Anatolian village environmentally exposed to tremolite asbestos. Brit J Ind Med 45:838-840.

Baris YI, Artvinli M, Sahin AA, et al. 1988b. Non-occupational asbestos related chest diseases in a small Anatolian village. Br J Ind Med 45:841-842.

*Barnes GD, Dourson M. 1988. Reference dose (RfD): Description and use in health risk assessments. Regul Toxicol Pharmacol 8:471-486.

Barnes D, Bellin J, DeRosa C, et al. 1987. Reference dose (RfD): Description and use in health risk assessments. Vol. I. Appendix A: Integrated risk information system supportive documentation. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment. EPA/600/8-86/032a.

Barnhart S, Thornquist M, Omenn GS, et al. 1990. The degree of roentgenographic parenchymal opacities attributable to smoking among asbestos-exposed subjects. Am Rev Respir Dis 141:1102-1106.

Barrett JC. 1993. Mechanisms of multistep carcinogenesis and carcinogen risk assessment. Environ Health Perspect 100(4):9-20, 109.

*Barrett JC, Lam PW, Wiseman RW. 1989. Multiple mechanisms for the carcinogenic effects of asbestos and other mineral fibers. Environ Health Perspect 81:81-89.

Barrett JC, Thomassen DG, Hesterberg TW. 1983. Role of gene and chromosomal mutations in cell transformation. Ann NY Acad Sci 407:291-300.

Bateman ED, Benatar SR. 1987. Asbestos-induced diseases: Clinical perspectives. Q J Med 62:183-194.

*Becklake MR. 1976. Asbestos-related disease of the lung and other organs: Their epidemiology and implications for clinical practice. Am Rev Resp Dis 114:187-227.

*Begin R, Martel M, Desmarais Y, et al. 1986. Fibronectin and procollagen 3 levels in bronchoalveolar lavage of asbestos-exposed human subjects and sheep. Chest 89:237-243.

Begin R, Masse S, Rola-Pleszczynski M, et al. 1987a. Asbestos exposure dose-bronchoalveolar milieu response in asbestos workers and the sheep model: Evidences of a threshold for chrysotile-induced fibrosis. Drug Chem Toxicol 10:87-107.

*Begin R, Boileau R, Peloquin S. 1987b. Asbestos exposure, cigarette smoking, and airflow limitation in long-term Canadian chrysotile miners and millers. Am J Ind Med 11:55-66.

Begin R, Cantin A, Masse S. et al. 1988. Effects of cyclophosphamide treatment in experimental asbestosis. Exp Lung Res 14:823-836.

Digitized by Google

8. REFERENCES

Begin R, Cantin A, Masse S. 1991. Influence of continued asbestos exposure on the outcome of asbestosis in sheep. Exp Lung Res 17:971-984.

Begin R, Cantin A, Sebastien P. 1990. Chrysotile asbestos exposures can produce an alveolitis with limited fibrosing activity in a subset of high fibre retainer sheep. Eur Respir J 3:81-90.

Begin R, Ostiguy G, Filion R, et al. 1992. Recent advances in the early diagnosis of asbestosis. Semin Roentgenol 27:121-139.

Beland FA, Poirier MC. 1991. Biomarkers of human exposure to carcinogens: An overview. Biomed Environ Sci 4(1-2):69-72.

*Bellmann B, Muhle H, Pott F, et al. 1987. Persistence of man-made mineral fibres (MMMF) and asbestos in rat lungs. Ann Occup Hyg 31:693-709.

Berger M, de Hazen M, Nejjari M, et al. 1993. Radical oxidation reactions of the purine moiety of 2'-deoxyribonucleosides and DNA by iron-containing minerals. Carcinogenesis 14(1):41-46.

Berlin J, Frumkin H. 1988. Exposure to asbestos and the risk of gastrointestinal cancer [Letter]. Br J Ind Med 45:575.

Berman J. 1984. Beshada v. Johns-Manville Products Corp.: The function of state of the art evidence in strict products liability. Am J Law Med 10:93-114.

Berman DW, Crump KS. 1989. Relative potency of asbestos fibers of different lengths. Toxicol Pathol 17:841-842.

*Bermudez E, Everitt J, Walker C. 1990. Expression of growth factor and growth factor receptor RNA in rat pleural mesothelial cells in culture. Exp Cell Res 190:91-98.

*Berry G, Newhouse ML. 1983. Mortality of workers manufacturing friction materials using asbestos. Br J Ind Med 40:1-7.

*Berry G, Gilson JC, Holmes S, et al. 1979. Asbestosis: A study of dose-response relationships in an asbestos textile factory. Br J Ind Med 36:98-112.

*Berry G, Newhouse ML, Antonis P. 1985. Combined effect of asbestos and smoking on mortality from lung cancer and mesothelioma in factory workers. Br J Ind Med 42:12-18.

Berry G, Rogers AJ, Pooley FD. 1989. Mesotheliomas - asbestos exposure and lung burden. IARC Sci Pub 90:486-496.

Bertrand R, Pezerat H. 1980. Fibrous glass: Carcinogenicity and dimensional characteristics. IARC Sci Publ 30:901-911.

Bevan DR, Ulman MR. 1991. Examination of factors that may influence disposition of benzo[a]pyrene in vivo: Vehicles and asbestos. Cancer Lett 57:173-179.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/150

8. REFERENCES

Bianchi C, Bittesini L, Brollo A. 1986. Asbestos exposure and Alzheimer disease. Ital J Neurol Sci 7:145-151.

Bianchi C, Brollo A, Ramani L, et al. 1993a. Asbestos-related mesothelioma in Monfalcone, Italy. Am J Ind Med 24(2):149-160.

*Bianchi C, Brollo A, Zuch C. 1993b. Asbestos-related familial mesothelioma. Eur J Cancer Prev 2(3):247-250.

*Bignon J, Jaurand MC. 1983. Biological *in vitro* and *in vivo* responses of chrysotile versus amphiboles. Environ Health Perspect 51:73-80.

*Bignon J, Sebastien P, DiMenza L, et al. 1979. French mesothelioma registry. Ann NY Acad Sci 330:455-466.

*Bisson G, Lamoureux G, Begin R. 1987. Quantitative gallium 67 lung scan to assess the inflammatory activity in the pneumoconioses. Seminars in Nuclear Medicine 1:72-80.

*Bissonnette E, Bubois C, Rola-Pleszczynski M. 1989. Changes in lymphocyte function and lung histology during the development of asbestosis and silicosis in the mouse. Res Commun Chem Pathol Pharmacol 65:211-227.

*Bissonnette E, Carre B, Dubois C, et al. 1990. Inhibition of alveolar macrophage cytotoxicity by asbestos: possible role of prostaglandins. J Leukoc Biol 47:129-134.

Blanc P. 1991. Cigarette smoking, asbestos, and parenchymal opacities revisited. Ann NY Acad Sci 133-141.

*Blanc PD, Golden JA, Gamsu G, et al. 1988. Asbestos exposure-cigarette smoking interactions among shipyard workers. JAMA 259:370-373.

Blot WJ, Harrington JM, Toledo A, et al. 1978. Lung cancer after employment in shipyards during World War II. The New England Journal of Medicine 299:620-624.

*Boatman ES, Merrill T, O'Neill A, et al. 1983. Use of quantitative analysis of urine to assess exposure to asbestos fibers in drinking water in the Puget Sound region. Environ Health Perspect 53:131-141.

Boehme DS, Maples KR, Henderson RF. 1992. Glutathione release by pulmonary alveolar macrophages in response to particles in vitro. Toxicol Lett 60:53-60.

*BOHS. 1968. Hygiene standards for chrysotile asbestos dust. British Occupational Hygiene Society. Ann Occup Hyg 11:47-69.

*BOHS. 1983. A study of the health experience in two U. K. asbestos factories. British Occupational Hygiene Society. Ann Occup Hyg 27:1-13.

Boltin WR, Clark BH, Detter-Hoskin L, et al. 1989. Alternative instrumentation in the analysis for asbestos in various media. American Laboratory (April):15-25.

Digitized by Google

8. REFERENCES

*Bolton RE, Davis JM, Lamb D. 1982a. The pathological effects of prolonged asbestos ingestion in rats. Environ Res 29:134-150.

*Bolton RE, Davis JM, Donaldson K, et al. 1982b. Variations in the carcinogenicity of mineral fibres. Ann Occup Hyg 26:569-582.

*Bolton RE, Vincent JH, Jones AD, et al. 1983. An overload hypothesis for pulmonary clearance of UICC amosite fibres inhaled by rats. Br J Ind Med 40:264-272.

*Bonneau L, Malard C, Pezerat H. 1986. Studies on surface properties of asbestos: II. Role of dimensional characteristics and surface properties of mineral fibers in the induction of pleural tumors. Environ Res 41:268-275.

Bonner JC, Goodell AL, Coin PG, et al. 1993. Chrysotile asbestos upregulates gene expression and production of alpha-receptors for platelet-derived growth factor (PDGF-AA) on rat lung fibroblasts. J Clin Invest 92(1):425-430.

Booth SJ, Weaver EJ. 1986. Malignant pleural mesothelioma five years after domestic exposure to blue asbestos [Letter]. Lancet 1:435.

Bourbeau J, Ernst P, Chrome J, et al. 1988. Relationship between respiratory impairment and asbestos related pleural disease in an active workforce [Abstract]. Am Rev Respir Dis 137 (Suppl): 92.

Botta M, Magnani C, Terracini B, et al. 1991. Mortality from respiratory and digestive cancers among asbestos cement workers in Italy. Cancer Detect Prev 15:445-447.

*Boutin G, Viallat JR, Steinbauer J, et al. 1989. Bilateral pleural plaques in Corsica: a marker of non-occupational asbestos exposure. IARC Sci Publ 90:406-410.

*Boylan AM, Ruegg C, Kim JK, et al. 1992. Evidence of a role for mesothelial cell-derived interleukin 8 in the pathogenesis of asbestos-induced pleurisy in rabbits. J Clin Invest 89:1257-1267.

*Brackett KA, Clark PJ, Millette JR. 1992. Method for the analysis of asbestos fibers in water using MCE filters. Microscope 40(3):159-163.

Branchaud RM, MacDonald JL, Kane AB. 1989. Induction of angiogenesis by intraperitoneal injection of asbestos fibers. FASEB J 3:1747-1752.

*Branchaud RM, Garant LJ, Kane AB. 1993. Pathogenesis of mesothelial reactions to asbestos fibers. Monocyte recruitment and macrophage activation. Pathobiology 61(3-4):154-163.

*Bravo MP, Del Rey-Calero J, Conde M. 1988. Bladder cancer and asbestos in Spain. Rev Epidem et Sante Publ 36:10-14.

*Bresnitz EA, Gilman MJ, Gracely EJ, et al. 1993. Asbestos-related radiographic abnormalities in elevator construction workers. Am Rev Respir Dis 147(6):1341-1344.

*Britton MG. 1982. Asbestos pleural disease. Br J Dis Chest 76:1-10.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/152

8. REFERENCES

*Brody AR. 1986. Pulmonary cell interactions with asbestos fibers *in vivo* and *in vitro*. Chest 89(Suppl 3):155S-159S.

Brody AR. 1993. Asbestos-induced lung disease. Environ Health Perspect 100(4):21-30.

Brown A. 1974. Lymphohematogenous spread of asbestos [Commentary]. Environ Health Perspect 9:203-204.

*Brown RC, Carthew P, Hoskins JA, et al. 1990. Surface modification can affect the carcinogenicity of asbestos. Carcinogenesis 11:1883-1885.

*Brown RC, Poole A, Fleming GTA. 1983. The influence of asbestos dust on the oncogenic transformation of C3HlOT1/2 cells. Cancer Letters 18:221-227.

*Brown RC, Sara EA, Hoskins JA, et al. 1991. Factors affecting the interaction of asbestos fibres with mammalian cells: a study using cells in suspension. Ann Occup Hyg 35:25-34.

*Browne K. 1983. Asbestos-related mesothelioma: Epidemiological evidence for asbestos as a promoter. Arch Environ Health 38:261-266.

*Browne K. 1986a. A threshold for asbestos related lung cancer. Br J Ind Med 43:556-558.

*Browne K. 1986b. Is asbestos or asbestosis the cause of increased risk of lung cancer in asbestos workers [Editorial]? Br J Ind Med 43:145-149.

Browne KA, 1991. Asbestos related malignancy and the Cairns hypothesis. [Letter] Br J Ind Med 48:73-76.

Brownson RC, Alavanja MCR, Chang JC. 1993. Occupational risk factors for lung cancer among nonsmoking women a case-control study in Missouri, United States. Cancer Causes Control 4(5):449-454.

Burdett GJ, Jaffrey SAMT, Rood AP. 1989. Airborne asbestos fibre levels in buildings: A summary of UK measurements. IARC Sci Pub 90:277-290.

Callahan KS, Griffith DE, Garcia JGN. 1990. Asbestos exposure results in increased lung procoagulant activity in vivo and in vitro. Chest 98:112-119.

*Cantin A, Dubois F, Begin R. 1988. Lung exposure to mineral dusts enhances the capacity of lung inflammatory cells to release superoxide. J Leukoc Biol 43:299-303.

*Cantin AM, Larivee P, Martel M, et al. 1992. Hyaluronan (hyaluronic acid) in lung lavage of asbestos-exposed humans and sheep. Lung 170:211-220.

*Carter RE, Taylor WF. 1980. Identification of a particular amphibole asbestos fiber in tissues of persons exposed to a high oral intake of the mineral. Environ Res 21:85-93.

Digitized by Google

8. REFERENCES

Carthew P, Hill RJ, Edwards RE, et al. 1992. Intrapleural administration of fibers induces mesothelioma in rats in the same relative order of hazard as occurs in man after exposure. Hum Exp Toxicol 11(6):530-534.

Carthew P, Edwards RE, Dorman BM, et al. 1993. A reappraisal of the carcinogenicity of surface modified asbestos fibers. Carcinogenesis 14(11):2413-2414.

Case BW. 1991. Health effects of tremolite. Now and in the future. Ann NY Acad Sci 491-504.

*Casey G. 1983. Sister-chromatid exchange and cell kinetics in CHO-Kl cells, human fibroblasts and lymphoblastoid cells exposed *in vitro* to asbestos and glass fibre. Mutat Res 116:369-377.

Castellan RM, Sanderson WT, Petersen MR. 1985. Prevalence of radiographic appearance of pneumoconiosis in an unexposed blue collar population. Am Rev Respir Dis 131:684-686.

*Cavalleri A, Gobba F, Bacchella L, et al. 1991. Evaluation of serum aminoterminal propeptide of type III procollagen as an early marker of the active fibrotic process in asbestos-exposed workers. Scand J Work Environ Health 17:139-144.

Cazzadori A, Malesani F, Romeo L. 1992. Malignant pleural mesothelioma caused by non-occupational childhood exposure to asbestos. Br J Ind Med 49:599

CCRIS. 1992. Chemical Carcinogenesis Research Information System. National Library of Medicine, Bethesda, MD. November 2, 1992.

CCTTE. 1988. Computerized Listing of Chemicals Being Tested for Toxic Effects. United Nations Environment Programme, International Programme on Chemical Safety, International Register of Potentially Toxic Chemicals, Geneva, Switzerland.

*CDC/ATSDR. 1990. Biomarkers of organ damage or dysfunction for the renal, hepatobiliary and immune systems. Atlanta, GA: CDC/ATSDR Subcommittee on Biomarkers of Organ Damage and Dysfunction, Centers for Disease Control, Agency for Toxic Substances and Disease Registery. Summary report, August 27, 1990.

*CELDS. 1994. Computer-Environmental Legislative Data Systems. University of Illinois, Urbana, IL. August 1994.

Chamberlain M, Brown RC. 1978. The cytotoxic effects of asbestos and other mineral dust in tissue culture cell lines. Br J Exp Pathol 59:183-189.

*Chamberlain M, Tarmy EM. 1977. Asbestos and glass fibres in bacterial mutation tests. Mutat Res 43:159-164.

Chan CK, Gee JB. 1988. Asbestos exposure and laryngeal cancer: An analysis of the epidemiologic evidence. J Occup Med 30:23-27.

*Chang L-Y, Overby LH, Brody AR, et al. 1988. Progressive lung cell reactions and extracellular matrix production after a brief exposure to asbestos. Am J Pathol 131:156-170.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/154

8. REFERENCES

*Chang MJ, Joseph LB, Stephens RE, et al. 1990. Modulation of biological processes by mineral fiber adsorption of macromolecules in vitro. JEPTO 10:89-93.

*Chao CC, Aust AE. 1994. Effect of long-term removal of iron from asbestos by desferrioxamine B on subsequent mobilization by other chelators and induction of DNA single-strand breaks. Arch Biochem Biophys 308(1):64-69.

Chatfield EJ, Dillon MJ, Stott WR. 1984. Evaluation of turbidometric methods for monitoring of asbestos fibers in water. Athens, GA: U.S. Environmental Protection Agency, Office of Research and Development. EPA-600/4-84-071. NTIS PB84-232511.

Chen CR, Chang HY, Suo J, et al. 1992. Occupational exposure and respiratory morbidity among asbestos workers in Taiwan. J Formos Med Assoc 91(12):1138-1142.

Cheng WN, Kong J. 1992. A retrospective mortality cohort study of chrysotile asbestos products workers in Tianjin 1972-1987. Environ Res 59(1):271-278.

*Chesson J, Hatfield J, Schultz B, et al. 1990. Airborne asbestos in public buildings. Environ Res 51:100-107.

*Choi I, Smith RW. 1972. Kinetic study of dissolution of asbestos fibers in water. J Colloid Interface Sci 40:253-262.

Chouroulinkov I. 1989. Experimental studies on ingested fibres. IARC Sci Publ 90:112-126.

*Churg A. 1986. Nonneoplastic asbestos-induced disease. Mt Sinai J Med (NY) 53:409-415.

*Churg A. 1988. Chrysotile, tremolite, and malignant mesothelioma in man. Chest 93:621-628.

*Churg A, DePaoli L. 1988. Environmental pleural plaques in residents of a Quebec chrysotile mining town. Chest 94:58-60.

Churg A, Stevens B. 1993. Absence of amosite asbestos in airway mucosa of non-smoking long term workers with occupational exposure to asbestos. Br J Ind Med 50(4):355-359.

*Churg A, Wright JL. 1989. Fibre content of lung in amphibole- and chrysotile-induced mesothelioma: Implications for environmental exposure. IARC Sci Pub 90:314-318.

*Churg A, Wright JL, Depaoli L, et al. 1989a. Mineralogic correlates of fibrosis in chrysotile miners and millers. Am Rev Respir Dis 139:891-896.

*Churg A, Wright JL, Gilks B, et al. 1989b. Rapid short-term clearance of chrysotile compared with amosite asbestos in the guinea pig. Am Rev Respir Dis 139:885-890.

*Churg A, Wright JL, Hobson J, et al. 1992. Effects of cigarette smoke on the clearance of short asbestos fibres from the lung and a comparison with the clearance of long asbestos fibres. Int J Exp path 73:287-297.

Digitized by Google

8. REFERENCES

*Churg A, Wright JL, Wiggs B, et al. 1990. Mineralogic parameters related to amosite asbestos-induced fibrosis in humans. Am Rev Respir Dis 142:1331-1336.

Cicioni C, London SJ, Garabrant DH, et al. 1991. Occupational asbestos exposure and mesothelioma risk in Los Angeles county: application of an occupational hazard survey job-exposure matrix. Am J Ind Med 20:371-379.

Clansky KB, ed. 1986. Chemical guide to the OSHA hazard communication standard. Burlingame, CA: Roytech Publications, Inc., 100, B-3, C-3, E-3.

CLC. 1988. Coordinated List of Chemicals. U. S. Environmental Protection Agency, Office of Research and Development, Washington, DC.

*Coin PG, Roggli VL, Brody AR. 1992. Deposition, clearance and translocation of chrysotile asbestos from peripheral and central regions of the rat lung. Environ Res 58:97-116.

*Cole RW, Ault JG, Hayden JH, et al. 1991. Crocidolite asbestos fibers undergo size-dependent microtubule-mediated transport after endocytosis in vertebrate lung epithelial cells. Cancer Res 51:4942-4947.

Conforti PM. 1983. Effect of population density on the results of the study of water supplies in five California counties. Environ Health Perspect 53:69-78.

*Conforti PM, Kanarek MS, Jackson LA, et al. 1981. Asbestos in drinking water and cancer in the San Francisco Bay Area: 1969-1974 incidence. J Chronic Dis 34:211-224.

*Constantinidis K. 1977. Pneumoconiosis and rheumatoid arthritis (Caplan's syndrome). Br J Clin Pract 31:25-31.

Constantopoulos SH, Dalavanga YA, Sakellariou K, et al. 1992. Lymphocytic alveolitis and pleural calcifications in nonoccupational asbestos exposure: Protection against neoplasia? Am Rev Respir Dis 146(6):1565-1570.

Cook PM. 1983. Review of published studies on gut penetration by ingested asbestos fibers. Environ Health Perspect 53:121-130.

*Cook PM, Olson GF. 1979. Ingested mineral fibers: Elimination in human urine. Science 204:195-198.

*Cook PM, Palekar LD, Coffin DL. 1982. Interpretation of the carcinogenicity of amosite asbestos and ferroactinolite on the basis of retained fiber dose and characteristics in vivo. Toxicol Lett 13:151-158.

*Cordier S, Lazar P, Brochard P, et al. 1987. Epidemiologic investigation of respiratory effects related to environmental exposure to asbestos inside insulated buildings. Arch Environ Health 42:303-309.

Corhay JL, Delavignette JP, Bury T, et al. 1990. Occult exposure to asbestos in steel workers revealed by bronchoalveolar lavage. Arch Environ Health 45:278-282.

Digitized by Google

8. REFERENCES

*Corpet DE, Pirot V, Goubet I. 1993. Asbestos induces aberrant crypt foci in the colon of rats. Cancer Letters 74(3):183-187.

Cote RJ, Jhanwar SC, Novick S, et al. 1991. Genetic alterations of the p53 gene are a feature of malignant mesotheliomas. Cancer Res 51(19):5410-5416.

Craighead JE. 1987. Current pathogenetic concepts of diffuse malignant mesothelioma. Hum Pathol 18:544-557.

Craighead JE, Mossman BT, Bradley BJ. 1980. Comparative studies on the cytotoxicity of amphibole and serpentine asbestos. Environ Health Perspect 34:37-46.

Craighead JE, Abraham JL, Churg A, et al. 1982. The pathology of asbestos-associated diseases of the lungs and pleural cavities: diagnostic criteria and proposed grading schema. Arch Pathol Lab Med 106:544-597.

*Craun GF, Millette JR, Woodhull RS, et al. 1977. Exposure to asbestos fibers in water distribution systems. In: Proceedings of the 97th Annual Conference of the American Waterworks Association, Anaheim, California, May 8-13, 1-13.

*CRISP Database. 1994. Computer Retrieval of Information on Scientific Projects. National Institutes of Health, Public Health Service, U.S. Department of Health and Human Services. Washington, DC. December 1992.

Crotty TB, Myers JL, Katzenstein A-L, et al. 1994. Localized malignant mesothelioma: A clinicopathologic and flow cytometric study. American Journal of Surgical Pathology 18(4):357-363.

*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(2):161-169.

Cunningham HM, Pontefract R. 1971. Asbestos fibres in beverages and drinking water. Nature 232:332-333.

*Cunningham HM, Pontefract RD. 1973. Asbestos fibers in beverages, drinking water, and tissues: Their passage through the intestinal wall and movement through the body. J AOAC 56:976-981.

*Cunningham HM, Pontefract RD. 1974. Placental transfer of asbestos. Nature 249:177-178.

*Cunningham HM, Pontefract RD, O'Brien RC. 1976. Quantitative relationship of fecal asbestos to asbestos exposure. J Toxicol Environ Health 1:377-379.

*Cunningham HM, Moodie CA, Lawrence GA, et al. 1977. Chronic effects of ingested asbestos in rats. Arch Environ Contam Toxicol 6:507-513.

Daniel FB. 1983. *In vitro* assessment of asbestos genotoxicity. Environ Health Perspect 53:163-167.

*Davies D, Andrews MI, Jones JS. 1991. Asbestos induced pericardial effusion and constrictive pericarditis. Thorax 46(6):429-432.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/157

8. REFERENCES

*Davis JM. 1970. The long term fibrogenic effects of chrysotile and crocidolite asbestos dust injected into the pleural cavity of experimental animals. Br J Exp Pathol 5:617-627.

*Davis JM. 1972. The fibrogenic effects of mineral dusts injected into the pleural cavity of mice. Br. J Exp Pathol 53:190-201.

Davis JM. 1975. The use of animal experiments in the study of asbestos bioeffects. Hefte Unfallheilkd (Iss 126):564-574.

Davis JM. 1979. The use of animal models for studies on asbestos bioeffects. Ann NY Acad Sci 330:795-798.

Davis JM. 1981. The biological effect of mineral fibres. Ann Occup Hyg 24:227-234.

Davis JM. 1984. The pathology of asbestos related disease. Thorax 39:801-808.

Davis JM, Coniam SW. 1973. Experimental studies on the effects of heated chrysotile asbestos and automobile brake lining dust injected into the body cavities of mice. Exp Mol Pathol 19:339-353.

*Davis JM, Cowie HA. 1990. The relationship between fibrosis and cancer in experimental animals exposed to asbestos and other fibers. Environ Health Perspect 88:305-309.

*Davis JM, 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 JM, Addison J, Bolton RE, et al. 1985. Inhalation studies on the effects of tremolite and brucite dust in rats. Carcinogenesis 6:667-674.

*Davis JM, Addison J, Bolton RE, et al. 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 JM, Beckett ST, Bolton RE, et al. 1980a. The effects of intermittent high asbestos exposure (peak dose levels) on the lungs of rats. Br J Exp Pathol 61:272-280.

*Davis JM, Beckett ST, Bolton RE, et al. 1980b. A comparison of the pathological effects in rats of the UICC reference samples of amosite and chrysotile with those of amosite and chrysotile collected from the factory environment. IARC Sci Publ 30:285-292.

*Davis JM, Bolton BG, Niven K. 1991a. Mesothelioma dose response following intraperitoneal injection of mineral fibres. Int J Exp Path 72:263-274.

Davis JM, Bolton RE, Brown D, et al. 1986b. Experimental lesions in rats corresponding to advanced human asbestosis. Exp Mol Pathol 44:207-221.

*Davis JM, Bolton RE, Douglas AN, et al. 1988. Effects of electrostatic charge on the pathogenicity of chrysotile asbestos. Br J Ind Med 45:292-299.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/158

8. REFERENCES

*Davis JM, Gylseth B, Morgan A. 1986c. Assessment of mineral fibres from human lung tissue. Thorax 41:167-175.

Davis JM, Jones AD, Miller BG. 1991b. Experimental studies in rats on the effects of asbestos inhalation coupled with the inhalation of titanium dioxide or quartz. Int J Exp Path 72:501-525.

Dawson A, Gibbs A, Browne K, et al. 1992. Familial mesothelioma details of 17 cases with histopathologic findings and mineral analysis. Cancer (Phila) 70(5):1183-1187.

Dawson A, Gibbs AR, Pooley FD, et al. 1993. Malignant mesothelioma in women. Thorax 48(3):269-274.

*deKlerk NH, Armstrong BK, Musk AW, et al. 1989. Cancer mortality in relation to measures of occupational exposure to crocidolite at Wittenoom Gorge in Western Australia. Br J Ind Med 46:529-536.

*deKlerk NH, Musk AW, Armstrong BK, et al. 1991. Smoking, exposure to crocidolite, and the incidence of lung cancer and asbestosis. Br J Ind Med 48:412-417.

deKlerk NH, Musk AW, Cookson WO, et al. 1993. Radiographic abnormalities and mortality in subjects with exposure to crocidolite. Br J Ind Med 50(10):902-906.

*Delahunty TJ, Hollander D. 1987. Toxic effect on the rat small intestine of chronic administration of asbestos in drinking water. Toxicol Lett 39:205-209.

Dement JM. 1991. Carcinogenicity of chrysotile asbestos: a case control study of textile workers. Cell Biol Toxicol 7:59-65.

*Dement JM, Harris RL, Symons MJ, et al. 1983. Exposures and mortality among chrysotile asbestos workers. Part II: Mortality. Am J Ind Med 4:421-433.

*DeShazo RD, Morgan J, Bozelka B, et al. 1988. Natural killer cell activity in asbestos workers: Interactive effects of smoking and asbestos exposure. Chest 94:482-485.

*De Vuyst P, Jedwab J, Dumortier P, et al. 1982. Asbestos bodies in bronchoalveolar lavage. Am Rev Resp Dis 126:972-976.

*DHHS. 1985. The health consequences of smoking: Cancer and chronic lung disease in the workplace. U.S. Department of Health and Human Services. Office on Smoking and Health, Rockville, MD, 13-14.

DHHS. 1986. Report on cancer risks associated with the ingestion of asbestos. U.S. Department of Health and Human Services. NTIS No. PB90-B0527.

*DiPaolo JA, DeMarinis AJ, Doniger J. 1983. Asbestos and benzo(a)pyrene synergism in the transformation of syrian hamster embryo cells. Pharmacology 27:65-73.

Dodoli D, Del Nevo M, Fiumalbi C, et al. 1992. Environmental household exposures to asbestos and occurrence of pleural mesothelioma. Am J Ind Med 21:681-687.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/159

8. REFERENCES

Dodson RF, Ford JO. 1991. Tissue reaction following a second exposure to amosite asbestos. Cytobios 68:53-62.

Dodson RF, Hurst GA, Williams MG, et al. 1988. Comparison of light and electron microscopy for defining occupational asbestos exposure in transbronchial lung biopsies. Chest 94:366-370.

Dodson RF, O'Sullivan M, Corn C. 1993. Technique dependent variations in asbestos burden as illustrated in a case of nonoccupational exposed mesothelioma. Am J Ind Med 24(2):235-40.

*Doll R. 1955. Mortality from lung cancer in asbestos workers. Br J Ind Med 12:81-86.

Doll R. 1987. The quantitative significance of asbestos fibres in the ambient air. Experientia [Suppl] 51:213-219.

*Doll R. 1989. Mineral fibres in the nonoccupational environment: Concluding remarks. IARC Sci Pub 90:511-518.

*Doll R, Peto J. 1985. Asbestos: Effects on health of exposure to asbestos. A report to the Health and Safety Commission. London, England, Her Majesty's Stationery Office.

*Donaldson K, Bolton RE, Jones A, et al. 1988a. Kinetics of the bronchoalveolar leucocyte response in rates during exposure to equal airborne mass concentrations of quartz, chrysolite asbestos, or titanium dioxide. Thorax 43:525-533.

Donaldson K, Brown GM, Brown DM, et al. 1989. Inflammation generating potential of long and short fibre amosite asbestos samples. Br J Ind Med 46:271-276.

Donaldson K, Slight J, Bolton RE. 1988b. Oxidant production by control and inflammatory bronchoalveolar leukocyte populations treated with mineral dusts in vitro. Inflammation 12:231-243.

Donaldson K, Brown RC, Brown GM. 1993. Respirable industrial fibers: Mechanisms of pathogenicity. Thorax 48(4):390-395.

*Dong H, Saint-Etienne L, Renier A, et al. 1994. Air samples from a building with asbestos-containing material: Asbestos content and *in vitro* toxicity on rat pleural mesothelial cells. Fundam Appl Toxicol 22:178-1855.

*Donham KJ, Berg JW, Will LA, et al. 1980. The effects of long-term ingestion of asbestos on the colon of F344 rats. Cancer (March suppl) 45:1073-1084.

Dossing M, Groth S, Vestbo J, et al. 1990. Small-airways dysfunction in never smoking asbestos exposed danish plumbers. Int Arch Occup Environ Health 62:209-212.

Dubes GR, Mack LR. 1988. Asbestos-mediated transfection of mammalian cell cultures. *In Vitro* Cellular Devel Biol 24:175-181.

*Dubois CM, Bissonnette E, Rola-Pleszczynski M. 1989. Asbestos fibers and silica particles stimulate rat alveolar macrophages to release tumor necrosis factor. Am Rev Respir Dis 139:1257-1264.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/160

8. REFERENCES

Dujic Z, Tocilj J, Saric M. 1991. Early detection of interstitial lung disease in asbestos exposed non-smoking workers by mid-expiratory flow rate and high resolution computed tomography. Br J Ind Med 48(10):663-664.

*Dujic Z, Tocilj J, Boshi S, et al. 1992. Biphasic lung diffusing capacity: detection of early asbestos induced changes in lung function. Br J Ind Med 49:260-267.

Dujic Z, Eterovic D, Tocilj J. 1993. Association between asbestos-related pleural plaques and resting hyperventilation. Scand J Work Environ Health 19(5):346-351.

*Dupre JS, Mustard JF, Uffen RJ, et al. 1984. Report of the Royal Commission on matters of health and safety arising from the use of asbestos in Ontario. Ontario, Canada: Ontario Ministy of the Attorney General, Publ., 73-112.

*Edelman DA. 1988a. Exposure to asbestos and the risk of gastrointestinal cancer: A reassessment. Br J Ind Med 45:75-82.

Edelman DA. 1988b. Exposure to asbestos and the risk of gastrointestinal cancer [Letter]. Br J Ind Med 45:574-576.

*Edelman DA. 1989. Laryngeal cancer and occupational exposure to asbestos. Int Arch Occup Environ Health 61:223-227.

Edelman DA. 1992. Does asbestos exposure increase the risk of urogenital cancer? Int Arch Occup Environ Health 63:469-475.

Ehrenreich T, Selikoff IJ. 1981. Asbestos fibers in human lung: Forensic significance. Am J Forensic Med Pathol 2:67-74.

Ehrlich A, Gordon RE, Dikman SH. 1991. Carcinoma of the colon in asbestos-exposed workers: analysis of asbestos content in colon tissue. Am J Ind Med 19:629-636.

*Ehrlich R, Lilis R, Chan E, et al. 1992. Long term radiological effects of short term exposure to amosite asbestos among factory workers. Br J Ind Med 49:268-275.

Elferink JGR. 1989. Chrysotile asbestos-induced cytotoxicity and calcium-dependent exocytosis in polymorphonuclear leukocytes. Res Commun Chem Pathol Pharmacol 65:361-372.

Elferink JGR, Kelters I. 1991. Chrysotile asbestos-induced membrane damage in human erythrocytes. Res Commun Chem Pathol Pharmacol 73:355-365.

Elmes P, Browne K. 1986. Mesothelioma shortly after brief exposure to asbestos [Letter]. Lancet 1:746.

Elstner EF, Schueltz W, Vogl G. 1988. Cooperative stimulation by sulfite and crocidolite asbestos fibres of enzyme catalyzed production of reactive oxygen species. Arch Toxicol 62:424-427.

*Emerit I, Jaurand MC, Saint-Etienne L, et al. 1991. Formation of a clastogenic factor by asbestos-treated rat pleural mesothelial cells. Agents Actions 34(3-4):410-415.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/161

8. REFERENCES

*Enarson DA, Embree V, MacLean L, et al. 1988. Respiratory health in chrysotile asbestos miners in British Columbia: A longitudinal study. Br J Ind Med 45:459-463.

Enterline PE, Kendrick MA. 1967. Asbestos-dust exposures at various levels and mortality. Arch Environ Health 15:181-186.

*Enterline PE, Henderson VL. 1987. Geographic patterns for pleural mesothelioma deaths in the United States, 1968-81. J Natl Cancer Inst 79:31-37.

*Enterline PE, Hartley J, Henderson V. 1987. Asbestos and cancer: A cohort followed up to death. Br J Ind Med 44:396-401.

*EPA. 1976. Asbestos fibers in natural runoff and discharges from sources manufacturing asbestos products. Pt II Non-point sources and point sources manufacturing asbestos products. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances. EPA-560/6-76-020. NTIS No. PB-263746.

*EPA. 1977. Movement of selected metals, asbestos, and cyanide in soil: Applications to waste disposal problems. Cincinnati, OH: U.S. Environmental Protection Agency, Office of Research and Development. EPA-600/2-77-020. NTIS No. PB-266905.

EPA. 1978a. Development of a rapid analytical method for determining asbestos in water. Report to U.S. Environmental Protection Agency, Office of Research and Development, Health Effects Research Laboratory, Athens, GA, by Battelle Columbus Laboratories. EPA-600/4-78-066.

EPA. 1978b. Fate of ingested chrysotile asbestos fiber in the newborn baboon. Report to U.S. Environmental Protection Agency, Office of Research and Development, Health Effects Research Laboratory, Cincinnati, OH, by University of Illinois, School of Public Health. EPA-600/1-78-069. NTIS PB 291686.

*EPA. 1979a. Effects of selected asbestos fibers on cellular and molecular parameters. Cincinnati, OH: U.S. Environmental Protection Agency, Office of Research and Development. EPA-600/1-79-021. NTIS No. PB-299199.

*EPA. 1979b. Exposure to asbestos from drinking water in the United States. Cincinnati, OH: U.S. Environmental Protection Agency, Office of Research and Development. EPA-600/1-79-028. NTIS No. PB-300444.

*EPA. 1979c. Water-related environmental fate of 129 priority pollutants. Vol I. Introduction and technical background, metals and inorganics, pesticides and PCBs. Washington, DC: U.S. Environmental Protection Agency, Office of Water Planning and Standards. EPA-440/4-79-029a. NTIS No. PB80-204373.

*EPA. 1980a. Ambient water quality criteria for asbestos. Washington, DC: U.S. Environmental Protection Agency, Office of Water Regulations and Standards. EPA 440/5-80-022. PB81-117335.

*EPA. 1980b. Interim method for determining asbestos in water. Atlanta, GA: U.S. Environmental Protection Agency, Office of Research and Development. EPA-600/4-80-005.

Digitized by Google

8. REFERENCES

EPA. 1982. Intermedia Priority Pollutant Guidance Documents. Washington, DC: U.S. Environmental Protection Agency, Office of Toxics Integration, Office of Pesticides and Toxic Substances.

EPA. 1983. Treatability manual. Vol I. Treatability data. Washington, DC: U.S. Environmental Protection Agency, Office of Research and Development. EPA-600/2-82-001a.

*EPA. 1984a. Health effects for asbestos. Washington, DC: U.S. Environmental Protection Agency, Office of Emergency and Remedial Response. EPA 540/1-86/049.

*EPA. 1984b. Final report: Asbestos in buildings: National survey of asbestos-containing friable materials. Washington, DC: U.S. Environmental Protection Agency, Office of Pesticides and Toxic Substances.

*EPA. 1985a. Drinking water criteria document for asbestos. Cincinnati, OH. U.S. Environmental Protection Agency, Environmental Criteria and Assessment office. EPA 600/X-84-199-1.

*EPA. 1985b. U.S. Environmental Protection Agency: Part II. Federal Register 50:13456-13522.

EPA. 1985c. U.S. Environmental Protection Agency: Part IV. Federal Register 50:46936-47022.

*EPA. 1986a. Airborne asbestos health assessment update. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environment Assessment. EPA/600/8-84/003F.

EPA. 1986b. U.S. Environmental Protection Agency. Federal Register 51:3738-3759.

EPA. 1986c. Reference values for risk assessment. Final draft. Cincinnati OH: U.S. Environmental Protection Agency, Office of Solid Waste. ECAO-CIN-477.

*EPA. 1986d. U.S. Environmental Protection Agency. Federal Register 51:15722-15733.

EPA. 1987a. U.S. Environmental Protection Agency: Part II. Federal Register 52:8140-8171.

*EPA. 1987b. U.S. Environmental Protection Agency: Part III. Federal Register 52:41826-41835.

EPA. 1987c. Toxic air pollutant/source crosswalk: A screening tool for locating possible sources emitting toxic air pollutants. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards. EPA-450/4-87-023a.

EPA. 1987d. Asbestos-containing materials in schools. U.S. Environmental Protection Agency. Federal Register 40CFR 763.

EPA. 1988a. U.S. Environmental Protection Agency: Part V. Federal Register 53:38642-38654.

*EPA. 1988b. U.S. Environmental Protection Agency: Part II. Federal Register 53:4500-4539.

*EPA. 1988c. EPA study of asbestos-containing materials in public buildings: A report to Congress. Washington, DC: U.S. Environmental Protection Agency.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/163

EPA. 1988d. Assessing asbestos exposure in public buildings. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances. EPA 560/5-88-002.

*EPA. 1988f. Comparative mesothelioma induction in rats by asbestos and nonasbestos mineral fibers: possible correlation with human exposure data. Research Triangle Park, NC: U.S. Environmental Protection Agency, Health Effects Research Laboratory, NTIS No. PB88-250246.

EPA. 1988g. Chromosomal changes associated with tumorigenic mineral fibers. Research Triangle Park, NC: U.S. Environmental Protection Agency, Health Effects Research Laboratory, Office of Research and Development, EPA/600/D-88/222, NTIS No. PB89-124739.

EPA. 1988h. Additional analysis of EPA's 1984 asbestos survey data. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances, EPA 560/5-88-010.

*EPA. 1988i. Asbestos exposure assessment. Revised report. Washington, DC: U.S. Environmental Protection Agency, Office of Pesticides and Toxic Substances.

*EPA. 1988j. Chromosomal changes associated with tumorigenic mineral fibers. Research Triangle Park, NC. EPA/600/0-88/222. PB89-124739.

*EPA. 1988k. General pretreatment regulations for existing and new sources of pollution. U.S. Environmental Protection Agency. Code of Federal Regulations 40 CFR 403 (plus Appendix B).

*EPA. 1988l. U.S. Environmental Protection Agency. Federal Register 53:40615.

EPA. 1989a. Exposure factors handbook. U.S. Environmental Protection Agency, Office of Health and Environmental Assessment. Washington, DC. EPA/600/8-89/043.

*EPA. 1989b. Interim Methods for Development of Inhalation References Doses. U.S. Environmental Protection Agency, Office of Health and Environmental Assessment. Washington, DC. EPA 600/8-88/066F.

EPA. 1989d. U.S. Environmental Protection Agency: Part III. Federal Register 54:912-937.

*EPA. 1989e. U.S. Environmental Protection Agency: Part II. Federal Register 54:22062-22160. (Retrieval in progress)

*EPA. 1989f. U.S. Environmental Protection Agency: Part III. Federal Register 54:29460-29513.

*EPA. 1989g. U.S. Environmental Protection Agency. Part V. Federal Register 54:32430, 33449-33450.

EPA. 1989h. Guidelines for conducting the AHERA TEM clearance test to determine completion of an asbestos abatement project. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances, NTIS No. PB90-171778.

EPA. 1989i. U.S. Environmental Protection Agency. Part III. Federal Register 54:15622-15627.

EPA. 1989j. U.S. Environmental Protection Agency. Federal Register 54:36315-36316, 38436

Digitized by Google

8. REFERENCES

*EPA. 1990a. U.S. Environmental Protection Agency. Part III. Federal Register 55:48406-48433.

EPA. 1990b. U.S. Environmental Protection Agency. Part V. Federal Register 55:5144-5162, 20522-20523.

*EPA. 1991a. U.S. Environmental Protection Agency. Part II. Federal Register 56:3526-3528, 3536, 3548, 3565, 11421-11422.

*EPA. 1991b. Indoor-air assessment: Indoor concentrations of environmental carcinogens. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment. EPA/600/8-90/042 NTIS No. PB91-193847.

*EPA. 1992a. U.S. Environmental Protection Agency. Part III. Federal Register 57:11364-11365.

*EPA. 1992b. U.S. Environmental Protection Agency. Part IV. Federal Register 57:31576-31592.

*EPA. 1992c. Asbestos concentrations two years after abatement in seventeen schools. Cincinnati, OH: U.S. Environmental Protection Agency, Office of Research and Development. EPA 600/R-92/027.

*EPA. 1992d. U.S. Environmental Protection Agency. Federal Register 57:11412-11413.

*EPA. 1993a. Test method for the determination of asbestos in bulk building materials. Washington, DC: U.S. Environmental Protection Agency. EPA 600/R-93/116.

EPA. 1993b. Quantitative evaluation of HEPA filtration systems at asbestos abatement sites. Cincinnati, OH: U.S. Environmental Protection Agency, Office of Research and Development, Risk Reduction Engineering Laboratory. EPA/600/J-93/498. NTIS PB94-136116.

*EPA. 1994. Drinking water regulations and health advisories. U.S. Environmental Protection Agency, Washington, DC. May 1994.

Epstein PE. 1992. Asbestos Inhalation and Nonmalignant Abnormalities of the Chest. Semin Roentgenol 27:85-93.

Erdreich LS. 1983. Comparing epidemiologic studies of ingested asbestos for use in risk assessment. Environ Health Perspect 53:99-104.

*Ernst P, Dales RE, Nunes F, et al. 1989. Relation of airway responsiveness to duration of work in a dusty environment. Thorax 44:116-120.

Erzen C, Eryilmaz M, Kalyoncu F, et al. 1991. CT findings in malignant pleural mesothelioma related to nonoccupational exposure to asbestos and fibrous zeolite (erionite). J Comput Assist Tomogr 15:256-260.

*Evans JC, Evans RJ, Holmes A, et al. 1973. Studies on the deposition of inhaled fibrous material in the respiratory tract of the rat and its subsequent clearance using radioactive tracer techniques. 1. UICC crocidolite asbestos. Environ Res 6:180-201.

EXICHEM Data Base. 1989. Organization for Economic Cooperation and Development.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/165

8. REFERENCES

Falgout DA. 1985. Environmental release of asbestos from commercial product shaping. Cincinnati, OH: U.S. Environmental Protection Agency, Water Engineering Research Laboratory. EPA/600/S2-85/044.

*Fasske E. 1988. Experimental lung tumors following specific intrabronchial application of chrysotile asbestos. Longitudinal light and electron microscopic investigations in rats. Respir 53:111-127.

Fasy TM. 1991. Asbestos fibers are mutagenic after all: new signs of orthodoxy for a paradoxical group of carcinogens. Ann NY Acad Sci 271-279.

*Fatma N, Jain AK, Rahman Q. 1991. Frequency of sister chromatid exchange and chromosomal aberrations in asbestos cement workers. Br J Ind Med 48:103-105.

*Fatma N, Khan SG, Aslam M, et al. 1992. Induction of chromosomal aberrations in bone marrow cells of asbestotic rats. Environ Res 57:175-180.

*FDA. 1994. Indirect food additives: Adhesives and components of coatings. U.S. Department of Health and Human Services, Food and Drug Administration. Code of Federal Regulations 21 CFR 175.

FEDRIP. 1994. Federal Research in Progress [database]. Dialog Information Retrieval System, CA.

Feige MA, Clark PJ, Brackett KA. 1993. Guidance and clarification for the current U.S. EPA test method for asbestos in drinking water. Environmental Choices Technical Supplement Fall 1993. IT Corp., Cincinnati, OH. NTIS publication no. PB94-126108.

*Finkelstein MM. 1983. Mortality among long-term employees of an Ontario asbestos-cement factory. Br J Ind Med 40:138-144.

*Finkelstein M. 1986. Pulmonary function in asbestos cement workers: A dose-response study. Br J Ind Med 43:406-413.

Finkelstein MM. 1989. Mortality among employees of an Ontario factory that manufactured construction materials using chrysotile asbestos and coal tar pitch. Am J Ind Med 16:281-287.

Finkelstein MM. 1991. Analysis of the exposure-response relationship for mesothelioma among asbestos-cement factory workers. Ann NY Acad Sci 85-89.

*Finn MB, Hallenbeck WH. 1984. Detection of chrysotile asbestos in workers' urine. Am Ind Hyg Assoc J 45:752-759.

Fischbein A, Luo J-C, Pinkston GR. 1991a. Asbestosis, laryngeal carcinoma, and malignant peritoneal mesothelioma in an insulation worker. Br J Ind Med 48(5):338-341.

Fischbein A, Luo J-C, Rosenfeld S, et al. 1991b. Respiratory findings among ironworkers: Results from a clinical survey in the New York metropolitan area and identification of health hazards from asbestos in place at work. Br J Ind Med 48(6):404-411.

Fischbein A, Luo J-C, Lacher M, et al. 1993. Respiratory findings among millwright and machinery erectors: Identification of health hazards from asbestos in place at work. Environ Res 61(1):25-35.

Digitized by Google

8. REFERENCES

Fisher GL, Mossman BT, McFarland AR, et al. 1987. A possible mechanism of chrysotile asbestos toxicity. Drug Chem Toxicol 10:109-131.

Fitzgerald EF, Stark AD, Vianna N, et al. 1991. Exposure to asbestiform minerals and radiographic chest abnormalities in a talc mining region of upstate New York. Arch Environ Health 46:151-154.

*Fontecave M, Jaouen M, Mansuy D, et al. 1990. Microsomal lipid peroxidation and oxy-radicals formation are induced by insoluble iron-containing minerals. Biochem Biophys Res Commun 173:912-918.

Frank Al. 1982. The epidemiology and etiology of lung cancer. Clin Chest Med 3:219-228.

Freed JA, Miller A, Gordon RE, et al. 1991. Desquamative interstitial pneumonia associated with chrysotile asbestos fibers. Br J Ind Med 48(5):332-337.

*Friedman AC, Fiel SB, Fisher MS, et al. 1988. Asbestos-related pleural disease and asbestosis: a comparison of CT and chest radiography. AJR Am J Roentgenol 150:269-275.

Friemann J, Mueller KM. 1990. Mesothelial proliferation due to asbestos and man-made fibres. Path Res Pract 186:117-123.

*Frumkin H, Berlin J. 1988. Asbestos exposure and gastrointestinal malignancy review and meta-analysis. Am J Ind Med 14:79-95.

*FSTRAC. 1990. Summary of state and federal drinking water standards and guidelines. Washington, DC: Federal-State Toxicology and Regulatory Alliance Committee, Chemical Communication Subcommittee.

Gabrielson EW, Rosen GM, Grafstrom RC, et al. 1986. Studies on the role of oxygen radicals in asbestos-induced cytopathology of cultured human lung mesothelial cells. Carcinogenesis 7:1161-1164.

Gabrielson EW, Van der Meeren A, Reddel RR, et al. 1992. Human mesothelioma cells and asbestos-exposed mesothelial cells are selectively resistant to amosite toxicity: a possible mechanism for tumor promotion by asbestos. Carcinogenesis 13:1359-1363.

Gaensler EA. 1992. Asbestos exposure in buildings. Occup Lung Diseases 13:231-242.

Gaensler EA, Jederlinic PJ, Churg A. 1991. Idiopathic pulmonary fibrosis in asbestos-exposed workers. Am Rev Respir Dis 144(3):689-696.

*Gamsu G, Aberle DR, Lynch D. 1989. Computed tomography in the diagnosis of asbestos-related thoracic disease. J Thorac Imag 4:61-67.

*Garabrant DH, Peters RK, Homa DM. 1992. Asbestos and colon cancer: Lack of association in a large case-control study. Am J Epidemiol 135:843-853.

*Garcia JGN, Gray LD, Dodson RF, et al. 1988. Asbestos-induced endothelial cell activation and injury. Demonstration of fiber phagocytosis and oxidant-dependent toxicity. Am Rev Respir Dis 138:958-964.

Digitized by Google

8. REFERENCES

*Garcia JGN, Griffith DE, Cohen AB, et al. 1989. Alveolar macrophages from patients with asbestos exposure release increased levels of leukotriene B_4. Am Rev Respir Dis 139:1494-1501.

Gardner MJ, Powell CA, Gardner AW, et al. 1988. Continuing high lung cancer mortality among ex-amosite asbestos factory workers and a pilot study of individual anti-smoking advice. J Soc Occup Med 38:69-72.

*Gaumer HR, Doll NJ, Kaimal J, et al. 1981. Diminished suppressor cell function in patients with asbestosis. Clin Exp Immunol 44:108-116.

*Gefter WB, Conant EF. 1988. Issues and controversies in the plain-film diagnosis of asbestos-related disorders in the chest. J Thorac Imaging 3:11-28.

Geisler O. 1991. Occupational health and hygiene following a fire in a warehouse with an asbestos cement roof [letter; comment]. J Soc Occup Med 41(3):143.

*Gendek EG, Brody AR. 1990. Changes in lipid ordering of model phospholipid membranes treated with chrysotile and crocidolite asbestos. Environ Res 53:152-167.

*Gerhardsson de Verdier M, Plato N, Steineck G, et al. 1992. Occupational exposures and cancer of the colon and rectum. Am J Ind Med 22(3):291-303.

Ghio AJ, Crumbliss AL. 1992. Surface complexation of Fe^{3+} by silica and silicate dusts increases *in vitro* oxidant generation but diminishes *in vitro* cytotoxicity. Durham, NC: Duke University Medical Center, Division of Allergy, Critical Care, and Respiratory Medicine, Department of Medicine.

Ghio AJ, Kennedy TP, Schapira RM, et al. 1990. Hypothesis: is lung disease after silicate inhalation caused by oxidant generation? Lancet 336:967-969.

Giarelli L, Bianchi C, Grandi G. 1992. Malignant mesothelioma of the pleura in Trieste, Italy. Am J Ind Med 22(4):521-530.

Giaroli C, Bruno C, Candela S, et al. 1994. Mortality study of asbestos cement workers. Int Arch Occup Environ Health 66(1):7-11.

*Gibbs GW. 1979. Etiology of pleural calcification: A study of Quebec chrysotile asbestos miners and millers. Arch Environ Health 34:76-83.

Gibbs AR, Griffiths DM, Pooley FD, et al. 1990. Comparison of fibre types and size distributions in lung tissues of paraoccupational and occupational cases of malignant mesothelioma. Br J Ind Med 47:621-626.

Gibbs AR, Stephens M, Griffiths DM, et al. 1991. Fibre distribution in the lungs and pleura of subjects with asbestos related diffuse pleural fibrosis. Br J Ind Med 48:762-770.

Gillam JD, Dement JM, Lemen RA, et al. 1976. Mortality patterns among hard rock gold miners exposed to an abestiform mineral. Ann NY Acad Sci 271:336-344.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/168

8. REFERENCES

Gilson JC. 1971. Asbestos. In: Encyclopedia of occupational health and safety. New York, NY: McGraw Hill, 120-124.

Glass W, Kawachi I, Pearce N. 1991. Lung cancer, smoking and exposure to asbestos in New Zealand. Journal of Occupational Health and Safety of Australia and New Zealand 7(1):43-47.

*Goldstein B, Coetzee FSJ. 1990. Experimental malignant mesothelioma in baboons. South Africa J Sci 86:89-93.

Gonzalez S, Friemann J, Mueller KM, et al. 1991. Ultrastructure of mesothelial regeneration after intraperitoneal injection of asbestos fibres on rat omentum. Path Res Pract 187:931-935.

*Goodglick LA, Kane AB. 1990. Cytotoxicity of long and short crocidolite asbestos fibers *in vitro* and *in vivo*. Cancer Res 50:5153-5163.

*Goodglick LA, Pietras LA, Kane AB. 1989. Evaluation of the causal relationship between crocidolite asbestos-induced lipid peroxidation and toxicity to macrophages. Am Rev Respir Dis 139:1265-1273.

Goodman GE, Omenn GS. 1992. Carotene and retinol efficacy trial: Lung cancer chemoprevention trial in heavy cigarette smokers and asbestos-exposed workers. CARET Coinvestigators and Staff. Adv Exp Med Biol 320:137-40.

Gormley IP, Bolton RE, Brown GM, et al. 1983. Some observations on the *in vitro* cytotoxicity of chrysotile prepared by the wet dispersion process. Environ Health Perspect 51:35-39.

Gosselin RE, Smith RP, Hodge HC. 1984. Toxicity information about selected ingredients. In: Clinical toxicology of commercial products. 5th ed. Baltimore, MD: Williams and Wilkins, II-94.

*Graceffa P, Weitzman SA. 1987. Asbestos catalyzes the formation of the 6-oxobenzo[a]pyrene radical from 6-hydroxybenzo[a]pyrene. Arch Biochem Biophysics 257:481-484.

*Greaves IA. 1979. Rheumatoid "pneumoconiosis" (Caplan's syndrome) in an asbestos worker: A 17 years' follow-up. Thorax 34:404-405.

*Green FH, Harley R, Vallyathan V, et al. 1986. Pulmonary fibrosis and asbestos exposure in chrysotile asbestos textile workers: Preliminary results. In: Accomplishments in oncology. The biological effects of chrysotile. Vol. 1, No. 2, 59-68.

Greenblatt J. 1984. Evaluation of the EPA asbestos-in-schools identification and notification rule. Report to Battelle Columbus Laboratories, Washington, DC, by Westat, Inc., Rockville, MD.

Greene R, Boggis C, Jantsch H. 1982. Asbestos-related pleural thickening: Effect of threshold criteria on interpretation. Radiology 152:569-573.

Greene R, Schaefer CM, Oliver LC. 1991. Improved detection of asbestos-related pleural plaques with digital radiography. Ann NY Acad Sci 643(12):90-96.

*Griffis LG, Pickrell JA, Carpenter PR, et al. 1983. Deposition of crocidolite asbestos and glass microfibers inhaled by the beagle dog. Amer Ind Hyg Assoc J 44(3):216-222.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/169

8. REFERENCES

*Griffith DE, Miller EJ, Gray LD, et al. 1994. Interleukin-1-mediated release of interleukin-8 by asbestos-stimulated human pleural mesothelial cells. Am J Respir Cell Mol Biol 10(3):245-52.

Grimson RC. 1987. Apportionment of risk among environmental exposures: Application to asbestos exposure and cigarette smoking. J Occup Med 29:253-255.

*Gross P, deTreville RT, Tolker EB, et al. 1967. Experimental asbestosis: The development of lung cancer in rats with pulmonary deposits of chrysotile asbestos dust. Arch Environ Health 15:343-355.

*Gross P, Harley RA, Swinburne LM, et al. 1974. Ingested mineral fibers: Do they penetrate tissue or cause cancer? Arch Environ Health 29:341-347.

*Guillemin B, Zhang Y, Lee TC, et al. 1991. Role of peptide growth factors in asbestos-related human lung cancer. Ann NY Acad Sci 245-257.

Guillemin MP, Madelaine P, Litzistorf G, et al. 1989. Asbestos in buildings. Aerosol Sci Technol 11:221-243.

Gulumian M, Bhoolia DJ, Du Toit RS, et al. 1993. Activation of UICC crocidolite: The effect of conversion of some ferric ions to ferrous ions. Environ Res 60(2):193-206.

*Gylseth B, Skaug V. 1986. Relation between pathological grading and lung fibre concentration in a patient with asbestosis. Br J Ind Med 43:754-759.

*Gylseth B, Churg A, Davis JM, et al. 1985. Analysis of asbestos fibers and asbestos bodies in tissue samples from human lung: An international interlaboratory trial. Scand J Work Environ Health 11:107-110.

*Habashi F, Awadalla FT, Page M. 1991. Surface modification of chrysotile asbestos with organic reagents: a preliminary *in vitro* toxicological study. CIM Bulletin 84:67-79.

Hahon N, Booth JA, Flowers L. 1990. Coinhibition of viral interferon induction by benzo[a]pyrene in association with occupation-related particles. Environ Res 52:83-98.

Hall EJ, Hei TK. 1985. Oncogenic transformation with radiation and chemicals. Int J Radiat Biol 48:1-18.

Hall NEL, Rosenmann KD. 1991. Cancer by industry: Analysis of a population-based cancer registry with an emphasis on blue-collar workers. Am J Ind Med 19(2):145-159.

Hallenbeck WH. 1983. Asbestos penetration of the gastrointestinal tract [Commentary]. Environ Health Perspect 53:153-154.

*Hallenbeck WH. 1988. Can we really evaluate the health risks due to exposure to airborne asbestos? The Environmental Professional 10:333-340.

*Hallenbeck WH, Patel-Mandlik KJ. 1979. Presence of fibers in the urine of a baboon gavaged with chrysotile asbestos. Environ Res 20:335-340.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/170

8. REFERENCES

*Hallenbeck WH, Chen EH, Hesse CS. 1978. Is chrysotile asbestos released from asbestos-cement pipe into drinking water? J AWWA (February):97-102.

Hammar SP. 1992. Controversies and uncertainties concerning the pathologic features and pathologic diagnosis of asbestosis. Sem Diag Path 9:102-109.

*Hammond EC, Selikoff IJ, Seidman H. 1979. Asbestos exposure, cigarette smoking and death rates. Ann NY Acad Sci 330:473-490.

*Hansen K, Mossman BT. 1987. Generation of superoxide ($O_2^{\cdot}$-) from alveolar macrophages exposed to asbestiform and nonfibrous particles. Cancer Res 47:1681-1686.

Hansen J, de Klerk NH, Eccles JL, et al. 1993. Malignant mesothelioma after environmental exposure to blue asbestos. Int J Cancer 54(4):578-581.

*Hansteen I-L, Hilt B, Lien JT, et al. 1993. Karyotypic changes in the preclinical and subsequent stages of malignant mesothelioma: A case report. Cancer Genet Cytogenet 70(2):94-98.

*Haque AK, Kanz MF, Mancuso MG, et al. 1991. Asbestos in the lungs of children. Ann NY Acad Sci 419-429.

*Haque AK, Mancugo MG, Williams MG, et al. 1992. Asbestos in organs and placenta of 5 stillborn infants suggests transplacental transfer. Environ Res 58(2):163-175.

*Hardy RJ, Highsmith VR, Costa DL, et al. 1992. Indoor asbestos concentrations associated with the use of asbestos-contaminated tap water in portable home humidifiers. Environ Sci Technol 26:680-689.

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 465-472.

Harrington JM, Craun GF, Meigs JW, et al. 1978. An investigation of the use of asbestos cement pipe for public water supply and the incidence of gastrointestinal cancer in Connecticut, 1935-1973. Am J Epidemiol 107:96-103.

Harrison PT, Health JC. 1988. Apparent synergy between chrysotile asbestos and N-nitrosoheptamethyleneimine in the induction of pulmonary tumours in rats. Carcinogenesis 9:2165-2171.

Hatch GE, Boykin E, Graham JA, et al. 1985. Inhalable particles and pulmonary host defense: *In vivo* and *in vitro* effects of ambient air and combustion particles. Environ Res 36:67-80.

*Hayes AA, Mullan B, Lovegrove FT, et al. 1989. Gallium lung scanning and bronchoalveolar lavage in crocidolite-exposed workers. Chest 96:22-26.

*Hayes AA, Venaille TJ, Rose AH, et al. 1990. Asbestos-induced release of a human alveolar macrophage-derived neutrophil chemotactic factor. Exp Lung Res 16:121-130.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/171

8. REFERENCES

*HAZDAT. 1994. Agency for Toxic Substances and Disease Registry (ATSDR), Atlanta, GA.

*HEI. 1991. Health Effects Institute. Asbestos in public and commercial buildings: A literature review and synthesis of current knowledge. Report of the asbestos literature review panel. Cambridge, MA: Health Effects Institute.

*HEI. 1992. Health Effects Institute. Asbestos in public and commercial buildings: Supplementory analyses of selected data previously considered by the literature review panel. Cambridge, MA: Health Effects Institute.

*Hei TK, Hall EJ, Osmak RS. 1984. Asbestos, radiation, and oncogenic transformation. Br J Cancer 50:717-720.

*Hei TK, Piao CQ, He ZY, et al. 1992. Chrysotile fiber is a strong mutagen in mammalian cells. Cancer Res 52:6305-6309.

*Henderson VL, Enterline PE. 1979. Asbestos exposure: Factors associated with excess cancer and respiratory disease mortality. Ann NY Acad Sci 330:117-126.

Henderson DW, Attwood HD, Constance TJ, et al. 1988. Lymphohistiocytoid mesothelioma: A rare lymphomatoid variant of predominantly sarcomatoid mesothelioma. Ultrastruct Pathol 12:367-384.

Hessel PA, Sluis-Cremer GK. 1989. X-ray findings, lung function, and respiratory symptoms in black South African vermiculite workers. Am J Ind Med 15:21-29.

*Hesterberg TW, Barrett JC. 1984. Dependence of asbestos- and mineral dust-induced transformation of mammalian cells in culture on fiber dimension. Cancer Res 44:2170-2180.

Hesterberg TW, Butterick CJ, Oshimura M, et al. 1986. Role of phagocytosis in Syrian hamster cell transformation and cytogenetic effects induced by asbestos and short and long glass fibers. Cancer Res 46:5795-5802.

Hill RJ, Edwards RE, Carthew P. 1990. Early changes in the pleural mesothelium following intrapleural inoculation of the mineral fibre erionite and the subsequent development of mesotheliomas. J Exp Path 71:105-118.

*Hillerdal G. 1980. The pathogenesis of pleural plaques and pulmonary asbestosis: Possibilities and impossibilities. Eur J Respir Dis 61:129-138.

Hillerdal G. 1983. Malignant mesothelioma 1982: Review of 4710 published cases. Br J Dis Chest 77:321-343.

Hillerdal G. 1991. Pleural plaques in the general population. Ann NY Acad Sci 430-437.

Hillerdal G. 1994. Pleural plaques and risk for bronchial carcinoma and mesothelioma: A prospective study. Chest 105(1):144-150.

Hillerdal G, Musk AW. 1990. Pleural lesions in crocidolite workers from Western Australia. Br J Ind Med 47:782-783.

Digitized by Google

8. REFERENCES

Hilt B, Andersen A, Rosenber J, et al. 1991. Cancer incidence among asbestos-exposed chemical industry workers: an extended observation period. Am J Ind Med 20:261-264.

Hirano S, Ono M, Aimoto A. 1988. Functional and biochemical effects on rat lung following instillation of crocidolite and chrysotile asbestos. J Toxicol Environ Health 24:27-39.

Hiraoka K, Horie A, Kido M. 1990. Study of asbestos bodies in Japanese urban patients. Am J Ind Med 18:547-554.

Hiroshima K, Murai Y, Suzuki Y, et al. 1993. Characterization of asbestos fibers in lungs and mesotheliomatous tissues of baboons following long-term inhalation. Am J Ind Med 23(6):883-901.

*Hnizdo E, Sluis-Cremer GK. 1988. Effect of tobacco-smoking on the presence of asbestosis at postmortem and on the reading of irregular opacities on roentgenograms in asbestos-exposed workers. Am Rev Respir Dis 138:1207-1212.

*Hobson J, Gilks B, Wright J, et al. 1988. Direct enhancement by cigarette smoke of asbestos fiber penetration and asbestos-induced epithelial proliferation in rat tracheal explants. J Natl Cancer Inst 80:518-521.

*Hobson J, Wright JL, Churg A. 1990. Active oxygen species mediate asbestos fiber uptake by tracheal epithelial cells. FASEB J 4:3135-3139.

Holleman JW, Ryon M, Hammons AS. 1980. Chemical contaminants in nonoccupationally exposed U.S. residents. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development. EPA-600/1-80-001. NTIS No. PB80-192339.

*Holt PF. 1974. Small animals in the study of pathological effects of asbestos. Environ Health Perspect 9:205-211.

*Holt PF. 1983. Translocation of inhaled dust to the pleura. Environ Res 31:212-220.

Holtz G, Bresnick E. 1988. Ascorbic acid inhibits the squamous metaplasia that results from treatment of tracheal explants with asbestos or benzo[a]pyrene-coated asbestos. Cancer Lett 42:23-28.

Hooper K, Ladou J, Resenbaum JS, et al. 1992. Regulation of priority carcinogens and reproductive or developmental toxicants. Am J Ind Med 22(6):793-808.

Horii H, Nagasaka Y, Yamada Y. 1992. Asbestos-related pleural thickenings in Japanese sake brewers. Int Arch Occup Environ Health 64(5):315-319.

*Howe HL, Wolfgang PE, Burnett WS, et al. 1989. Cancer incidence following exposure to drinking water with asbestos leachate. Public Health Reports 104:251-256.

*HSDB. 1994. Hazardous Substances Data Bank. National Library of Medicine, National Toxicology Information Program, Bethesda, MD.

*Hsiao TM, Ho CK, Su WP, et al. 1993. Asbestos related pleural plaques in retired boiler room workers. Kao Hsiung I Hsueh Ko Hsueh Tsa Chih 9(2):74-79.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/173

*Huang SL. 1979. Amosite, chrysotile and crocidolite asbestos are mutagenic in Chinese hamster lung cells. Mutat Res 68:265-274.

Hughes JM. 1994. Human evidence: Lung cancer mortality risk from chrysotile exposure. Ann Occup Hyg 38(4):555-560.

*Hughes J, Weill H. 1980. Lung cancer risk associated with manufacture of asbestos-cement products. IARC Sci Publ 30:627-635.

Hughes JM, Weill H. 1991. Asbestosis as a precursor of asbestos related lung cancer: Results of a prospective mortality study. Br J Ind Med 48(4):229-233.

*Hughes JM, Weill H, Hammad YY. 1987. Mortality of workers employed in two asbestos cement manufacturing plants. Br J Ind Med 44:161-174.

*Huilan Z, Zhiming W. 1993. Study of occupational lung cancer in asbestos factories in China. Br J Ind Med 50(11):1039-1042.

Huncharek M. 1986. The biomedical and epidemiological characteristics of asbestos-related diseases: A review. Yale J Biol Med 59:435-451.

Huncharek M. 1994. Asbestos and cancer: Epidemiological and public health controversies. Cancer Invest 12(2):214-222.

Huncharek M, Muscat J. 1991. Metastatic laryngeal carcinoma mimicking pleural mesothelioma. Respiration 58(3-4):204-206.

Hunting KL, Welch LS. 1993. Occupational exposure to dust and lung disease among sheet metal workers. Br J Ind Med 50(5):432-442.

*Hurbankova M, Kaiglova A. 1993. The changes of some immunological parameters in subjects exposed to asbestos in dependence on age, duration of exposure, radiological findings, and smoking habits. Zentralbl Hyg Umweltmed 195(1):55-65.

*Hurlbut CS Jr, Klein C. 1977. Manual of mineralogy. 19th ed. New York, NY: John Wiley and Sons, 338-339.

*IARC. 1977. IARC monographs on the evaluation of the carcinogenic risk of chemicals to man: Asbestos. Vol 14. World Health Organization, Lyon, France, 33-35.

IARC. 1982. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Vol 1-29 (Supplement 4): Chemicals, industrial processes and industries associated with cancer in humans. World Health Organization, Lyon, France, 33-35.

*IARC. 1987. Asbestos and certain asbestos compounds. In: IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Chemicals, industrial processes and industries associated with cancer in humans. IARC monographs, Vol 1 to 42. IARC monographs supplement 7. Lyon, France: World Health Organization, International Agency for Research on Cancer, 29-33,56-58.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/174

8. REFERENCES

*Iguchi H, Kojo S. 1989. Possible generation of hydrogen peroxide and lipid peroxidation of erythrocyte membrane by asbestos: cytotoxic mechanism of asbestos. Biochem Int 18:981-990.

*Iguchi H, Kojo S, Ikeda M. 1993. Lipid peroxidation and disintegration of the cell membrane structure in cultures of rat lung fibroblasts treated with asbestos. J Appl Toxicol 13(4):269-275.

Ilgren EB, Browne K. 1991. Asbestos-related mesothelioma: evidence for a threshold in animals and humans. Regul Toxicol Pharmacol 13:116-132.

Inase N, Takayama S, Nakayama M, et al. 1991. Pleural mesothelioma after neighborhood exposure to asbestos during childhood. Jpn J Med 30(4):343-345.

*IRIS. 1993. Integrated Risk Information System. U.S. Environmental Protection Agency, Washington, DC. July 1, 1993.

IRPTC. 1989. IRPTC data profile: Asbestos. International Register of Potentially Toxic Chemicals, United Nations Environment Programme, Geneva, Switzerland. January 1989.

Irvine HD, Lemont DW, Hole DJ, et al. 1993. Asbestos and lung-cancer in Glasgow and the west of Scotland. BMJ 306(6891):1503-1506.

*Irwig LM, du Toit RS, Sluis-Cremer GK, et al. 1979. Risk of asbestosis in crocidolite and amosite mines in South Africa. Ann NY Acad Sci 330:35-52.

Jabbour AJ, Holian A, Scheule RK. 1991. Lung lining fluid modification of asbestos bioactivity for the alveolar macrophage. Toxicol App Pharmacol 110:283-294.

Jackson JH, Schraufstatter IU, Hyslop PA, et al. 1987. Role of oxidants in DNA damage: Hydroxyl radical mediates the synergistic DNA damaging effects of asbestos and cigarette smoke. J Clin Invest 80:1090-1095.

*Jacobs R, Humphrys J, Dodgson KS, et al. 1978a. Light and electron microscope studies of the rat digestive tract following prolonged and short-term ingestion of chrysotile asbestos. Br J Exp Pathol 59:443-453.

*Jacobs R, Weinzweig M, Dodgson KS, et al. 1978b. Nucleic acid metabolism in the rat following short-term and prolonged ingestion of chrysotile asbestos or cigarette-smoke condensate. Br J Exp Pathol 59:594-600.

*Jaenicke R. 1980. Natural aerosols. Ann NY Acad Sci 338:317-325.

*Jakobsson K, Albin M, Hagmar L. 1994. Asbestos, cement, and cancer in the right part of the colon. Occup Environ Med 51(2):95-101.

*Janssen YMW, Marsh JP, Absher MP, et al. 1992. Expression of antioxidant enzymes in rat lungs after inhalation of asbestos or silica. J Biol Chem 267:10625-10630.

Jarvholm B, Brisman J. 1988. Asbestos associated tumours in car mechanics. Br J Ind Med 45:645-646.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/175

8. REFERENCES

*Jarvholm B, Larsson S. 1988. Do pleural plaques produce symptoms? A brief report. J Occup Med 30:345-347.

Jarvholm B, Sanden A. 1988. Asbestos-associated diseases in Swedish shipyard workers. Arh Hig Rada Toksikol 39:437-440.

*Jarvholm B, Arvidsson, H, Bake B, et al. 1986. Pleural plaques -asbestos - ill-health. Eur J Respir Dis Suppl 68(Suppl 145):1-59.

Jarvholm B, Malker H, Malker B, et al. 1988. Pleural mesotheliomas and asbestos exposure in the pulp and paper industries: a new risk group identified by linkage of official registers. Am J Ind Med 13:561-567.

Jarvholm B, Larsson S, Hagberg S, et al. 1993. Quantitative importance of asbestos as a cause of lung cancer in a Swedish industrial city: A case-referent study. Eur Respir J 6(9):1271-1275.

Jaurand MC. 1991. Observations on the carcinogenicity of asbestos fibers. Ann NY Acad Sci 258-270.

*Jaurand MC, Fleury J, Monchaux G, et al. 1987. Pleural carcinogenic potency of mineral fibers (asbestos, attapulgite) and their cytotoxicity on cultured cells. J Natl Cancer Inst 79:797-804.

*Jaurand MC, Gaudichet A, Halpern S, et al. 1984. *In vitro* biodegradation of chrysotile fibers by alveolar macrophages and mesothelial cells in culture: comparison with a pH effect. Br J Ind Med 41:389-395.

Jaurand MC, Magne L, Bignon J. 1979. Inhibition by phospholipids of haemolytic action of asbestos. Br J Ind Med 36:113-116.

Jaurand MC, Renier A, Gaudichet A, et al. 1988. Short-term tests for the evaluation of potential cancer risk of modified asbestos fibers. Ann NY Acad Sci 741-753.

Johansson L, Albin M, Jakobsson K, et al. 1992. Histological type of lung carcinoma in asbestos cement workers and matched controls. Br J Ind Med 49(9):626-30.

Johnson NF. 1994. Phagosomal pH and glass fiber dissolution in cultured nasal epithelial cells and alveolar macrophages: A preliminary study. Environ Health Perspect 102(Suppl 5):97-102.

Johnson NF, Edwards RE, Munday DE, et al. 1984. Pluripotential nature of mesotheliomata induced by inhalation of erionite in rats. Br J Exp Pathol 65:377-388.

*Johnson NF, Haslam PL, Dewar A, et al. 1988. Identification of inorganic dust particles in bronchoalveolar lavage macrophages by energy dispersive X-ray microanalysis. Arch Environ Health 41:133-144.

Johnson NF, Hoover MD, Thomassen DG, et al. 1992. In vitro activity of silicon carbide whiskers in comparison to other industrial fibers using four cell culture systems. Am J Ind Med 21:807-823.

Digitized by Google

8. REFERENCES

Johnson NF, Wagner JC, Wills HA. 1980a. Endocrine cell proliferation in the rat lung following asbestos inhalation. Lung 158:221-228.

Johnson NF, Wagner JC, Wills HA. 1980b. Neuroendocrine cell proliferation in the rat lung following asbestos inhalation [Abstract]. J Pathol 131:261-262.

Johnson NF, Wagner JC, Brown DG, et al. 1982. The ultrastructure of asbestos induced rat pleural mesotheliomas following transplantation into syngeneic animals [Abstract]. J Pathol 137:80.

Jolicoeur C, Poisson D. 1987. Surface physico-chemical studies of chrysotile asbestos and related minerals. Drug Chem Toxicol 10:1-47.

*Jones AD, McMillan CH, Johnston AM, et al. 1988a. Pulmonary clearance of UICC amosite fibres inhaled by rats during chronic exposure at low concentration. Br J Ind Med 45:300-304.

Jones AD, Vincent JH, McIntosh C, et al. 1989. The effect of fibre durability on the hazard potential of inhaled chrysotile asbestos fibres. Exp Pathol 37:98-102.

*Jones JS, Pooley FD, Smith PG, et al. 1980a. The consequences of exposure to asbestos dust in a wartime gas-mask factory. IARC Sci Publ 30:637-653.

*Jones JS, Pooley FD, Clark NJ, et al. 1980b. The pathology and mineral content of lungs in cases of mesothelioma in the United Kingdom in 1976. IARC Sci Publ 30:187-199.

*Jones RN, McLoud T, Rockoff SD. 1988b. The radiographic pleural abnormalities in asbestos exposure: Relationship to physiologic abnormalities. J Thorac Imaging 3:57-66.

Joubert L, Seidman H, Selikoff IJ. 1991. Mortality experience of family contacts of asbestos factory workers. Ann NY Acad Sci 416-418.

Kagamimori S, Scott MP, Brown DG, et al. 1980. Effects of chrysotile asbestos on mononuclear cells *in vitro*. Br J Exp Pathol 61:55-60.

*Kagan E. 1988. Current issues regarding the pathobiology of asbestosis: A chronologic perspective. J Thorac Imaging 3:1-9.

*Kagan E, Solomon A, Cochrane JC, et al. 1977. Immunological studies of patients with asbestosis: I. Studies of cell-mediated immunity. Clin Exp Immunol 28:261-267.

*Kamal AA, El Khafif M, Koraah S, et al. 1992. Blood superoxide dismutase and plasma malondialdehyde among workers exposed to asbestos. Am J Ind Med 21:353-361.

*Kamal AA, Gomaa A, El Khafif M, et al. 1989. Plasma lipid peroxides among workers exposed to silica or asbestos dusts. Eviron Res 49:173-180.

*Kambic V, Radsel Z, Gale N. 1989. Alterations in the laryngeal mucosa after exposure to asbestos. Br J Ind Med 46:717-723.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/177

8. REFERENCES

Kamp DW, Graceffa P, Pryor WA, et al. 1992. The role of free radicals in asbestos-induced diseases. Free Rad Biol Med 12:293-315.

Kamp DW, Dunne M, Dykewicz MS, et al. 1993. Asbestos-induced injury to cultured human pulmonary epithelial-like cells: Role of neutrophil elastase. J Leukoc Biol 54(1):73-80.

Kanarek MS. 1983. The San Francisco Bay epidemiology studies on asbestos in drinking water and cancer incidence: Relationship to studies in other locations and pointers for further research [Commentary]. Environ Health Perspect 53:105-106.

*Kanarek MS. 1989. Epidemiological studies on ingested mineral fibers: Gastric and other cancers. IARC Sci Pub 90:428-437.

*Kanarek MS, Conforti PM, Jackson LA, et al. 1980. Asbestos in drinking water and cancer incidence in the San Francisco Bay Area. Am J Epidemiol 112:54-72.

*Kanarek MS, Conforti PM, Jackson LA, et al. 1981. Chrysotile asbestos fibers in drinking water from asbestos-cement pipe. Environ Sci Technol 15:923-925.

Kanazawa K, Birbeck MS, Carter RL, et al. 1969. Migration of asbestos fibers from subcutaneous injection sites in mice. Br J Cancer 24:96-106.

Kannerstein M. 1979. Recent advances and perspectives relevant to the pathology of asbestos-related diseases in man. IARC Sci Publ 30:149-162.

*Kaplan DE. 1993. Unregulated disposal of asbestos contaminated shower water effluent: A question of public health risk. J Environ Health 55(6):6-8.

*Kaplan H, Renier A, Javrand MG, et al. 1980. Sister chromatid exchanges in mesothelial cells cultured with chrysotile fibers. In: Brown et al., eds. the *in vitro* effects of mineral dusts, London, England: Acad. Press, 251.

Karjalainen A, Anttila S, Heikkila L, et al. 1993a. Asbestos exposure among Finnish lung cancer patients: Occupational history and fiber concentration in lung tissue. Am J Ind Med 23(3):461-471.

Karjalainen A, Anttila S, Heikkila L. 1993b. Lobe of origin of lung cancer among asbestos-exposed patients with or without diffuse interstitial fibrosis. Scand J Work Environ Health 19(4):102-107.

Karjalainen A, Meurman LO, Pukkala E. 1994a. Four cases of mesothelioma among Finnish anthophyllite miners. Occup Environ Med 51(3):212-215.

Karjalainen A, Vanhala E, Karhunen PJ, et al. 1994b. Asbestos exposure and pulmonary fiber concentrations of 300 Finnish urban men. Scand J Work Environ Health 20(1):34-41.

Karn CM, Socinski MA, Fletcher JA, et al. 1994. Cardiac synovial sarcoma with translocation (X;18) associated with asbestos exposure. Cancer 73(1):74-78.

Kehrer JP, Mossman BT, Sevanian A, et al. 1988. Free radical mechanisms in chemical pathogenesis. Toxicol App Pharmacol 95:349-362.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/178

8. REFERENCES

*Kelsey KT, Yano E, Liber HL, et al. 1986. The *in vitro* genetic effects of fibrous erionite and crocidolite asbestos. Br J Cancer 54:107-114.

*Kenne K, Ljungquist S, Ringertz NR. 1986. Effects of asbestos fibers on cell division, cell survival, and formation of thioguanine-resistant mutants in Chinese hamster ovary cells. Environ Res 39:448-464.

Kennedy SM, Vedal S, Mueller N, et al. 1991. Lung function and chest radiograph abnormalities among construction insulators. Am J Ind Med 20:673-684.

*Kennedy TP, Dodson R, Rao NV, et al. 1989. Communication. Dusts causing pneumoconiosis generate OH and produce hemolysis by acting as Fenton catalysts. Arch Biochem Biophys 269:359-364.

Khan SG, Ali S, Rahman Q. 1990. Protective role of ascorbic acid against asbestos induced toxicity in rat lung: *in vitro* study. Drug and Chemical Toxicol 13:249-256.

*Khan SG, Ali S, Rahman Q. 1992. Interaction of mineral fibres with lung cytochrome P-450 system: impairment of drug metabolizing enzyme activities. Chemosphere 24:959-968.

Kilburn KH, Warshaw RH. 1992a. Irregular opacities in the lung, occupational asthma, and airways dysfunction in aluminum workers. Am J Ind Med 21:845-853.

Kilburn KH, Warshaw RH. 1992b. Severity of pulmonary asbestosis as classified by international labour organisation profusion of irregular opacities in 8749 asbestos-exposed American workers: Those who never smoked compared with those who ever smoked. Arch Intern Med 152(2):325-327.

Kimizuka G, Azuma M, Ishibashi M, et al. 1993. Co-carcinogenic effect of chrysotile and amosite asbestos with benzo(*a*)pyrene in the lung of hamsters. Acta Pathol Jpn 43(4):149-153.

*Kimizuka G, Shinozaki K, Hayashi Y. 1992. Comparison of the pulmonary responses to chrysotile and amosite asbestos administered intratracheally. I. Early phase of cellular reactions. Acta Pathol Jpn 42(10):707-711.

Kiritani EW. 1990. Asbestos and stomach cancer in Japan - a connection? Med Hypotheses 33:159-160.

Kishimoto T. 1992a. Cancer due to asbestos exposure. Chest 101:58-63.

Kishimoto T. 1992b. Coexistence of a malignant fibrous histiocytoma and asbestos exposure. Brief report. Pathobiology 60(6):332-334.

Kishimoto T. 1992c. Intensity of exposure to asbestos in metropolitan Kure City as estimated by autopsied cases. Cancer 69(10):2598-2602.

Kishimoto T, Ishikura M. 1991. Intensities of asbestos exposure in patients admitted to Kure Kyosai Hospital, Japan. Jpn J Chest Dis 50(8):637-641.

Digitized by Google

8. REFERENCES

Kishimoto T, Okada K. 1988. The relationship between lung cancer and asbestos exposure. Chest 94:486-490.

Kishimoto T, Ono T, Okada K, et al. 1989. Relationship between number of asbestos bodies in autopsy lung and pleural plaques on chest x-ray film. Chest 95:549-552.

*Kishimoto T, Hashimoto H, Ono T, et al. 1992. Synchronous double malignancy: Adenocarcinoma of lung and malignant astrocytoma induced by asbestos exposure. Cancer Invest 10(2):129-133.

*Klaas VE. 1993. A diagnostic approach to asbestosis, utilizing clinical criteria, high resolution computed tomography, and gallium scanning. Am J Ind Med 23(5):801-809.

Kleinfeld M, Messite J, Kooyman O, et al. 1967. Mortality among talc miners and millers in New York State. Arch Environ Health 14:663-667.

*Kleinfeld M, Messite J, Zaki H. 1974. Mortality experiences among talc workers: A follow-up study. J Occup Med 16:345-349.

Klockars M, Savolainen H. 1992. Tumour necrosis factor enhances the asbestos-induced production of reactive oxygen metabolites by human polymorphonuclear leucocytes (PMN). Clin Exp Immunol 90(1):68-71.

*Koerten HK, de Bruijn JD, Daems WT. 1990a. The formation of asbestos bodies by mouse peritoneal macrophages. Am J Pathol 137:121-134.

*Koerten HK, Hazekamp J, Kroon M. et al. 1990b. Asbestos body formation and iron accumulation in mouse peritoneal granulomas after the introduction of crocidolite asbestos fibers. Am J Pathol 136:141-157.

*Kokkola K, Huuskonen MS. 1979. Electrocardiographic signs of cor pulmonale in asbestosis. Int Arch Occup Environ Health 43:167-175.

*Korkina LG, Durnev AD, Suslova TB, et al. 1992. Oxygen radical-mediated mutagenic effect of asbestos on human lymphocytes: suppression by oxygen radical scavengers. Mutat Res 265:245-253.

Koshi K, Kohyama N, Myojo, et al. 1991. Cell toxicity, hemolytic action and clastogenic activity of asbestos and its substitutes. Ind Health 29:37-56.

Koustas RN. 1991. Control of incidental asbestos exposure at hazardous waste sites. J Air Waste Manage Assoc 41:1004-1009.

Kramer JR. 1976. Fibrous cummingtonite in Lake Superior. Can Mineral 14:91-98.

Kronenberg RS, Levin JL, Dodson RF, et al. 1991. Asbestos-related disease in employees of a steel mill and a glass bottle-manufacturing plant. Ann NY Acad Sci 397-403.

Landrigan PJ. 1991. A population of children at risk of exposure to asbestos in place. Ann NY Acad Sci 283-286.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/180

8. REFERENCES

*Lange A, Garncarek D, Tomeczko J, et al. 1986. Outcome of asbestos exposure (lung fibrosis and antinuclear antibodies) with respect to skin reactivity: An 8-year longitudinal study. Environ Res 41:1-13.

Langer AM, Pooley FD. 1973. Identification of single asbestos fibres in human tissue. IARC Sci Publ 8:119-125.

Lasky JA, Bonner JC, Brody AR. 1991. The pathobiology of asbestos-induced lung disease: a proposed role for macrophage-derived growth factors. Ann NY Acad Sci 239-244.

*Lavappa KS, Fu MM, Epstein SS. 1975. Cytogenetic studies on chrysotile asbestos. Environ Res 10:165-173.

Le Bouffant L, Martin JC, Durif S, et al. 1973. Structure and composition of pleural plaques. IARC Sci Publ 8:249-257.

*Lechner JF, Haugen A, Trump BF, et al. 1983. Effects of asbestos and carcinogenic metals on cultured human bronchial epithelium. In: Harris CC, Autrup HN, eds. Human carcinogenesis. New York, NY: Academic Press, Inc., 561-585.

Lee DH. 1974. Biological effects of ingested asbestos: Report and commentary. Environ Health Perspect 9:113-122.

Leigh J, Corvalan CF, Grimwood A, et al. 1991. The incidence of malignant mesothelioma in Australia 1982-1988. Am J Ind Med 20:643-655.

Lemaire I. 1991. Selective differences in macrophage populations and monokine production in resolving pulmonary granuloma and fibrosis. Am J Pathol 138:487-495.

Lemaire I, Gingras D, Lemaire S. 1986. Effects of chrysotile asbestos on DNA synthesis and growth of human embryonic lung fibroblasts. J Environ Pathol Toxicol Oncol 6:169-180.

*Lemen RA, Dement JM, Wagoner JK. 1980. Epidemiology of asbestos-related diseases. Environ Health Perspect 34:1-11.

*Lemen R, Becking GC, Cantor K, et al. 1987. Report on cancer risks associated with the ingestion of asbestos. Environ Health Perspect 72:253-265.

*Lerman Y, Selikoff IJ, Lilis R, et al. 1986. Clinical findings among asbestos workers in V.S.: Influences of cigarette smoking. Am J Ind Med 10:449-458.

Lesage S. 1993. Methods for the analysis of hazardous wastes. J Chromatogr 642(1-2):65-74.

Levin SM, Selikoff IJ. 1991. Radiological abnormalities and asbestos exposure among custodians of the New York City board of education. Ann NY Acad Sci 530-539.

*Levy BS, Sigurdson E, Mandel J, et al. 1976. Investigating possible effects of asbestos in city water: Surveillance of gastrointestinal cancer incidence in Duluth, Minnesota. Am J Epidemiol 103:362-368.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/181

8. REFERENCES

*Lew F, Tsang P, Holland JF, et al. 1986. High frequency of immune dysfunctions in asbestos workers and in patients with malignant mesothelioma. J Clin Immunol 6:225-233.

Li XY, Lamb D, Donaldson K. 1992. Intratracheal injection of crocidolite asbestos depresses the secretion of tumor necrosis factor by pleural leukocytes in vitro. Exp Lung Res 18:359-372.

Li XY, Lamb D, Donaldson K. 1994. Mesothelial cell injury caused by pleural leukocytes from rats treated with intratracheal instillation of crocidolite asbestos or *Corynebacterium parvum*. Environ Res 64(2):181-191.

*Libbus BL, Illenye SA, Craighead JE. 1989. Induction of DNA strand breaks in cultured rat embryo cells by crocidolite asbestos as assessed by nick translation. Cancer Res 49:5713-5718.

Liddell FD, Hanley JA. 1985. Relations between asbestos exposure and lung cancer SMRS in occupational cohort studies. Br J Ind Med 42:389-396.

Lilienfeld DE, Mandel JS, Coin P, et al. 1988. Projection of asbestos related diseases in the United States, 1985-2009 I. Cancer. Br J Ind Med 45:283-291.

Lilienfeld DE. 1991a. Asbestos-associated pleural mesothelioma in school teachers: A discussion of four cases. Ann NY Acad Sci 643:454-486.

Lilienfeld DE. 1991b. The silence: The asbestos industry and early occupational cancer research--a case study. Am J Public Health 81(6):791-800.

Lilis R, Miller A, Godbold J, et al. 1991. Radiographic abnormalities in sbestos insulators: effects of duration from onset of exposure and smoking. Relationships of dyspnea with parenchymal and pleural fibrosis. Am J Ind Med 20:1-15.

Linnalnmaa K, Pelin K, Vanhala E, et al. 1993. Gap junctional intercellular communication of primary and asbestos-associated malignant human mesothelial cells. Carcinogenesis 14(8):1597-1602.

Lippmann M. 1988. Review: Asbestos exposure indices. Environ Res 46:86-106.

*Lippmann M. 1990. Effects of fiber characteristics on lung deposition, retention, and disease. Environ Health Perspect 88:311-317.

Lison D, Knoops B, Lauwerys R. 1989. Effect of retinoic acid on asbestos induced plasminogen activator activity of peritoneal macrophages. Br J Ind Med 46:496-497.

*Livingston GK, Rom WN, Morris MV. 1980. Asbestos-induced sister chromatid exchanges in cultured Chinese hamster ovarian fibroblast cells. J Environ Pathol Toxicol 3:373-382.

Lozewicz S, Reznek RH, Herdman M, et al. 1989. Role of computed tomography in evaluating asbestos related lung disease. Br J Indust Med 46:777-781.

*Lu J, Keane MJ, Ong T, et al. 1994. *In vitro* genotoxicity studies of chrysotile asbestos fibers dispersed in simulated pulmonary surfactant. Mutat Res 320(4):253-259.

Digitized by Google

8. REFERENCES

*Lund LG, Aust AE. 1991a. Iron-catalyzed reactions may be responsible for the biochemical and biological effects of asbestos. BioFactors 3:83-89.

*Lund LG, Aust AE. 1991b. Mobilization of iron from crocidolite asbestos by certain chelators results in enhanced crocidolite-dependent oxygen consumption. Arch Biochem Biophys 287:91-96.

*Lund LG, Aust AE. 1992. Iron mobilization from crocidolite asbestos greatly enhances crocidolite-dependent formation of DNA single-strand breaks in ØX174 RFI DNA. Carcinogenesis 13:637-642.

Lund LG, Williams MG, Dodson RF, et al. 1994. Iron associated with asbestos bodies is responsible for the formation of single strand breaks in ϕ X174 RFI DNA. Occup Environ Med 51(3):200-204.

*Luo SQ, Liu XZ, Wang CJ. 1992. An investigation of crocidolite contamination and experimental study in southwestern China. J Hyg Epidemiol Microbiol Immunol 36(2):223-224.

Luo J-C, Zehab R, Anttila S. 1994. Detection of serum p53 protein in lung cancer patients. J Occup Med 36(2):155-160.

MacRae KD. 1988. Asbestos in drinking water and cancer. J R Coll Physicians Lond 22:7-10.

Magnani C, Borgo G, Betta GP, et al. 1991. Mesothelioma and non-occupational environmental exposure to asbestos [Letter]. Lancet 338(50):8758.

*Magnani C, Terracini B, Ivaldi C, et al. 1993. A cohort study on mortality among wives of workers in the asbestos cement industry in Casale Monferrato, Italy. Br J Ind Med 50(9):779-784.

Maguire GP, Meggs LG, Addonizio J, et al. 1991. Association of asbestos exposure, retroperitoneal fibrosis, and acute renal failure. NY State J Med 91(8):357-359.

*Mahmood N, Khan SG, Ali S, et al. 1993. Asbestos induced oxidative injury to DNA. Ann Occup Hyg 37(3):315-319.

*Malorni W, Iosi F, Falchi M, et al. 1990. On the mechanism of cell internalization of chrysotile fibers: an immunocytochemical and ultrastructural study. Environ Res 52:164-177.

Maltoni C, Minardi F. 1989. Recent results of carcinogenicity bioassays of fibres and other particulate materials. Bologna, Italy: Institute of Oncology, 46-53.

Maltoni C, Pinto C, Mobiglia A. 1991. Mesotheliomas following exposure to asbestos used in railroads: the Italian cases. Toxicol Ind Health 7:1-45.

Manning LS, Davis MR, Robinson BWS. 1991. Asbestos fibres inhibit the *in vitro* activity of lymphokine-activated killer (LAK) cells from healthy individuals and patients with malignant mesothelioma. Clin Exp Immunol 83:85-91.

*Manos CG, Patel-Mandlik KJ, Ross BJ, et al. 1991. Prevalence of asbestos in sewage sludges from 51 large and small cities in the united states. Chemosphere 22:963-973.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/183

8. REFERENCES

Manos CG, Patel-Mandlik KJ, Lisk DJ. 1992. Prevalence of asbestos in composted waste from 26 communities in the United States. Arch Environ Contam Toxicol 23 (2):266-269.

*Manos CG, Patel-Mandlik KJ, Lisk DJ. 1993. Asbestos in yard or sludge composts from the same community as a function of time-of-waste-collection. Chemosphere 26(8):1537-1540.

Maples KR, Johnson NF. 1992. Fiber-induced hydroxyl radical formation: Correlation with mesothelioma induction in rats and humans. Carcinogenesis 13(11):2035-2039.

*Marczynski B, Czuppon AB, Marek W, et al. 1994. Increased incidence of DNA double-strand breaks and anti-ds DNA antibodies in blood of workers occupationally exposed to asbestos. Hum Exp Toxicol 13(1):3-9.

*Marsh GM. 1983. Critical review of epidemiologic studies related to ingested asbestos. Environ Health Perspect 53:49-56.

*Marsh JP, Mossman BT. 1991. Role of asbestos and active oxygen species in activation and expression of ornithine decarboxylase in hamster tracheal epithelial cells. Cancer Res 51:167-173.

Masson TJ, McKay FW, Miller RW. 1974. Asbestos-like fibers in Duluth water supply: Relation to cancer mortality. JAMA 228:1019-1020.

Mays CW, Spiess H. 1984. Bone sarcomas in patients given radium-224. In: Boice JD Jr, Fraumeni JF Jr, eds. Radiation carcinogenesis: Epidemiology and biological significance. New York, NY: Raven Press, 241-252.

McCaughey WT. 1986. Neoplastic asbestos-induced disease. Mt Sinai J Med (NY) 53:416-420.

McConnochie K, Simonato L, Mayrides P, et al. 1987. Mesothelioma in Cyprus: The role of tremolite. Thorax 42:342-347.

McConnell EE, Rutter HA, Ulland BM, et al. 1983a. Chronic effects of dietary exposure to Amosite Asbestos and tremolite in F344 rats. Environ Health Perspect 53:27-44.

McConnell EE, Shefner AM, Rust JH, et al. 1983b. Chronic effects of dietary exposure to amosite and chrysotile asbestos in Syrian golden hamsters. Environ Health Perspect 53:11-25.

*McDonald JC, Liddell FD, Gibbs GW, et al. 1980. Dust exposure and mortality in chrysotile mining, 1910-75. Br J Ind Med 37:11-24.

*McDonald AD, Fry JS, Woolley AJ, et al. 1982. Dust exposure and mortality in an American factory using chrysotile, amosite, and crocidolite in mainly textile manufacture. Br J Ind Med 39:368-374.

*McDonald AD, Fry JS, Wodley AJ, et al. 1983. Dust exposure and mortality in an American chrysotile textile plant. Br J Ind Med 40:361-367.

*McDonald AD, Fry JS, Wooley AJ, et al. 1984. Dust exposure and mortality in an American chrysotile asbestos friction products plant. Br J Ind Med 41:151-157.

Digitized by Google

8. REFERENCES

*McDonald JC, McDonald AD, Armstrong B, et al. 1986. Cohort study of mortality of vermiculite miners exposed to tremolite. Br J Ind Med 43:436-444.

*McDonald JC, Armstrong B, Case B, et al. 1989. Mesothelioma and asbestos fiber type. Evidence from lung tissue analysis. Cancer 63:1544-1547.

McDonald JC, Sebastien P, Case B. 1992. Ferruginous body counts in sputum as an index of past exposure to mineral fibers. Ann Occup Hyg 36(3):271-82.

*McDonald JC, Liddell FD, Dufresne A, et al. 1993. The 1891-1920 birth cohort of Quebec chrysotile miners and millers: Mortality 1976-88. Br J Ind Med 50(12):1073-1081.

*McFadden D, Wright J, Wiggs B, et al. 1986. Cigarette smoke increases the penetration of asbestos fibers into airway walls. Am J Pathol 123:95-99.

*McGavin CR, Sheers G. 1984. Diffuse pleural thickening in asbestos workers: Disability and lung function abnormalities. Thorax 39:604-607.

*McGavran PD, Butterick CJ, Brody AR. 1989. Tritiated thymidine incorporation and the development of an interstitial lesion in the bronchiolar-alveolar regions of the lungs of normal and complement deficient mice after inhalation of chrysotile asbestos. JEPTO 9:377-391.

McLachlan MS, Wagner JC. 1974. Radiological diagnosis of crocidolite induced pleural mesotheliomata in the rat. Br J Exp Pathol 55:164-168.

McMillan CH, Jones AD, Vincent JH, et al. 1989. Accumulation of mixed mineral dusts in the lungs of rats during chronic inhalation exposure. Environ Res 48:218-237.

McNeill KR, Waring S. 1992. Vitrification of contaminated soils. In: Rees JF, ed. Contamination and land treatment technology (International Public Conference), 143-159.

MDEQE. 1989. Summary of Massachusetts' Methodology for developing allowable ambient limits. Boston, MA: Massachusetts Department of Environmental Quality Engineering. Written Communication (May 8).

Meek ME. 1983. Transmigration of ingested asbestos. Environ Health Perspect 53:149-152.

*Menard H, Noel L, Khorami J, et al. 1986. The adsorption of polyaromatic hydrocarbons on natural and chemically modified asbestos fibers. Environ Res 40:84-91.

Meranger JC, Davey ABC. 1989. Non-asbestos fibre content of selected consumer products. Ottawa, Ontario, Canada: Environmental Health Directorate, Health and Welfare Canada, 347-353.

*Meurman LO, Kiviluoto R, Hakama M. 1974. Mortality and morbidity among the working population of anthophyllite asbestos miners in Finland. Br J Ind Med 31:105-112.

*Meurman LO, Pukkala E, Hakama M. 1994. Incidence of cancer among anthrophyllite asbestos miners in Finland. Occup Environ Med 51(6):421-425.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/185

Miller K. 1985. Immunotoxicology. Clin Exp Immunol 61:219-223.

Miller K, Brown RC. 1985. The immune system and asbestos-associated disease. In: Dean J et al., eds. Immunotoxicology and immunopharmacology. New York, NY: Raven Press, 429-440.

Miller A, Miller JA. 1993. Diffuse thickening superimposed on circumscribed pleural thickening related to asbestos exposure. Am J Ind Med 23(6):859-871.

*Miller K, Webster I, Handfield RI, et al. 1978. Ultrastructure of the lung in the rat following exposure to crocidolite and asbestos and quartz. J Pathol 124:39-44.

*Miller A, Teirstein AS, Selikoff I. 1983. Ventilatory failure due to asbestos pleurisy. American Journal of Medicine. 75:911-919.

*Miller A, Lilis R, Godbold J. 1992. Relationship of pulmonary function to radiographic interstitial fibrosis in 2,611 long-term asbestos insulators: An assessment of the International Labour Office profusion score. Am Rev Respir Dis 145(2):263-270.

*Millette JR, Clark PJ, Pansing MF. 1980. Concentration and size of asbestos in water supplies. Environ Health Perspect 34:13-25.

Millette JR, Clark PJ, Stober J, et al. 1983a. Asbestos in water supplies of the United States. Environ Health Perspect 53:45-48.

Millette JR, Craun GF, Stober JA, et al. 1983b. Epidemiology study of the use of asbestos-cement pipe for the distribution of drinking water in Escambia County, Florida. Environ Health Perspect 53:91-98.

Milosevic M, Petrovic L. 1988. Environmental exposure to chrysotile asbestos and cancer epidemiology. Arh Hig Rada Toksikol 39:489-498.

Minardi F, Maltoni C. 1988. Results of recent experimental research on the carcinogenicity of natural and modified asbestos. Ann NY Acad Sci 754-761.

Minowa M, Hatano S, Ashizawa, et al. 1991. A case-control study of lung cancer with special reference to asbestos exposure. Environ Health Perspect 94:39-42.

*Molinini R, Paoletti L, Albrizio M, et al. 1992. Occupational exposure to asbestos and urinary bladder cancer. Environ Res 58(2):176-183.

Mollo F, Andrion A, Pira E, et al. 1983. Indicators of asbestos exposure in autopsy routine. 2. Pleural plaques and occupation. Med Lav 74:137-142.

Mollo F, Piolatto G, Bellis D, et al. 1990. Asbestos exposure and histologic cell types of lung cancer in surgical and autopsy series. Int J Cancer 46:576-580.

Monchaux G, Chameaud J, Morlier JP, et al. 1989. Translocation of subcutaneously injected chrysotile fibres: potential cocarcinogenic effect on lung cancer induced in rats by inhalation of radon and its daughters. IARC Sci Pub 90:161-166.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/186

8. REFERENCES

Moniewska A, Szyba K, Jazwiec B, et al. 1989. Chrysotile A affects YAC-1 cytolytic activity of spleen cells. Arch Imm Et Therap 37:61-68.

Morgan RW. 1991. Re: meta-analysis of asbestos and gastrointestinal cancer. Am J Ind Med 19:407-408.

Morgan A, Holmes A. 1983. Distribution and characteristics of amphibole asbestos fibres, measured with the light microscope, in the left lung of an insulation worker. Br J Ind Med 40:45-50.

*Morgan A, Holmes A. 1986. Solubility of asbestos and man-made mineral fibers *in vitro* and *in vivo*: Its significance in lung disease. Environ Res 39:475-484.

*Morgan A, Evans JC, Evans RJ, et al. 1975. Studies on the deposition of inhaled fibrous material in the respiratory tract of the rat and its subsequent clearance using radioactive tracer techniques: II. Deposition of the UICC standard reference samples of asbestos. Environ Res 10:196-207.

Morgan A, Davies P, Wagner JC, et al. 1977. The biological effects of magnesium-leached chrysotile asbestos. Br J Exp Pathol 58:465-473.

*Morgan A, Talbot RJ, Holmes A. 1978. Significance of fiber length in the clearance of asbestos fibres from the lung. Br J Ind Med 35:146-153.

*Morgan RW, Foliart DE, Wong O. 1985. Asbestos and gastrointestinal cancer. West J Med 143:60-65.

Morgan A, Collier CG, Morris KJ, et al. 1993. A radioactive tracer technique to determine *in vivo* the number of fibers in the lungs of rats following their administration by intratracheal instillation. Environ Res 63(2):182-190.

Morimoto Y, Kido M, Tanaka I, et al. 1993. Synergistic effects of mineral fibers and cigarette smoke on the production of necrosis factor by alveolar macrophages of rats. Br J Ind Med 50(10):955-960.

Mossman BT. 1983. *In vitro* approaches for determining mechanisms of toxicity an carcinogenicity by asbestos in the gastrointestinal and respiratory tracts. Environ Health Perspect 53:155-161.

Mossman BT. 1988. Carcinogenic potential of asbestos and nonasbestos fibers. J Environ Sci Health 6:151-195.

Mossman BT. 1990. *In vitro* studies on the biologic effects of fibers: correlation with *in vivo* bioassays. Environ Health Perspect 88:319-322.

Mossman BT, Craighead JE. 1979. Use of hamster tracheal organ cultures for assessing the cocarcinogenic effects of inorganic particulates on the respiratory epithelium. Prog Exp Tumor Res 24:37-47.

Mossman BT, Marsh JP. 1989. Evidence supporting a role for active oxygen species in asbestos-induced toxicity and lung disease. Environ Health Perspect 81:91-94.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/187

8. REFERENCES

*Mossman B, Light W, Wei E. 1983a. Asbestos: Mechanisms of toxicity and carcinogenicity in the respiratory tract. Ann Rev Pharmacol Toxicol 23:595-615.

*Mossman BT, Eastman A, Landesman JM, et al. 1983b. Effects of crocidolite and chrysotile asbestos on cellular uptake and metabolism of benzo(a)pyrene in hamster epithelial cells. Environ Health Perspect 51:331-335.

*Mossman BT, Eastman A, Bresnick E. 1984. Asbestos and benzo[a]pyrene act synergistically to induce squamous metaplasia and incorporation of [^{3}H]thymidine in hamster tracheal epithelium. Carcinogenesis 5:1401-1405.

*Mossman BT, Bignon J, Corn M, et al. 1990a. Asbestos: scientific developments and implications for public policy. Science 247:294-301.

*Mossman BT, Marsh JP, Sesko A, et al. 1990b. Inhibition of lung injury, inflammation, and interstitial pulmonary fibrosis by polyethylene glycol-conjugated catalase in a rapid inhalation model of asbestosis. Am Rev Respir Dis 141:1266-1271.

Murai Y, Kitagawa M. 1992. Asbestos fiber analysis in 27 malignant mesothelioma cases. Am J Ind Med 22(2):193-207.

*Muscat JE, Wynder EL. 1991. Cigarette smoking, asbestos exposure, and malignant mesothelioma. Cancer Res 51:2263-2267.

Muscat JE, Wynder EL. 1992. Tobacco, alcohol, asbestos, and occupational risk factors for laryngeal cancer. Cancer 69:2244-2251.

Nadeau Denis, Lane DA. 1989. On the cytotoxicity of chrysotile asbestos fibers toward pulmonary alveolar macrophages. Toxicol App Pharmacol 98:144-158.

*NAS. 1977. Drinking water and health. Washington, DC: National Academy of Sciences, 144-168.

*NAS. 1982. Drinking water and health. Vol 4. Washington, DC: National Academy Press, 42-61.

*NAS. 1983. Drinking water and health. Vol 5. Washington, DC: National Academy Press, 123-147.

*NAS/NRC. 1989. Biologic markers in reproductive toxicology. National Academy of Sciences/National Research Council. Washington, DC: National Academy Press, 15-35.

NATICH. 1988. NATICH data base report on state, local and EPA air toxics activities. U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards, National Air Toxics Information Clearinghouse, Research Triangle Park, NC. EPA 450/5-88-007. NTIS No. PB89-106983.

NATICH. 1991. NATICH data base report on state, local and EPA air toxics activities. Report to U.S. Environmental Protection Agency, Office of Air Quality Planning Standards, National Air Toxics Information Clearinghouse, Research Triangle Park, NC, by Radian Corporation, Austin, TX. EPA 68/08-0065.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/188

8. REFERENCES

*NATICH. 1992. NATICH data base report on state, local and EPA air toxics activities. U. S. Environmental Protection Agency, Office of Air Quality Planning and Standards, National Air Toxics Information Clearinghouse, Research Triangle Park, NC. September 1992.

Nettesheim P, Topping DC, Jamasbi R. 1981. Host and environmental factors enhancing carcinogenesis in the respiratory tract. Ann Rev Pharmacol Toxicol 21:133-163.

Neuberger M, Kundi M. 1990. Individual asbestos exposure: smoking and mortality-a cohort study in the asbestos cement industry. Br J Ind Med 47:615-620.

*Neugut AI, Murray TI, Garbowski GC, et al. 1991. Association of asbestos exposure with colorectal adenomatous polyps and cancer. J Natl Cancer Inst 83:1827-1828.

*Newhouse ML, Berry G. 1976. Predictions of mortality from mesothelial tumours in asbestos factory workers. Br J Ind Med 33:147-151.

*Newhouse ML, Berry G. 1979. Patterns of mortality in asbestos factory worker 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, et al. 1972. A study of the mortality of female asbestos workers. Br J Ind Med 29:134-141.

Newhouse ML, Berry G, Wagner JC. 1985. Mortality of factory workers in east London 1933-1980. Br J Ind Med 42:4-11.

Newman HA, Saat YA, Hart RW. 1980. Putative inhibitory effects of chrysotile, crocidolite, and amosite mineral fibers on the more complex surface membrane glycolipids and glycoproteins. Environ Health Perspect 34:103-111.

Nicholson WJ. 1971. Measurement of asbestos in ambient air. Final report. National Air Pollution Control Administration. [Unpublished]

Nicholson WJ. 1978. Chrysotile asbestos in air samples collected in Puerto Rico. Report to the Consumer Products Safety Commission by the City University of New York, Mount Sinai School of Medicine, Environmental Sciences Laboratory, New York, NY. CPSC 77128000.

*Nicholson WJ. 1987. Airborne levels of mineral fibres in the non-occupational environment. New York, NY: City University of New York, Mount Sinai School of Medicine, Division of Environmental and Occupational Medicine.

Nicholson WJ. 1989. Airborne mineral fibre levels in the non-occupational environment. In: Bignon J, Peto J, Saracci R, eds. Lyon, France: International Agency for Research on Cancer, World Health Organization.

Nicholson WJ. 1991. Comparative dose-response relationships of asbestos fiber types: magnitude and uncertainties. Ann NY Acad Sci 74-84.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/189

8. REFERENCES

*Nicholson WJ, Pundsack FL. 1973. Asbestos in the environment. In: Biological effects of asbestos, proceedings of a working conference held at IARC 26 October, 1972. IARC Sci Publ 8:126-132.

Nicholson WJ, Rohl AN, Weisman I. 1975. Asbestos contamination of the air in public buildings. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards. EPA-450/3-76-004. NTIS No. PB-250980.

*Nicholson WJ, Selikoff IJ, Seidman H, et al. 1979. Long-term mortality experience of chrysotile miners and millers in Thetford Mines, Quebec. Ann NY Acad Sci 330:11-21.

*Nicholson WJ, Perkel G, Selikoff IJ. 1982. Occupational exposure to asbestos: populations at risk and projected mortality--1980-2030. Am J Ind Med 3:259-311.

*Nigam SK, Suthar AM, Patel MM, et al. 1993. Humoral immunological profile of workers exposed to asbestos in asbestos mines. Indian J Med Res 98(12):274-7.

NIOSH. 1975. Asbestos exposure during servicing of motor vehicle brake and clutch assemblies. Current intelligence bulletin 5. Rockville, MD: U.S. Department of Health, Education, and Welfare, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health.

*NIOSH. 1976. Revised recommended asbestos standard. Washington, DC: U.S. Department of Health, Education, and Welfare, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health. DHEW (NIOSH) Publication No. 77-169.

NIOSH. 1984. Chrysotile asbestos - method 9000. In: NIOSH manual of analytical methods. 3rd ed. Cincinnati, OH: National Institute for Occupational Safety and Health, 9000-1 - 9000-7.

NIOSH. 1985. NIOSH pocket guide to chemical hazards. Washington, DC: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, 54.

*NIOSH. 1987. Fibers - method 7400. In: NIOSH manual of analytical methods. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health. Revision 2. August 15, 1987.

NIOSH. 1988a. National occupational exposure survey. Cincinnati, OH: National Institute for Occupational Safety and Health.

NIOSH. 1988b. National occupational hazard survey. Cincinnati, OH: National Institute for Occupational Safety and Health.

NIOSH. 1988d. Asbestos-induced intrathoracic tissue reactions. Cincinnati, OH: National Institute for Occupational Safety and Health, NTIS No. PB88-248380.

*NIOSH. 1989a. Fibers - method 7400. In: NIOSH manual of analytical methods. 3rd ed. Supplement. Cincinnati, OH: National Institute for Occupational Safety and Health, 7400-1 - 7400-13.

Digitized by Google

8. REFERENCES

*NIOSH. 1989b. Asbestos fibers - method 7402. In: NIOSH manual of analytical methods. 3rd ed. Supplement. Cincinnati, OH: National Institute for Occupational Safety and Health, 7402-1 - 7402-8.

*NIOSH. 1989c. Fibers - method 9002. In: NIOSH manual of analytical methods. 3rd ed. Supplement. Cincinnati, OH: National Institute for Occupational Safety and Health, 9002-1 to 9002-10.

NIOSH. 1989d. Control of asbestos exposure during brake drum service. Cincinnati, OH: National Institute for Occupational Safety and Health, NTIS no. PB90-168501.

NIOSH. 1990a. Asbestos related disease - a community epidemic in the making. Cincinnati, OH: National Institute for Occupational Safety and Health, NTIS no. PB90-155896.

*NIOSH. 1990b. National Institute for Occupational Safety and Health. NIOSH pocket guide to chemical hazards. Washington, DC: U.S. Department of Health and Human Services.

NIOSH. 1990c. Testimony of the National Institute for Occupational Safety and Health on the occupational safety of proposed rulemaking on occupational exposure to asbestos, tremolite, anthrophyllite, and actinolite. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health. 2 CFR 1910 and 1926. May 9, 1990. NTIS no. PB91-152-439.

*NIOSH. 1992. NIOSH recommendations for occupational safety and health. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, iv-vi, 51, 140.

NLM. 1988. Chemline. National Library of Medicine, Bethesda, MD. December 1988.

Noksokoivisto P, Pukkala E. 1994. Past exposure to asbestos and combustion products and incidence of cancer among Finnish locomotive drivers. Occup Environ Med 51(5):330-334.

*NRC (National Research Council). 1984. Asbestiform fibers: Nonoccupational health risks. Washington, DC: National Academy Press.

*NTP. 1983. National Toxicology Program. Technical report series no. 249. Lifetime carcinogenesis studies of amosite asbestos (cas no. 121-72-73-5) in Syrian golden hamsters (feed studies). Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. NIH Publication No. 84-2505.

*NTP. 1985. National Toxicology Program. Technical report series no. 295. Toxicology and carcinogenesis studies of chrysotile asbestos (cas no. 12001-29-5) in F344/N rats (feed studies). Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. NIH Publication No. 86-2551.

*NTP. 1988. National Toxicology Program. Technical report on the toxicology and carcinogenesis studies of crocidolite asbestos (cas no. 12001-28-4) in F344/N rats (feed studies). Research Triangle Park, NC: U. S. Department of Health and Human Services, Public Health Service, National Institutes of Health. NIH Publication No. 88-2536.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/191

8. REFERENCES

*NTP. 1990a. National Toxicology Program. Technical report on the carcinogenesis lifetime studies of chrysotile asbestos (cas no. 12001-29-5) in Syrian golden hamsters (feed studies). Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. NIH Publication No. 90-2502.

*NTP. 1990b. National Toxicology Program. Technical report series no. 279. Toxicology and carcinogenesis studies of amosite asbestos F344/N rats. Report to National Institute of Environmental Health Sciences, Research Triangle Park, NC, by Technical Resources, Inc., Rockville, MD. NTP 91-2535.

*NTP. 1990c. National Toxicology Program. Technical report on the toxicology and carcinogenesis studies of tremolite (cas no. 14567-73-8) in Fischer 344 rats (feed study). Research Triangle Park, NC: U. S. Department of Health and Human Services, Public Health Service, National Institutes of Health. NIH Publication No. 90-2531.

*NTP. 1991. National Toxicology Program. Sixth annual report on carcinogens 1991 summary. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Institute of Health. 27-33.

NTP. 1994. National Toxicology Program. Management status report. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, Division of Toxicology Research and Testing.

*Nyberg P, Klockars M. 1991. Interferon-γ and immunoglobulin enhance mineral dust-induced production of reactive oxygen metabolites by human macrophages. Clin Immunol Immunopathol 60:128-136.

Oehlert GW. 1991. A reanalysis of the Stanton et al. pleural sarcoma data. Environ Res 54:194-205.

*Ogino S, Fukumori N, Yasuno T, et al. 1988. Asbestos fibers in sake. J Food Protection 51:737-739.

*Ohlson C-G, Rydman T, Sundell L, et al. 1984. Decreased lung function in long-term asbestos cement workers: A cross-sectional study. Am J Ind Med 5:359-366.

*Ohlson C-G, Bodin L, Rydman T, et al. 1985. Ventilatory decrements in Former asbestos cement workers: A four year follow up. Br J Ind Med 42:612-616.

*Oksa P, Koskinen H, Rinne JP, et al. 1992. Parenchymal and pleural fibrosis in construction workers. Am J Ind Med 21:561-567.

*Oksa P, Suoranto H, Koshinen H, et al. 1994. High resolution computed tomography in the early detection of asbestosis. Int Arch Occup Environ Health 65(5):299-304.

Oliver LC, Sprince NL, Greene R. 1991. Asbestos-related abnormalities in school maintenance personnel. Ann NY Acad Sci 521-529.

*Olofsson K, Mark J. 1989. Specificity of asbestos-induced chromosomal aberrations in short-term cultured human mesothelial cells. Cancer Genet Cytogenet 41:33-39.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/192

8. REFERENCES

Omenn GS. 1991/92. CARET, the beta-carotene and retinal efficacy trial to prevent lung cancer in high-risk populations. Public Health Rev 19(1-4):205-208.

Omenn GS, Goodman G, Grizzle J, et al. 1992. Recruitment for the β-carotene and retino efficacy trial (caret) to prevent lung cancer in smokers and asbestos-exposed workers. West J Med 156:540-544.

Omenn GS, Goodman G, Thornquist M, et al. 1994. The beta-carotene and retinol efficacy trial (CARET) for chemoprevention of lung cancer in high risk populations: Smokers and asbestos-exposed workers. Cancer Res 54(Suppl 7):2038s-2043s.

Omenn GS, Goodman GE, Thornquist MD, et al. 1993. The carotene and reinol efficacy trial (CARET) to prevent lung-cancer in high risk populations--pilot study with asbestos-exposed workers. Cancer Epidemiol Biomarkers Prev 2(4):381-387.

*Osgood C, Sterling D. 1991. Chrysotile and amosite asbestos induce germ-line aneuploidy in Drosophila. Mutat Res 261:9-13.

*OSHA. 1986. U.S. Department of Labor, Occupational Safety and Health Administration: Part II. Federal Register 51:22612-22790.

*OSHA. 1988. U.S. Department of Labor, Occupational Safety and Health Administration: Part III. Federal Register 53:35610-35629.

*OSHA. 1990. U.S. Department of Labor, Occupational Safety and Health Administration: Part II. Federal Register 55:29712-29753.

OSHA. 1992. U.S. Department of Labor, Occupational Safety and Health Administration: Part II. 57:7877-7878, 24310-24331, 49657-49661.

*OSHA. 1994. Occupational exposure to asbestos. U.S. Department of Labor, Occupational Safety and Health Administration. Federal Register 59(153):40964-41162.

Oshimura M, Hesterberg TW, Tsutsui T, et al. 1984. Correlation of asbestos-induced cytogenetic effect with cell transformation of Syrian hamster embryo cells in culture. Cancer Res 44:5017-5022

*Oshimura M, Hesterberg TW, Barrett JC. 1986. An early, nonrandom karyotypic change in immortal Syrian hamster cell lines transformed by asbestos: Trisomy of chromosome 11. Cancer Genet Cytogenet 22:225-237.

OTA. 1990. Neurotoxicity: Identifying and controlling poisons of the nervous system. Washington, DC: Office of Technology Assessment, U.S. Congress. OTA-BA-436. April 1990.

Paci E, Zappa M, Paoletti L, et al. 1991. Further evidence of an excess of risk of pleural malignant mesothelioma in textile workers in Prato [Italy]. Br J Cancer 64(2):377-378.

Pailes WH, Judy DJ, Resnick H, et al. 1984. Relative effects of asbestos and wollastonite on alveolar macrophages. J Toxicol Environ Health 14:497-510.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/193

8. REFERENCES

Pairon JC, Orlowski E, Iwatsubo Y, et al. 1994. Pleural mesothelioma and exposure to asbestos: Evaluation from work histories and analysis of asbestos bodies in bronchoalveolar lavage fluid or lung tissue in 131 patients. Occup Environ Med 51(4):244-249.

*Palekar LD, Eyre JF, Most BM, et al. 1987. Metaphase and anaphase analysis of V79 cells exposed to erionite, UICC chrysotile and UICC crocidolite. Carcinogenesis 8:553-560.

Palekar LD, Most BM, Coffin DL. 1988. Significance of mass and number of fibers in the correlation of V79 cytotoxicity with tumorigenic potential of mineral fibers. Environ Res 46:142-152.

*Pang TW, Schonfeld-Starr FA, Patel K. 1989. An improved membrane filter technique for evaluation of asbestos fibers. Am Ind Hyg Assoc J 50:174-180.

Parkin DM, Wahrendorf J, Demaret E, et al. 1987. Directory of on-going research in cancer epidemiology. Lyon, France: International Agency for Research on Cancer.

*Parnes SM. 1990. Asbestos and cancer of the larynx: Is there a relationship? Laryngoscope 100:254-261.

Parnes SM, Sherman M. 1991. Head and neck surveillance program for factory personnel exposed to asbestos. Ann Otol Rhinol Laryngol 100(9 Pt 1):731-736.

Parry WT. 1985. Calculated solubility of chrysotile asbestos in physiological systems. Environ Res 37:410-418.

Pasqualetti P, Casale R, Colantonio D, et al. 1991. Occupational risk for hematological malignancies. Am J Hematol 38(2):147-149.

*Patel-Mandlik KJ, Millette JR. 1983. Chrysotile asbestos in kidney cortex of chronically gavaged rats. Arch Environ Contam Toxicol 12:247-255.

*Patel-Mandlik KJ, Manos CG, Lisk DJ, et al. 1988. Identification of asbestos and glass fibers in sewage sludges of small New York state cities. Chemosphere 17:1025-1032.

Pearce N. 1988. Multistage modelling of lung cancer mortality in asbestos textile workers. Int J Epidemiol 17:747-752.

*Pelin-Enlund K, Husgafvel-Pursiainen K, Tammilehto L, et al. 1990. Asbestos-related malignant mesothelioma: Growth, cytology, tumorigenicity and consistent chromosome findings in cell lines from five patients. Carcinogenesis 11:673-681.

Perderiset M, Marsh JP, Mossman BT. 1991. Activation of protein kinase C by crocidolite asbestos in hamster tracheal epithelial cells. Carcinogenesis 12:1499-1502.

*Perkins RC, Scheule RK, Hamilton R, et al. 1993. Human alveolar macrophage cytokine release in response to *in vitro* and *in vivo* asbestos exposure. Exp Lung Res 19(1):55-65.

*Pernis B, Vigliani EC, Selikoff IJ. 1965. Rheumatoid factor in serum of individuals exposed to asbestos. Ann NY Acad Sci 132:112-120.

Digitized by Google

8. REFERENCES

Peterson JT Jr, Greenberg SD, Buffler PA. 1984. Non-asbestos-related malignant mesothelioma: A review. Cancer 54 (September 1):951-960.

*Peterson MW, Walter ME, Gross TJ. 1993. Asbestos directly increases lung epithelial permeability. Am J Physiol 265(3 Pt 1):L308-L317.

*Peto J. 1980. The incidence of pleural mesothelioma in chrysotile asbestos textile workers. IARC Sci Pub 30:703-711.

Peto J. 1989. Fibre carcinogenesis and environmental hazards. IARC Sci Pub 90:457-470.

*Peto J, Seidman H, Selikoff IJ. 1982. Mesothelioma mortality in asbestos workers: Implications for models of carcinogenesis and risk assessment. Br J Cancer 45:124-135.

*Peto J, Doll R, Hermon C, et al. 1985. Relationship of mortality to measures of environmental asbestos pollution in an asbestos textile factory. Ann Occup Hyg 29:305-345.

*Petruska JM, Leslie KO, Mossman BT. 1991. Enhanced lipid peroxidation in lung lavage of rats after inhalation of asbestos. Free Radical Biol Med 11:425-432.

PHRED. 1988. Public Health Risk Evaluation Database. U. S. Environmental Protection Agency, Washington, DC. March 1988.

*Pinkerton KE, Brody AR, Miller FJ, et al. 1989. Exposure to low levels of ozone results in enhanced pulmonary retention of inhaled asbestos fibers. Am Rev Respir Dis 140:1075-1081.

*Pinkerton KE, Plopper CG, Mercer RR, et al. 1986. Airway branching patterns influence asbestos fiber location and the extent of tissue injury in the pulmonary parenchyma. Lab Invest 55:688-695.

*Pitt R. 1988. Asbestos as an urban area pollutant. J Water Pollut Control Fed 60:1993-2001.

*Platek SF, Groth DH, Ulrich CE, et al. 1985. Chronic inhalation of short asbestos fibers. Fundam Appl Toxicol 5:327-340.

*Plowman PN. 1982. The pulmonary macrophage population of human smokers. Ann Occup Hyg 25:393-405.

*Polissar L, Severson RK, Boatman ES, et al. 1982. Cancer incidence in relation to asbestos in drinking water in the Puget Sound region. Am J Epidemiol 116:314-328.

Polissar L, Severson RK, Boatman ES. 1983. Cancer risk from asbestos in drinking water: Summary of a case-control study in western Washington. Environ Health Perspect 53:57-60.

*Polissar L, Severson RK, Boatman ES. 1984. A case-control study of asbestos in drinking water and cancer risk. Am J Epidemiol 119:456-471.

Pontefract RD. 1974. Penetration of asbestos through the digestive wall in rats [Commentary]. Environ Health Perspect 9:213-214.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/195

8. REFERENCES

*Pontefract RD, Cunningham HM. 1973. Penetration of asbestos through the digestive tract of rats. Nature 243:352-353.

*Pooley FD. 1976. An examination of the fibrous mineral content of asbestos lung tissue from the Canadian chrysotile mining industry. Environ Res 12:281-298.

Pooley FD, Clark NJ. 1979. Quantitative assessment of inorganic fibrous particulates in dust samples with an analytical transmission electron microscope. Ann Occup Hyg 22:253-271.

Pott F. 1987. [The fibre as a carcinogenic agent.] Zentralbl Bakteriol Hyg [B] 184:1-23. (German)

Pott F, Bellman B, Muhle H, et al. 1989a. Proceedings of the First International Conf. on Health Related Effects of Phyllosilicates, Paris, France.

Pott F, Roller M, Ziem U, et al. 1989b. Carcinogenicity studies on natural and man-made fibres with the intraperitoneal test in rats. IARC Sci Pub 90:173-179.

Price B, Crump KS, Baird EC 3d. 1992. Airborne asbestos levels in buildings: Maintenance worker and occupant exposures. J Expo Anal Environ Epidemiol 2(3):357-374.

*Price-Jones MJ, Gubbings G, Chamberlain M. 1980. The genetic effects of crocidolite asbestos; comparison of chromosome abnormalities and sister-chromatid exchanges. Mutat Res 79:331-336.

Prior AJ, Ball ABS. 1993. Intestinal obstruction complicating malignant mesothelioma of the pleura. Respir Med 87(2):147-148.

Pylev LN. 1987. [The role of modifying factors in the carcinogenic effects of asbestos and asbestos-containing dusts.] Eksp Onkol 9:14-17. (Russian)

Pylev LN, Kogan FM, Kulagina TF. 1988. [Carcinogenic activity of asbestos cement dust.] Gig Tr Prof Zabol (July):55-57 (Russian).

*Raffn E, Lynge E, Juel K, et al. 1989. Incidence of cancer and mortality among employees in the asbestos cement industry in Denmark. Br J Ind Med 46:90-96.

Rafnsson V, Jahannesdottir SG, Oddsson H, et al. 1988. Mortality and cancer incidence among marine engineers and machinists in Iceland. Scand J Work Environ Health 14:197-200.

*Rahman Q, Khan SG, Ali S. 1990. Effect of chrysotile asbestos on cytochrome P-450 - dependent monooxygenase and glutathione-s-transferase activities in rat lung. Chem Biol Interactions 75:305-314.

Raithel HJ, Weltle D, Bohlig H, et al. 1989. Health hazards from fine asbestos dusts. Int Arch Occup Environ Health 61:527-541.

Rajan KT, Wagner JC, Evans PH. 1972. The response of human pleura in organ culture to asbestos. Nature 238:346-347.

Rapiti, E, Turi E, Forastiere F, et al. 1992. A mortality cohort study of seamen in Italy. Am J Ind Med 21(6):863-872.

Digitized by Google

8. REFERENCES

*Reeves AL, Puro HE, Smith RG, et al. 1971. Experimental asbestos carcinogensis. Environ Res 4:496-511.

*Reeves AL, Puro HE, Smith RG. 1974. Inhalation carcinogenesis from various forms of asbestos. Environ Res 8:178-202.

Reid AS, Causton BE, Jones JS, et al. 1991. Malignant mesothelioma after exposure to asbestos in dental practice [letter]. Lancet 338(8768):696.

Reiss B, Solomon S, Weisburger JH, et al. 1980a. Comparative toxicities of different forms of asbestos in a cell culture assay. Environ Res 22:109-129.

Reiss B, Millette JR, Williams GM. 1980b. The activity of environmental samples in a cell culture test for asbestos toxicity. Environ Res 22:315-321.

*Reiss B, Solomon S, Tong C, et al. 1982. Absence of mutagenic activity of three forms of asbestos in liver epithelial cells. Environ Res 27:389-397.

Reiss B, Tong C, Telang S, et al. 1983. Enhancement of benzo[a]pyrene mutagenicity by chrysotile asbestos in rat liver epithelial cells. Environ Res 31:100-104.

*Ren H, Lee DR, Hruban RH, et al. 1991. Pleural plaques do not predict asbestosis: High-resolution computed tomography and pathology study. Mod Pathol 4(2):201-209.

Renke W. 1990. Evaluation of pathological changes in respiratory system of workers exposed to asbestos dust. Bull Inst Mar Trop Med Gdynia 41:5-15.

*Rey F, Boutin C, Steinbauer J, et al. 1993. Environmental pleural plaques in an asbestos exposed population of northeast Corsica. Eur Respir J 6(7):978-982.

Ribak J, Lilis R, Suzuki Y, et al. 1988. Malignant mesothelioma in a cohort of asbestos insulation workers: clinical presentation, diagnosis, and causes of death. Br J Ind Med 45:182-187.

Ribak J, Seidman H, Selikoff IJ. 1989. Amosite mesothelioma in a cohort of asbestos workers. Scan J Work Environ Health 15:106-110.

Ribak J, Lilis R, Suzuki Y, et al. 1991. Death certificate categorization of malignant pleural and peritoneal mesothelioma in a cohort of asbestos insulation workers. J Soc Occup Med 41(3):137-139.

*Rickards, AL. 1994. Levels of workplace exposure. Ann Occup Hyg 38(4):469-475.

Robb JA, Hammar SP, Yokoo H. 1993. Pseudomesotheliomatous lung carcinoma a rare asbestos-related malignancy readily separable from epithelial pleural mesothelioma. 1993 Annual Meeting of the United States and Canadian 68(1):134A.

Robins TG, Green MA. 1988. Respiratory morbidity in workers exposed to asbestos in the primary manufacture of building materials. Am J Ind Med 14:433-448.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/197

8. REFERENCES

Robinson BWS. 1989. Asbestos and cancer: human natural killer cell activity is suppressed by asbestos fibers but can be restored by recombinant interleukin-2. Am Rev Respir Dis 139:897-901.

Roe FJ, Carter RL, Walters MA, et al. 1967. The pathological effects of subcutaneous injections of asbestos fibres in mice: Migration of fibres to submesothelial tissues and induction of mesotheliomata. Int J Cancer 2:628-638.

*Rogan WJ, Gladen BC, Ragan NB, et al. 1987. U.S. prevalence of occupational pleural thickening: A look at chest x-rays from the first National Health And Nutrition Examination Survey. Am J Epidemiol 126:893-900.

*Rogers AJ, Leigh J, Berry G, et al. 1991. Relationship between lung asbestos fiber type and concentration and relative risk of mesothelioma. Cancer 67:1912-1920.

Roggli VL, Benning TL. 1990. Asbestos bodies in pulmonary Hilar lymph nodes. Modern Pathol 3:513-517.

*Roggli VL, Longo WE. 1991. Mineral fiber content of lung tissue in patients with environmental exposure: household contacts vs. building occupants. Ann NY Acad Sci 511-518.

*Roggli VL, George MH, Brady AR. 1987a. Clearance and dimensional changes of crocidolite asbestos fibers isolated from lungs of rats following short-term exposure. Environ Res 42:94-105.

Roggli VL, Kolbeck J, Sanfilippo F, et al. 1987b. Pathology of human mesothelioma: Etiologic and diagnostic considerations. Pathol Annu 22(Pt 2):91-131.

Roggli VL, Pratt PC, Brody AR. 1986. Asbestos content of lung tissue in asbestos associated diseases: A study of 110 cases. Br J Ind Med 43:18-28.

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(4):605-614.

*Rom WN. 1991. Relationship of inflammatory cell cytokines to disease severity in individuals with occupational inorganic dust exposure. Am J Ind Med 19:15-27

Rom WN. 1992. Accelerated loss of lung function and alveolitis in a longitudinal study of non-smoking individuals with occupational exposure to asbestos. Am J Ind Med 21:835-844.

*Rom WN, Travis WD. 1992. Lymphocyte-macrophage alveolitis in nonsmoking individuals occupationally exposed to asbestos. Chest 101(3):779-786.

*Rom WN, Livingston GK, Casey KR, et al. 1983. Sister chromatid exchange frequency in asbestos workers. J Natl Cancer Inst 70:45-48.

Rom WN, Travis WD, Brody AR. 1991. Cellular and molecular basis of the asbestos-related diseases. Am Rev Respir Dis 143:408-422.

*Roney PL, Holian A. 1989. Possible mechanism of chrysotile asbestos-stimulated superoxide anion production in guinea pig alveolar macrophages. Toxicol App Pharmacol 100:132-144.

Digitized by Google

8. REFERENCES

Rubino GF, Piolatto G, Newhouse ML, et al. 1979. Mortality of chrysotile asbestos workers at the Balangero Mine, Northern Italy. Br J Ind Med 36:187-194.

Rudd RM. 1988. Exposure to asbestos and the risk of gastrointestinal cancer [Letter]. BR J Ind Med 45:573-574.

*Rudd R. 1989. Malignant mesothelioma. J R Soc Med 82:126-129.

Saffiotti U, Stinson SF. 1988. Lung cancer induction by crystalline silica: Relationships to granulomatous reactions and host factors. J Environ Sci Health 6:197-222.

*Sahin AA, Coplu L, Selcuk ZT, et al. 1993. Malignant pleural mesothelioma caused by environmental exposure to asbestos or erionite in rural Turkey: CT findings in 84 patients. AJR Am J Roentgenol 161(3):533-537.

Sahu AP. 1989. Effect on choline and mineral fibres (chrysotile asbestos) on guinea-pigs. New Delhi, India: Scientific Commission for Continuing Studies on Effects of Bhopal Gas Leakage on Life Systems, 185-189.

Sakai K, Hisanaga N, Huang J, et al. 1994. Asbestos and nonasbestos fiber content in lung tissue of Japanese patients with malignant mesothelioma. Cancer 73(7):1825-1835.

*Sampson C, Hansell DM. 1992. The prevalence of enlarged mediastinal lymph nodes in asbestos-exposed individuals a CT study. Clin Radiol 45(5):340-342.

Samudra AV, Harwood CF. 1977. Electron microscope measurement of airborne asbestos concentrations: A provisional methodology manual. Report to U. S. Environmental Protection Agency, Office of Research and Development, Research Triangle Park, NC, by IIT Research Institute, Chicago, IL. EPA 600/2-77-178. NTIS No. PB-285945.

Sanden A, Jarvholm B, Larsson S, et al. 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.

Sanden A, Jarvholm B, Larsson S. 1993. The importance of lung-function, nonmalignant diseases associated with asbestos, and symptoms as predictors of ischemic heart disease in shipyard workers exposed to asbestos. Br J Ind Med 50(9):785-790.

*Saracci R. 1987. The interactions of tobacco-smoking and other agents in cancer etiology. Epidemiol Rev 9:175-193.

Sax NI, Lewis RJ Sr. 1987. Hawley's condensed chemical dictionary. llth ed. New York, NY: Van Nostrand Reinhold Company, 100-101.

Scatarige JC, Stitik FP. 1988. Induction of thoracic malignancy in inorganic dust pneumoconiosis. J Thorac Imaging 3:67-79.

Schimmelpfeng J, Seidel A. 1991. Cytotoxic effects of quartz and chrysotile asbestos: in vitro interspecies comparison with alveolar macrophages. J Toxicol Environ Health 33:131-140.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/199

8. REFERENCES

*Schneider U, Maurer RR. 1977. Asbestos and embryonic development. Teratology 15:273-280.

Schoenberger CI, Hunninghake GW, Kawanami 0, et al. 1982. Role of alveolar macrophages in asbestosis: Modulation of neutrophil migration to the lung after acute asbestos exposure. Thorax 37:803-809.

Scholze H, Conradt R. 1987. An *in vitro* study of the chemical durability of siliceous fibres. Ann Occup Hyg 31:683-692.

*Schwartz DA, Fuortes LJ, Galvin JR, et al. 1990. Asbestos-induced pleural fibrosis and impaired lung function. Am Rev Respir Dis 141:321-326.

Schwartz DA, Galvin JR, Merchant RK, et al. 1992. Influence of cigarette smoking on bronchoalveolar lavage cellularity in asbestos-induced lung disease. Am Rev Respir Dis 145(2):400-405.

*Schwartz DA, Galvin JR, Frees KL, et al. 1993. Clinical relevance of cellular mediators of inflammation in workers exposed to asbestos. Am Rev Respir Dis 148(1):68-74.

*Sebastien P, Begin R, Masse S. 1990. Mass, number and size of lung fibres in the pathogenesis of asbestosis in sheep. J Exp Path 71:1-10.

Sebastien P, Bignon J, Barris YI, et al. 1984. Ferruginous bodies in sputum as an indication of exposure to airborne mineral fibers in the mesothelioma villages of Cappadocia. Arch Environ Health 39:18-23.

*Sebastien P, Janson X, Gaudichet A, et al. 1980a. Asbestos retention in human respiratory tissues: Comparative measurements in lung parenchyma and in parietal pleura. IARC Sci Publ 30:237-246.

*Sebastien P, Masse R, Bignon J. 1980b. Recovery of ingested asbestos fibers from the gastrointestinal lymph in rats. Environ Res 22:201-216.

Sebastien P, McDonald JC, Mcdonald AD, et al. 1989. Respiratory cancer in chrysotile textile and mining industries: exposure inferences from lung analysis. Br J Ind Med 46:180-187.

*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.

Sekhon H, Keeling B, Churg A. 1993. Rat pleural mesotheliomal cells show damage after exposure to external but not internal cigarette smoke. Environ Health Perspect 101(4):326-330.

*Selcuk ZT, Coplu L, Emri S, et al. 1992. Malignant pleural mesothelioma due to environmental mineral fiber exposure in Turkey: Analysis of 135 cases. Chest 102(3):790-796.

Selikoff IJ. 1990. Historical developments and perspectives in inorganic fiber toxicity in man. Environ Health Perspect 88:269-276.

Digitized by Google

8. REFERENCES

*Selikoff IJ, Lee DHK, eds. 1978. Asbestos and disease. New York, NY: Academic Press, 143-187, 357-375, 377-392.

Selikoff IJ, Lilis R. 1991. Radiological abnormalities among sheet-metal workers in the construction industry in the United States and Canada: relationship to asbestos exposure. Arch Environ Health 46:30-36.

*Selikoff IJ, Hammond EC, Churg J. 1968. Asbestos exposure, smoking and neoplasia. JAMA 204:104-110.

*Selikoff IJ, Hammond EC, Seidman H. 1979. Mortality experience of insulation workers in the United States and Canada, 1943-1976. Ann NY Acad Sci 330:91-116.

Selikoff IJ, Lilis R, Levin G. 1990. Asbestotic radiological abnormalities among United States merchant marine seamen. Br J Ind Med 47:292-297.

*Selikoff IJ, Nicholson WJ, Langer AM. 1972. Asbestos air pollution. Arch Environ Health 25:1-13.

*Selikoff IJ, Seidman H, Hammond EC. 1980. Mortality effects of cigarette smoking among amosite asbestos factory workers. J Natl Cancer Inst 65:507-513.

*Serio G, Ceppi M, Fonte A, et al. 1992. Malignant mesothelioma of the testicular tunica vaginalis. Eur Urol 21(2):174-176.

*Seshan K. 1983. How are the physical and chemical properties of chrysotile asbestos altered by a lO-year residence in water and up to 5 days in simulated stomach acid? Environ Health Perspect 53:143-148.

Shabad LM, Pylev LN, Krivosheeva LV, et al. 1974. Experimental studies on asbestos carcinogenicity. J Natl Cancer Inst 52:1175-1180.

*Shatos MA, Doherty JM, Marsh JP, et al. 1987. Prevention of asbestos-induced cell death in rat lung fibroblasts and alveolar macrophages by scavengers of active oxygen species. Environ Res 44:103-116.

Sheehan MJ, Reynolds JW. 1992. Airborne asbestos analysis of low fiber density samples: A comparison of the A and B counting rules of the NIOSH method 7400. Applied Occupational Environmental Hygiene 7(1):38-41.

Shepherd KE, Oliver LC, Kazemi H. 1989. Diffuse malignant pleural mesothelioma in an urban hospital: clinical spectrum and trend in incidence over time. Am J Ind Med 16:373-383.

Sigurdson EE. 1983. Observations of cancer incidence surveillance in Duluth, Minnesota. Environ Health Perspect 53:61-67.

*Sigurdson EE, Levy BS, Mandel J, et al. 1981. Cancer morbidity investigations: Lessons from the Duluth study of possible effects of asbestos in drinking water. Environ Res 25:50-61.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/201

8. REFERENCES

*Sincock AM. 1977. Preliminary studies of the *in vitro* cellular effects of asbestos and fine glass dusts. In: Hiatt HH, Watson JD, Winsten JA, eds. Origins of human cancer. Book B: Mechanisms of carcinogenesis. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 941-954.

*Sincock A, Seabright M. 1975. Induction of chromosome changes in Chinese hamster cells by exposure to asbestos fibres. Nature 257:56-58.

*Sincock AM, Delhanty JD, Casey G. 1982. A comparison of the cytogenetic response to asbestos and glass fibre in Chinese hamster and human cell lines: Demonstration of growth inhibition in primary human fibroblasts. Mutat Res 101:257-268.

Siracusa A, Forcina A, Volpi R, et al. 1988. An 11-year longitudinal study of the occupational dust exposure and lung function of polyvinyl chloride, cement and asbestos cement factory workers. Scand J Work Environ Health 14:181-188.

Sittig M. 1985. Handbook of toxic and hazardous chemicals and carcinogens. 2nd ed. Park Ridge, NJ: Noyes Publications, 92-96.

Skinner HC, Ross M, Frondel C. 1988. Health effects of inorganic fibers. In: Asbestos and other fibrous materials: Mineralogy, crystal chemistry, and health effects. New York, NY: Oxford University Press, 103-162.

*Sluis-Cremer GK. 1991. Asbestos disease at low exposure after long residence time in amphibole miners. Toxicol Ind Health 7:89-95.

Sluis-Cremer GK, Bezuidenhout BN. 1989. Relation between asbestosis and bronchial cancer in amphibole asbestos miners. Br J Ind Med 46:537-540.

*Sluis-Cremer GK, Liddell FDK, Logan WPD, et al. 1992. The mortality of amphibole miners in South Africa 1946-80. Br J Ind Med 49:566-575.

*Sluis-Cremer GK, Thomas RG, Schmaman IB. 1984. The value of computerized axial tomography in the assessment of workers exposed to asbestos. Am J Ind Med 6:27-35.

*Smith AH, Handley MA, Wood R. 1990. Epidemiological evidence indicates asbestos causes laryngeal cancer. J Occup Med 32:499-507.

*Smith AH, Shearn VI, Wood R. 1989. Asbestos and kidney cancer: the evidence supports a causal association. Am J Ind Med 16:159-166.

Smith CM, Batcher S, Catanzaro A, et al. 1987. Sequence of bronchoalveolar lavage and histopathologic findings in rat lungs early in inhalation asbestos exposure. J Toxicol Environ Health 20:147-161.

Smith WE, Miller L, Churg J. 1970. An experimental model for study of cocarcinogenesis in the respiratory tract. In: Nettesheim P, Hanna MG Jr, Deatherage JW Jr, eds. Morphology of experimental respiratory carcinogenesis. Oak Ridge, TN: U.S. Atomic Energy Commission, AEC Symposium Series 21, 299-316.

Digitized by Google

8. REFERENCES

*Spengler JD, Ozkaynak H, McCarthy JF, et al. 1989. Symposium on health aspects of exposure to asbestos in buildings, December 14-16, 1988. Cambridge, MA: Energy and Environmental Policy Center, Harvard University. 1-297.

*Sprince NL, Oliver LC, Mcloud TC, et al. 1991. Asbestos exposure and asbestos-related pleural and parenchymal disease. Am Rev Respir Dis 143:822-828.

*Sprince NL, Oliver LC, Mcloud TC, et al. 1992. T-cell alveolitis in lung lavage of asbestos-exposed subjects. Am J Ind Med 21:311-319.

Spurny KR. 1989. Asbestos fibre release by corroded and weathered asbestos-cement products. IARC Sci Pub 90:367-371.

*Spurny KR. 1994. Sampling, analysis, identification and monitoring of fibrous dusts and aerosols. Analyst (Cambridge, UK) 119(1):41-51.

*SRI. 1982. Chemical economics handbook. Asbestos-salient statistics. Menlo Park, CA: SRI International.

*Stanton MF, Layard M, Tegeris A, et al. 1981. Relation of particle dimension to carcinogenicity in amphibole asbestoses and other fibrous minerals. J Natl Cancer Inst 57:965-975.

*Steenland K, Thun M. 1986. Interaction between tobacco smoking and occupational exposures in the causation on lung cancer. J Occup Med 28:110-118.

*Stephens M, Gibbs AR, Pooley FD, et al. 1987. Asbestos induced diffuse pleural fibrosis: Pathology and mineralogy. Thorax 42:583-588.

Stokinger HE. 1981. The halogens and the nonmetals boron and silicon. In: Clayton GD, Clayton FE, eds. Patty's industrial hygiene and toxicology. 3rd ed. Vol. 2B. Toxicology. New York, NY: John Wiley and Sons, 3021-3023.

*Storeygard AR, Brown AL Jr. 1977. Penetration of the small intestinal mucosa by asbestos fibers. Mayo Clin Proc 52:809-812.

*Tagesson C, Chabiuk D, Axelson O, et al. 1993. Increased urinary excretion of the oxidative DNA adduct, 8-hydroxydeoxyguanosine, as a possible indicator of occupational cancer hazards in the asbestos, rubber, and azo-dye industries. Pol J Occup Med Environ Health 6(4):357-368.

Takagi M. 1991. Histopathological changes in the lung with low-dose asbestos exposure. Acta Med Biol 39(1):11-20.

Talcott JA, Thurber WA, Kantor AF, et al. 1989. Asbestos-associated diseases in a cohort of cigarette-filter workers. N E J Med 321:1220-1223.

Tammilehto L. 1992. Malignant mesothelioma: Prognostic factors in a prospective study of 98 patients. Lung Cancer (The Netherlands) 8(3-4):175-184.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/203

8. REFERENCES

*Tammilehto L, Tuomi T, Tiainen M, et al. 1992. Malignant mesothelioma: Clinical characteristics, asbestos mineralogy and chromosomal abnormalities of 41 patients. Eur J Cancer 28A:1373-1379.

Tarchi M, Orsi D, Comba P, et al. 1994. Cohort mortality study of rock salt workers in Italy. Am J Ind Med 25(2):251-256.

Tarter ME, Cooper RC, Freeman WR. 1983. A graphical analysis of the interrelationships among waterborne asbestos, digestive system cancer and population density. Environ Health Perspect 53:79-89.

*Thomas DC, Whittmore AS. 1988. Methods for testing interactions, with applications to occupational exposures, smoking, and lung cancer. Am J Ind Med 13:131-147.

*Tiainen M, Tammilehto L, Rautonen J, et al. 1989. Chromosomal abnormalities and their correlations with asbestos exposure and survival in patients with mesothelioma. Br J Cancer 60(4):618-626.

Tilkes F, Beck EG. 1989. Cytotoxicity and carcinogenicity of chrysotile fibres from asbestos-cement products. IARC Sci Pub 90:190-196.

*Timbrell V. 1982. Deposition and retention of fibres in the human lung. Ann Occup Hyg 26:347-369.

Tocilj J, Dujic Z, Boschi S, et al. 1990. Correlation between radiological and functional findings in workers exposed to chrysotile asbestos. Med Lav 81:373-381.

*Toft P, Wigle D, Meranger JC, et al. 1981. Asbestos and drinking water in Canada. Sci Total Environ 18:77-89.

*Tomasini M, Chiappino G. 1981. Hemodynamics of pulmonary circulation in asbestosis: Study of 16 cases. Am J Ind Med 2:167-174.

*Topping DC, Nettesheim P. 1980. Two-stage carcinogenesis studies with asbestos in Fischer 344 rats. J Natl Cancer Inst 65:627-630.

*TRI92. 1994. Toxic chemical release inventory. National Library of Medicine, National Toxicology Information Program, Bethesda, MD.

Truhaut R, Chouroulinkov I. 1989. Effect of long-term ingestion of asbestos fibres in rats. IARC Sci Pub 90:127-133.

*Tulchinsky TH, Ginsberg GM, Shihab S, et al. 1992. Mesothelioma mortality among former asbestos-cement workers in Israel, 1953-90. Isr J Med Sci 28(8-9):543-547.

Tuomi T. 1992. Fibrous minerals in the lungs of mesothelioma patients: comparison between data on SEM, TEM and personal interview information. Am J Ind Med 21:155-162.

Tuomi T, Huuskonen MS, Virtamo M, et al. 1991a. Relative risk of mesothelioma associated with different levels of exposure to asbestos. Scad J Work Environ Health 17:404-408.

Digitized by Google

8. REFERENCES

Tuomi T, Huuskonen MS, Tammilehto L, et al. 1992. Occupational exposure to asbestos evaluated from work histories and analysis of lung tissues from patients with mesothelioma. Br J Ind Med 48:48-52.

Tuomi T, Oksa P, Anttila S, et al. 1991b. Fibres and asbestos bodies in bronchoalveolar lavage fluids of asbestos sprayers. Br J Ind Med 49:480-485.

*U.S. Bureau of Mines. 1992. Mineral commodity summaries. Asbestos, 28-29.

*U.S. Bureau of Mines. 1994. Mineral commodity summaries. Asbestos, 26-27.

Vainio H, Husgafvel-Pursiainen K, Antilla S, et al. 1993. Interaction between smoking and asbestos in human lung adenocarcinoma. Environ Health Perspect 101 (Supp 3):189-192.

*Valerio F, De Ferrari M, Ottaggio L, et al. 1980. Cytogenetic effect of Rhodesian chrysotile on human lymphocytes *in vitro*. IARC Sci Publ 30:485-489.

Valic F, Beritic-Stahuljak D, Cigula M. 1990. Ventilatory lung function changes in family members of asbestos workers. Acta Med Iug 44:205-209.

Vallyathan V, Green FH. 1985. The role of analytical techniques in the diagnosis of asbestos-associated disease. CRC Crit Rev Clin Lab Sci 22:1-42.

Van Der Meeren A, Fleury J, Nebut M, et al. 1992. Mesothelioma in rats following intrapleural injection of chrysotile and phosphorylated chrysotile (chrysophosphate). Int J Cancer 50:937-942.

van Gelder T, Hoogsteden HC, Versnel MA, et al. 1989. Malignant peritoneal mesothelioma: a series of 19 cases. Digestion 43:222-227.

Varouchakis G, Velonakis EG, Amfilochiou S, et al. 1991. Asbestos in strange places: Two case reports of mesothelioma among merchant seamen. Am J Ind Med 19(5):673-676.

Versar. 1988. Final report: Asbestos modeling study. Report to U. S. Environmental Protection Agency, Office of Toxic Substances, Washington, DC, by Versar, Inc., Springfield, VA. EPA 560/3-88/091.

*Viallat JR, Boutin C. 1980. Radiographic changes in chrysotile mine and mill ex-workers in Corsica: A survey 14 years after cessation of exposure. Lung 157:155-163.

*Viallat JR, Raybuad F, Passarel M, et al. 1986. Pleural migration of chrysotile fibers after intratracheal injection in rats. Arch Environ Health 41:282-286.

Vineis P, Ciccone G, Magnino A. 1993. Asbestos exposure, physical activity and colon cancer: A case-control study. Tumori 79(5):301-303.

*Volkheimer G. 1974. Passage of particles through the wall of the gastrointestinal tract. Environ Health Perspect 9:215-225.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/205

Voytek P, Anver M, Thorslund T, et al. 1990. Mechanism of asbestos carcinogenicity. J Am Coll Toxicol 9:541-550.

Wagner JC. 1972. Current opinions on the asbestos cancer problem. Ann Occup Hyg 15:61-64.

Wagner JC. 1975. Asbestos carcinogenesis. Br J Cancer 32:258-259.

Wagner JC. 1979. Diseases associated with exposure to asbestos dusts. Practitioner 223:28-33.

Wagner JC. 1983. The risk assessment of asbestos carcinogenicity in the normal population. Animal to human correlations. VDI-Berichte Nr 475:305-308.

Wagner JC. 1984. Mineral fiber carcinogenesis. In: Searle CE, ed. Chemical carcinogens. 2nd ed. Vol 1. Washington, DC: American Chemical Society, 634-641.

Wagner JC, Berry G. 1969. Mesotheliomas in rats following inoculation with asbestos. Br J Cancer 23:567-581.

Wagner JC, Pooley FD. 1986. Mineral fibers and mesothelioma [Editorial]. Thorax 41:161-166.

Wagner JC, Gilson JC, Berry G, et al. 1971. Epidemiology of asbestos cancer. Br Med Bull 27:71-76.

*Wagner JC, Berry G, Timbrell V. 1973. Mesotheliomata in rats after inoculation with asbestos and other materials. Br J Cancer 28:173-185.

*Wagner JC, Berry G, Skidmore JW, et al. 1974. The effects of the inhalation of asbestos in rats. Br J Cancer 29:252-269.

*Wagner JC, Berry G, Skidmore JW, et al. 1980a. The comparative effects of three chrysotiles by injection and inhalation in rats. IARC Sci Publ 30:363-372.

Wagner JC, Hill RJ, Berry G, et al. 1980b. Treatments affecting the rate of asbestos-induced mesotheliomas. Br J Cancer 41:918-922.

*Wagner JC, Pooley FD, Berry G, et al. 1982a. A pathological and mineralogical study of asbestos-related deaths in the United Kingdom in 1977. Ann Occup Hyg 26:423-431.

*Wagner JC, Berry G, Pooley FD. 1982b. Mesotheliomas and asbestos type in asbestos textile workers: A study of lung contents. Br Med J 285:603-606.

*Wagner JC, Moncrieff CB, Coles R, et al. 1986. Correlation between fibre content of the lungs and disease in naval dockyard workers. Br J Ind Med 43:391-395.

Walker C, Bermudez E, Everitt J. 1991a. Growth factor and receptor expression by mesothelial cells: a comparison between rodents and humans. In: Cellular and molecular aspects of fiber carcinogenesis. Cold Spring Harbor Laboratory Press, 149-158.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/206

Walker C, Bermudez E, Stewart W, et al. 1991b. Growth factor and growth factor receptor expression in transformed rat mesothelial cells. In: Brown RC, ed. Mechanisms in fibre carcinogenesis. New York, NY: Plenum Press, 377-383.

*Walker C, Bermudez E, Stewart W, et al. 1992a. Characterization of platelet-derived growth factor and platelet-derived growth factor receptor expression in asbestos-induced rat mesothelioma. Cancer Res 52:301-306.

Walker C, Everitt J, Barrett JC. 1992b. Possible cellular and molecular mechanisms for asbestos carcinogenicity. Am J Ind Med 21:253-273.

Walton WH. 1982. The nature, hazards and assessment of occupational exposure to airborne asbestos dust: A review. Ann Occup Hyg 25:117-247.

*Ward JM, Frank AL, Wenk M, et al. 1980. Ingested asbestos and intestinal carcinogenesis in F344 rats. J Environ Pathol Toxicol 3:301-312.

*Warner M. 1988. Asbestos. Anal Chem 60:395A-396A.

Warnock ML. 1989. Lung asbestos burden in shipyard and construction workers with mesothelioma: comparison with burdens in subjects with asbestosis or lung cancer. Environ Res 50:68-85.

*Warwick MT, Parkes R, Hanson A, et al. 1973. Immunology and asbestos. IARC Sci Publ 8:258-263.

Watanabe Y, Yamaguchi M, Kawakami Y, et al. 1993. Human CD4+ CD45RA+ T lymphocytes can be stimulated by crocidolite, anthophyllite and amosite asbestos *in vitro*. Int J Oncol 2(2):209-212.

Weant GE, McCormick GS. 1984. Nonindustrial sources of potentially toxic substances and their applicability to source apportionment methods. Research Triangle Park, NC: U.S. Environmental Protection Agency (MD 14). EPA-450/4-84-003. NTIS No. PB84-231232.

*Webber JS, Covey JR, King MV. 1989. Asbestos in drinking water supplied through grossly deteriorated a-c pipe. J AWWA (February 1989):80-85.

*Webber JS, Syrotynski S, King MV. 1988. Asbestos-contaminated drinking water: its impact on household air. Environ Res 46:153-167.

*Webster I, Goldstein B, Coetzee FS, et al. 1993. Malignant mesothelioma induced in baboons by inhalation of amosite asbestos. Am J Ind Med 24(6):659-666.

Weidner N. 1991. Malignant mesothelioma of peritoneum. Ultrastruct Pathol 15(4-5):515-520.

*Weill H, Ziskind MM, Waggenspack C, et al. 1975. Lung function consequences of dust exposure in asbestos cement manufacturing plants. Arch Environ Health 30:88-97.

*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.

Digitized by Google

8. REFERENCES

*Weinzweig M, Richards RJ. 1983. Quantitative assessment of chrysotile fibrils in the bloodstream of rats which have ingested the mineral under dietary conditions. Environ Res 31:245-255.

*Weiss W. 1984. Cigarette smoke, asbestos, and small irregular opacities. Amer Rev Respir Dis 130:293-301.

Weiss W. 1990. Asbestos and colorectal cancer. Gastroenterology 99:876-884.

Weiss W. 1993. Asbestos-related pleural plaques and lung cancer. Chest 103(6):1854-1859.

*Weitzman SA, Graceffa P. 1984. Asbestos catalyzes hydroxyl and superoxide radical generation from hydrogen peroxide. Arch Biochem Biophysics 228:373-376.

*Weitzman SA, Chester JF, Graceffa P. 1988. Binding of deferoxamine to asbestos fibers *in vitro* and *in vivo*. Carcinogenesis 9:1643-1645.

*West JB, ed. 1985. Best and Taylor's physiological basis of medical practice. 11th ed. Baltimore, MD: Williams and Wilkins, 386-389.

*Westlake GE, Spjut HJ, Smith MN. 1965. Penetration of colonic mucosa by asbestos particles: An electron microscopic study in rats fed asbestos dust. Lab Invest 14:2029-2033.

White KL Jr, Munson AE. 1986. Suppression of the *in vitro* humoral immune response by chrysotile asbestos. Toxicol Appl Pharmacol 82:493-504.

Whitwell F. 1978. Problems in the pathology of disease caused by asbestos. J R Soc Med 71:919-922.

*Whitwell F, Scott J, Grimshaw M. 1977. Relationship between occupations and asbestos-fibre content of the lungs in patients with pleural mesothelioma, lung cancer, and other diseases. Thorax 32:377-386.

WHO. 1984. Asbestos. In: Guidelines for drinking water quality. Vol. 2. Health criteria and other supporting information. Geneva, Switzerland: World Health Organization, 68-75.

*WHO. 1986. Asbestos and other natural mineral fibers. Environmental health criteria 53. Geneva, Switzerland: World Health Organization, 10-31, 166-167, 178-179.

*Wigle DT. 1977. Cancer mortality in relation to asbestos in municipal water supplies. Arch Environ Health 32:185-190.

*Wignall BK, Fox AJ. 1982. Mortality of female gas mask assemblers. Br J Ind Med 39:34-38.

Windholz M, Budavari S, eds. 1983. The Merck index: An encyclopedia of chemicals, drugs, and biologicals. 10th ed. Rahway, NJ: Merck and Company, Inc., 119.

*Wollmer P, Eriksson L, Jonson B, et al. 1987. Relation between lung function, exercise capacity, and exposure to asbestos cement. Br J Ind Med 44:542-549.

*Wortley P, Vaughan TL, Davis S, et al. 1992. A case-control study of occupational risk factors for laryngeal cancer. Br J Ind Med 49(12):837-844.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/208

8. REFERENCES

Wozniak H, Wiecek E, Tossavainen A, et al. 1986. Comparative studies of fibrogenic properties of wollastonite, chrysotile and crocidolite. Med Pr 37:288-296.

Wright A, Donaldson K, Davis JM. 1983. Cytotoxic effect of asbestos on macrophages in different activation states. Environ Health Perspect 51:147-152.

Wright A, Cowie H, Gormley IP, et al. 1986. The *in vitro* cytotoxicity of asbestos fibers: I. $P288D_1$ cells. Am J Ind Med 9:371-384.

Wright JL, Tron V, Wiggs, B, et al. 1988. Cigarette smoke potentiates asbestos-induced airflow abnormalities. Exp Lung Res 14:537-548.

Wright JL, Wiggs B, Churg A. 1991. Pulmonary hypertension induced by amosite asbestos: a physiological and morphologic study in the guinea pig. Lung 169:31-42.

Wylie AG, Bailey KF. 1992. The mineralogy and size of airborne chrysotile and rock fragments: Ramifications of using the NIOSH 7400 method. Am Ind Hyg Assoc J 53(7):442-447.

Wylie AG, Bailey KF, Kelse JW, et al. 1993. The importance of width in asbestos fiber carcinogenicity and its implications for public policy. Am Ind Hyg Assoc J 54(5):239-252.

Yamaguchi N, Kido M, Hoshuyama T, et al. 1992. A case-control study on occupational lung cancer risks in an industrialized city of Japan. Jpn J Cancer Res 83(2):134-140.

*Yano E. 1988. Mineral fiber-induced malondialdehyde formation and effects of oxidant scavengers in phagocytic cells. Int Arch Occup Environ Health 61:19-23.

*Yegles M, Saint-Etienne L, Renier A, et al. 1993. Induction of metaphase and anaphase/telophase abnormalities by asbestos fibers in rat pleural mesothelial cells *in vitro*. Am J Respir Cell Mol Biol 9(2):186-91.

Zelen M. 1985. Products liability issues in school asbestos litigation. Am J Law Med 10:467-489.

*Zerva LV, Constantopoulos SH, Moutsopoulos HM. 1989. Humoral immunity alterations after environmental asbestos exposure. Respiration 55:237-241.

Zheng W, Blot WJ, Shu X-O, et al. 1992. Diet and other risk factors for laryngeal cancer in Shanghai China. Am J Epidemiol 136(2):178-191.

Zhu HL, Wang ZM. 1993. Study of occupational lung-cancer in asbestos factories in China. Br J Ind Med 50(11):1039-1042.

Digitized by Google

9. GLOSSARY

Actinolite — A type of asbestos in the amphibole group; it is not used commercially, but is a common impurity in chrysotile asbestos.

Acute Exposure — Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption Coefficient (K_{oc}) — The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd) — The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Amosite — A type of asbestos in the amphibole group; it is also known as brown asbestos.

Amphibole — The group name for a family of naturally occurring minerals, characterized by a double chain of silicate ions. This group includes amosite, actinolite, crocidolite, and tremolite forms of asbestos.

Bioconcentration Factor (BCF) — The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Cancer Effect Level (CEL) — The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen — A chemical capable of inducing cancer.

Ceiling Value — A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure — Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Chrysotile — The most common form of asbestos used commercially, also referred to as white asbestos.

Crocidolite — A type of asbestos in the amphibole group; it is also known as blue asbestos.

Developmental Toxicity — The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/210

Embryotoxicity and Fetotoxicity — Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

EPA Health Advisory — An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH) — The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

Intermediate Exposure — Exposure to a chemical for a duration of 15-364 days, as specified in the Toxicological Profiles.

Immunologic Toxicity — The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In Vitro — Isolated from the living organism and artificially maintained, as in a test tube.

In Vivo — Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO}) — The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50}) — A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{LO}) — The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50}) — The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50}) — A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL) — The lowest dose of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Malformations — Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level — An estimate of daily human exposure to a dose of a chemical that is likely to be without an appreciable risk of adverse noncancerous effects over a specified duration of exposure.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/211

Mutagen — A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity — The occurrence of adverse effects on the nervous system following exposure to chemical.

No-Observed-Adverse-Effect Level (NOAEL) — The dose of chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow}) — The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Permissible Exposure Limit (PEL) — An allowable exposure level in workplace air averaged over an 8-hour shift.

q_1* — The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and $\mu g/m^3$ for air).

Recommended Exposure Limit (REL) — An occupational exposure limit recommended by NIOSH as being protective of worker health and safety over a working lifetime. This limit is commonly expressed as a time-weighted average (TWA) exposure for up to 10 hours/day during a 40-hour workweek. The REL may also be expressed as (1) a short-term exposure limit (STEL) that should never be exceeded and is to be determined in a specified sampling time (usually 15 minutes) or (2) a ceiling limit that should never be exceeded, even instantaneously, unless specified over a given time period.

Reference Dose (RfD) — An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ) — The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity — The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/212

Short-Term Exposure Limit (STEL) — The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

Target Organ Toxicity — This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen — A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV) — A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-Weighted Average (TWA) — An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose (TD_{50}) — A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Tremolite — A type of asbestos in the amphibole group; it is not used commercially in the United States, but is a common impurity in chrysotile asbestos.

Uncertainty Factor (UF) — A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/213

APPENDIX A

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in nontechnical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or substance release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the substance.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-1 and 2-2) are used to summarize health effects by duration of exposure and end point and to illustrate graphically levels of exposure associated with those effects. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs) for Less Serious and Serious health effects, or Cancer Effect Levels (CELs). In addition, these tables and figures illustrate differences in response by species, Minimal Risk Levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text.

The legends presented below demonstrate the application of these tables and figures. A representative example of LSE Table 2-1 and Figure 2-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-1

(1). Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-1) and oral (LSE Figure 2-2) routes.

(2). Exposure Duration Three exposure periods: acute (14 days or less); intermediate (15 to 364 days); and chronic (365 days or more) are presented within each route of exposure. In this example, an inhalation study of intermediate duration exposure is reported.

Digitized by Google

(3). Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table.

(4). Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to define a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in Figure 2-1).

(5). Species The test species, whether animal or human, are identified in this column.

(6). Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to [substance x] via inhalation for 13 weeks, 5 days per week, for 6 hours per day.

(7). System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated in this study.

(8). NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9). LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest exposure level used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The "Less Serious" respiratory effect reported in key number 18 (hyperplasia) occurred at a LOAEL of 10 ppm.

(10). Reference The complete reference citation is given in Chapter 8 of the profile.

(11). CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiological studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses which did not cause a measurable increase in cancer.

(12). Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See LSE Figure 2-1

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure levels for particular exposure duration.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/215

TABLE 2-1. Levels of Significant Exposure to [Chemical x] - Inhalation

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
INTERMEDIATE EXPOSURE							
Systemic							
18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
Cancer							
38	Rat	18 mo 5d/wk 7hr/d				20 (CEL, multiple organs)	Wong et al. 1982
39	Rat	89-104 wk 5d/wk 6hr/d				10 (CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79-103 wk 5d/wk 6hr/d				10 (CEL, lung tumors, hemangiosarcomas)	NTP 1982

[a] The number corresponds to entries in Figure 2-1.

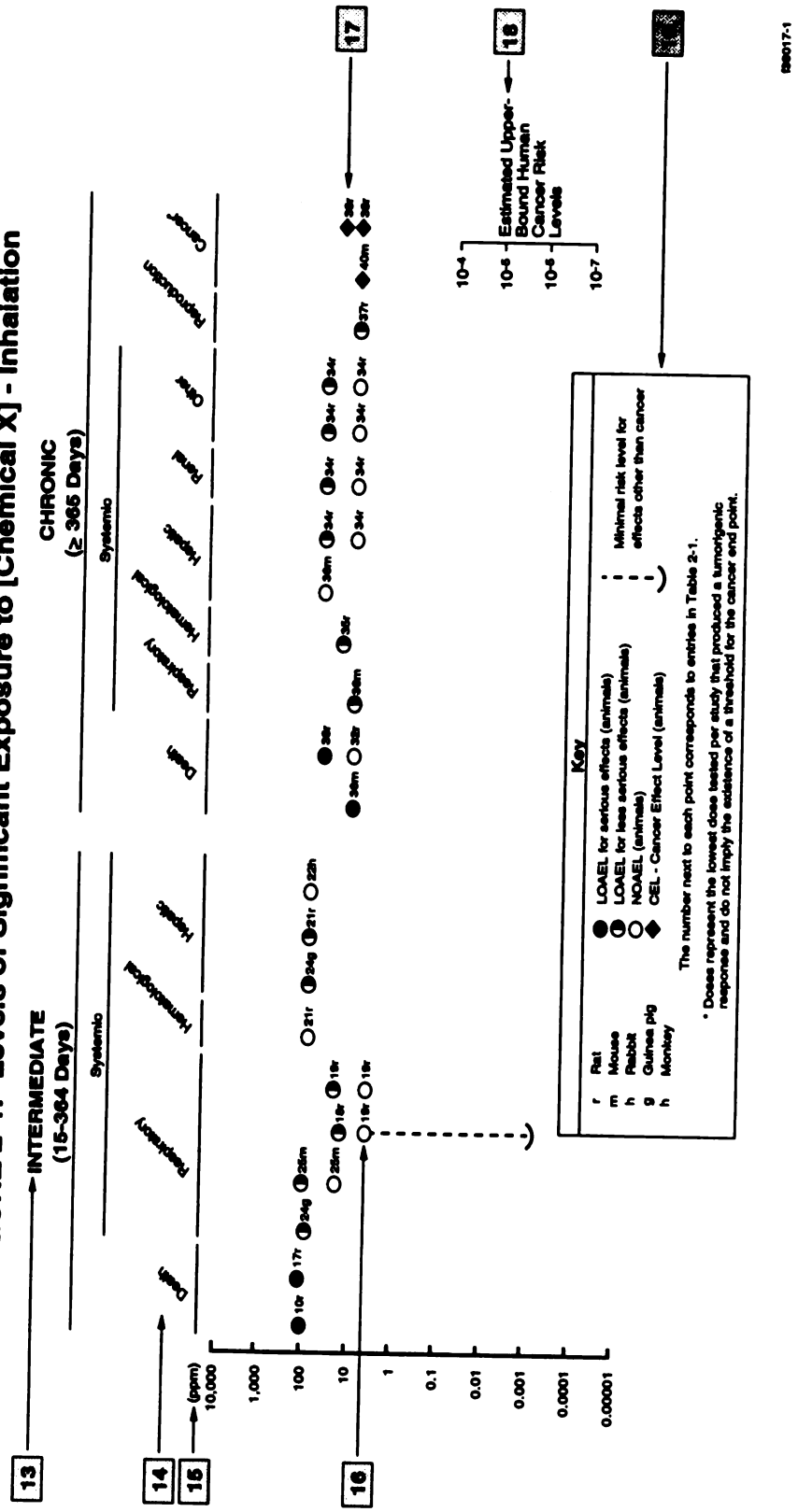
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5 x 10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

CEL = cancer effect level; d = day(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

Digitized by Google
Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/216

SAMPLE

FIGURE 2-1. Levels of Significant Exposure to [Chemical X] - Inhalation



Digitized by Google

(13). Exposure Duration The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14). Health Effect These are the categories of health effects for which reliable quantitative data exist. The same health effects appear in the LSE table.

(15). Levels of Exposure Exposure levels for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure levels are reported on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16). NOAEL In this example, 18r NOAEL is the critical end point for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates a NOAEL for the test species (rat). The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17). CEL Key number 38r is one of three studies for which Cancer Effect Levels (CELs) were derived. The diamond symbol refers to a CEL for the test species (rat). The number 38 corresponds to the entry in the LSE table.

(18). Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1^*).

(19). Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

Chapter 2 (Section 2.4)

Relevance to Public Health

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicological, epidemiological, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section discusses health effects by end point. Human data are presented first, then animal data. Both are organized by route of exposure (inhalation, oral, and dermal) and by duration (acute, intermediate, and chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/218

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. MRLs for noncancer end points if derived, and the end points from which they were derived are indicated and discussed in the appropriate section(s).

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Identification of Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information was available, MRLs were derived. MRLs are specific for route (inhalation or oral) and duration (acute, intermediate, or chronic) of exposure. Ideally, MRLs can be derived from all six exposure scenarios (e.g., Inhalation - acute, -intermediate, -chronic; Oral - acute, -intermediate, - chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a substance emission, given the concentration of a contaminant in air or the estimated daily dose received via food or water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicological information on which the number is based. Section 2.4, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.6, "Interactions with Other Chemicals" and 2.7, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology used by the Environmental Protection Agency (EPA) (Barnes and Dourson 1988; EPA 1989a) to derive reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential effects (e.g., systemic, neurological, and developmental). In order to compare NOAELs and LOAELs for specific end points, all inhalation exposure levels are adjusted for 24hr exposures and all intermittent exposures for inhalation and oral routes of intermediate and chronic duration are adjusted for continuous exposure (i.e., 7 days/week). If the information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. The NOAEL is the most suitable end point for deriving an MRL. When a NOAEL is not available, a Less Serious LOAEL can be used to derive an MRL, and an uncertainty factor of (1, 3, or 10) is employed. MRLs are not derived from Serious LOAELs. Additional uncertainty factors of (1, 3, or 10) are used for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and (1, 3, or 10) are used for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. Generally an uncertainty factor of 10 is used; however, the MRL workgroup reserves the right to use uncertainty factors of (1, 3, or 10) based on scientific judgement. The product is then divided into the adjusted inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

Digitized by Google

APPENDIX B

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
C	Centigrade
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
d	day
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
F	Fahrenheit
F_1	first filial generation
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
fpm	feet per minute
ft	foot
FR	Federal Register
g	gram
GC	gas chromatography
gen	generation
HPLC	high-performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill

Digitized by Google

APPENDIX B

LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
ng	nanogram
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio
STEL	short term exposure limit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
yr	year
WHO	World Health Organization
wk	week
>	greater than

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/221

APPENDIX B

≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micron
μg	microgram

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/222

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/223

APPENDIX C

RISK ASSESSMENT SUMMARY

1.0 LUNG CANCER

Most studies of the risk of asbestos-related lung cancer in occupationally exposed workers indicate that the dose-response relationship is best described by a relative risk model, given by the equation:

$$\text{Relative Risk} = 1.00 + K_L \cdot (\text{cumulative dose}).$$

Using this equation, EPA (1986a) calculated the value of K_L (the fractional increase in relative risk of lung cancer per f-yr/mL) for a number of epidemiological studies in which quantitative exposure-risk data were available. The resulting values varied widely, ranging from 0.0006 $(\text{f-yr/mL})^{-1}$ (McDonald et al. 1980) to 0.067 $(\text{f-yr/mL})^{-1}$ (Finkelstein 1983). The geometric mean of all the studies was 0.065 $(\text{f-yr/mL})^{-1}$. When studies involving mining and milling were excluded (these were judged to be less typical of the risks likely to be encountered in the environment), the resulting value was 0.010 $(\text{f-yr/mL})^{-1}$. It is important to stress that this relates to fibers measured by phase contrast microscopy, and not to the total number of fibers measured by transmission electron microscopy.

Since this is a relative risk model, the absolute risk of lung cancer due to asbestos exposure depends not only on cumulative asbestos dose, but also on the underlying risk of lung cancer due to other causes:

$$\text{Absolute Risk} = \text{Relative Risk} \times \text{Underlying Risk}$$

Based on national average lung cancer risk data for male and female smokers and nonsmokers, EPA (1986a) calculated that lifetime exposure to 0.0001 f/mL corresponded to the excess lung cancer risks tabulated in Table C-1.

For the purposes of preparing a simplified graphical display of cancer risk levels for presentation in Figure 2-1, risks from males and females were averaged, both for smokers and nonsmokers, and the cumulative doses corresponding to a lifetime lung cancer risk of 1×10^{-4} were calculated as shown in Table D-1.

2.0 MESOTHELIOMA

Several studies (e.g., Newhouse and Berry 1976; Nicholson et al. 1982; Peto et al. 1982) indicate that the risk of mesothelioma from a given level of exposure to asbestos depends primarily upon the time elapsed since exposure (latency), with risk increasing exponentially with time after a lag period of about 10 years. Based on this, EPA (1986a) fit exposure-incidence data from four studies (Finkelstein 1983; Peto 1980; Peto et al. 1982; Seidman 1984) to the following equation:

$$\text{Incidence} = K_M \cdot f \cdot [(T-10)^3 - (T-10-d)^3]$$

where:

K_M = empirical constant
f = intensity of exposure (f/mL)
T = latency (years since first exposure)
d = duration of exposure (years)

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/224

APPENDIX C

TABLE C-1 Risk Assessment for Asbestos-Associated Lung Cancer

Parameter	Smokers			Nonsmokers		
	Male[a]	Female[a]	Average[b]	Male[a]	Female[a]	Average[b]
Lung cancer risk from lifetime exposure to 0.0001 f/mL	2.4E-5	1.5E-5	2.0E-5	0.2E-5	0.2E-5	0.2E-5
Concentration (f/mL) corresponding to lifetime excess risk level of 10^{-4}			5.0E-4			5.0E-3
Cumulative dose (f·yr/mL) for a 70-yr exposure corresponding to 10^{-4} risk level			3.5E-2			3.5E-1

[a]Source: EPA(1986a)
[b]Average of males and females

Digitized by Google

The resulting values of K_M ranged from 1 x 10^{-8} to 3 x 10^{-8} for three of the studies, with one study (Finkelstein 1983) giving a higher value (12 x 10^{-8}). Based on an analysis of the relative risk of mesothelioma compared to lung cancer in other studies, a value of 1 x 10^{-8} was identified as the most reasonable estimate for K_M (EPA 1986a). Although this value has considerable uncertainty (about a factor of 10), it can be used to make rough predictions of mesothelioma incidence at low exposure levels, similar to those likely to be encountered in the environment. Assuming lifetime continuous exposure to air containing 0.0001 f/mL, the expected incidence is 2 to 3 mesothelioma deaths per 100,000 persons (EPA 1986a), as shown in Table C-2.

For the purposes of preparing a simple graphical presentation of these risk estimates for inclusion in Figure 2-1, the data from all four groups were combined (since there is little difference between males and females or between smokers and nonsmokers), to yield an average 10^{-4} risk level of 3.1 x 10^{-2} f-yr/mL.

3.0 COMBINED RISK OF LUNG CANCER AND MESOTHELIOMA

The combined risk of lung cancer and mesothelioma has been estimated by EPA (IRIS 1994), based on the risk calculations presented in EPA (1986a). The average unit risk value was calculated as a composite value for males and females. The epidemiological data show that cigarette smoking and asbestos exposure interact synergistically for production of lung cancer and do not interact with regard to mesothelioma. The unit risk value is based on risks calculated using United States general population cancer rates and mortality patterns without consideration of smoking habits. The risks associated with occupational exposure were adjusted to continuous exposure by applying a factor of 140/50, based on the assumption of 20 m^3/day (140 m^3/week) for total ventilation and 10 m^3/8-hour workday (40 m^3/week) in the occupational setting. The results of these calculations indicate that a concentration of 4E-4 f/mL corresponds to a lifetime excess risk level of 10^{-4}. This combined risk estimate was not presented in Figure 2-1, since both the text and the Figure deal with lung cancer and mesothelioma separately.

The Health Effect Institute estimates lifetime cancer risks from lung cancer and mesothelioma combined based on levels of asbestos detected in 198 ACM-containing buildings (HEI 1991). These estimates, presented in Table C-3, should be interpreted with caution because of uncertainty associated with the estimation of average exposure levels and with the risk assessment model. The "high" levels represented in the table are approximately equal to the upper 95th percentile of the exposure levels detected. It should be noted that if the single highest public building sample were excluded from the calculation of the average exposure level, the average value would be reduced from 0.0002 to 0.00008 TEM f/mL and risk would be similarly reduced by one half. The occupational exposure level of 0.1 f/mL is equivalent to the PEL proposed by OSHA. Actual worker exposures are expected to be lower.

4.0 GASTROINTESTINAL CANCER

4.1 Risk Estimate Based on Animal Data

In a lifetime feeding study in rats, exposure to intermediate length chrysotile fibers lead to an increased incidence of intestinal polyps (NTP 1985). Based on these data, EPA (1985b) calculated that the 10^{-4} risk level corresponded to an asbestos concentration of 7.1x10^8 f/L in drinking water.

In order to present this risk estimate in Figure 2-4, the concentration of 7.1 x 10^8 f/L was converted to a dose of 2.0x10^7 f/kg/day (assuming ingestion of 2 L/day by a 70-kg adult), and this was converted to a dose of 0.16 mg/kg/day by dividing by 0.129x10^9 f/mg (reported in NTP 1985).

Digitized by Google

APPENDIX C

TABLE C-2 Risk Assessment for Asbestos-Related Mesothelioma

	Smokers[a]		Nonsmokers[a]		
	Male	Female	Male	Female	Average[b]
Lung cancer risk from lifetime exposure to 0.0001 f/mL	1.8E-5	2.5E-5	2.2E-5	2.7E-5	2.2E-5
Concentration (f/mL) corresponding to lifetime excess risk level of 10^{-4}					4.5E-4
Cumulative dose (f·yr/mL) for a 70-yr exposure corresponding to 10^{-4} risk level					3.1E-2

[a]Source: EPA (1986a)
[b]Average of all four groups.

Digitized by Google

APPENDIX C

TABLE C-3 Estimated Lifetime Risks of Lung Cancer and Mesothelium Combined for Different Scenarios of Exposure to Airborne Asbestos Fibers

Conditions	Premature Cancer Deaths (Lifetime Risks) per Million Exposed Persons (Male and Female)
Lifetime, continuous outdoor exposure	
· 0.00001 TEM f/mL (2E-7 PCM f/mL) from birth (rural)	4
· 0.0001 TEM f/mL (2E-6 PCM f/mL) from birth (high urban)	40
Exposure in a school containing ACM, from age 5 to 18 years (180 days/year, 5 hours/day)	
· 0.0005 TEM f/mL (8E-6 PCM f/mL) (average)	6
· 0.005 TEM f/mL (8E-5 PCM f/mL) (high)	60
Exposure in a public building containing ACM age 25 to 45 years (240 days/year, 8 hours/day)	
· 0.0002 TEM f/mL (3E-6 PCM f/mL) (average)	4
· 0.002 TEM f/mL (3E-5 PCM f/mL) (high)	40
Occupational exposure from age 25 to 45	
· 0.1 PCM f/mL (current occupational levels)	2,000
· 10 PCM f/mL (historical industrial exposures)	200,000

Source: HEI (1991)

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/228

4.2 Risk Estimate Based on Human Inhalation Data

Since there are no human studies in which ingestion of a known amount of asbestos can be associated with a clear increase in gastrointestinal cancer risk, NAS (1983) extrapolated data on gastrointestinal risk from epidemiological studies of workers exposed to asbestos by inhalation. These calculations indicated that lifetime ingestion of 1.1×10^6 TEM fibers/liter of water corresponded to an excess gastrointestinal cancer risk of 10^{-4} (NAS 1983).

In order to present this risk estimate in Figure 2-4, the concentration of 1.1×10^6 f/L was converted to a dose of 3.1×10^4 f/kg/day (assuming ingestion of 2 L/day by a 70-kg adult), and this was converted to a dose of 1.6×10^{-5} mg/kg/day by multiplying by a factor of 5.0×10^{-10} mg/TEM fiber (NRC 1984).

* U.S. GOVERNMENT PRINTING OFFICE:1995-639-298

Digitized by Google

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/230

Digitized by Google

Digitized by Google

Published by AsbestosClaims.Law
asbestosclaims.law/library/10942/232

UNIVERSITY OF ILLINOIS-URBANA
615.92539224T667 C001
TOXICOLOGICAL PROFILE FOR ASBESTOS$ WASH
1995
3 0112 005954968

Digitized by Google