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Seventh Annual Report on

Carcinogens

Summary 1994

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HEALTH AND HUMAN SERVICES
Public Health Service

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effectiveness of the these measures. CPSC determined that arsenic, arsenic trioxide, and arsenic compounds were not present in consumer products under CPSC jurisdiction. Subsequently, CPSC requested public comment to verify the accuracy of this information. EPA regulates arsenic and certain arsenic compounds under the Clean Air Act (CAA), Clean Water Act (CWA), Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), Food, Drug, and Cosmetic Act (FD&CA), Resource Conservation and Recovery Act (RCRA), Safe Drinking Water Act (SDWA), and Superfund Amendments and Reauthorization Act (SARA). Arsenic emissions from smelters and other facilities are regulated under CAA. CWA has established effluent guidelines controlling the environmental release of arsenic compounds for certain industrial categories. Reportable quantities (RQs) have been established under CERCLA and CWA for arsenic and certain arsenic compounds. EPA has issued a Rebuttable Presumption Against Registration (RPAR) for eleven inorganic arsenic pesticide products under FIFRA. Tolerances for residues of arsenical pesticides have been established under FD&CA. Under RCRA, EPA regulates arsenic as a hazardous constituent of waste. SDWA limits arsenic in drinking water to a maximum level of 0.05 mg/l. SARA has established threshold planning quantities for some arsenic compounds and subjects arsenic and arsenic compounds to reporting requirements. FDA enforces tolerances set by EPA under FD&CA for residues of pesticides containing arsenic in fruits and vegetables, field crops, and livestock. FDA has also set tolerance limits for the residue of arsenic compounds when used as veterinary drugs. OSHA has promulgated a final standard of 10 $\mu g/m^3$ for occupational exposure to inorganic arsenic compounds. Additionally, this standard requires personal protective equipment, training, medical surveillance, signs and labeling, and engineering controls. A permissible exposure limit (PEL) of 0.5 mg/m^3 for organic arsenic as an 8-hr TWA also has been adopted by OSHA. NIOSH recommended lowering of the OSHA standard to a 2 $\mu g/m^3$ ceiling sampled over 15 minutes, based on evidence of carcinogenicity in humans. OSHA regulates arsenic and certain arsenic compounds under the Hazard Communication Standard and as chemical hazards in laboratories.

ASBESTOS
CAS No. 1332-21-4

CARCINOGENICITY

There is sufficient evidence for the carcinogenicity of asbestos and the following forms of commercial asbestos in experimental animals: chrysotile (12001-29-5), amosite (12172-73-5), anthophyllite (17068-78-9), and crocidolite (12001-28-4) (IARC V.2, 1973; IARC V.14, 1977; IARC S.1, 1979; IARC S.4, 1982; IARC S.7, 1987). When administered by inhalation, chrysotile, crocidolite, amosite, and anthophyllite induced mesotheliomas and lung carcinomas in rats and mesotheliomas after intrapleural administration. Chrysotile, crocidolite, amosite, and anthophyllite induced mesotheliomas in hamsters after intrapleural administration.

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fruits and vegetables, field livestock. FDA has also set limits for the residue of mpounds when used as drugs. OSHA has ed a final standard of 10 occupational exposure to arsenic compounds. , this standard requires protective equipment, edical surveillance, signs g, and engineering controls. ble exposure limit (PEL) of for organic arsenic as an 8- so has been adopted by NIOSH recommended the OSHA standard to a 2 ling sampled over 15 based on evidence of icity in humans. OSHA arsenic and certain arsenic s under the Hazard a' Standard and as s in laboratories.

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Intraperitoneal administration of chrysotile, crocidolite, and amosite induced peritoneal tumors, including mesotheliomas, in mice and rats. Given by the same route, crocidolite induced abdominal tumors in hamsters, and actinolite induced abdominal tumors in rats. When filter material containing chrysotile was added to the diet, a statistically significant increase in the incidence of malignant tumors was observed in rats. Tumor incidence was not increased by oral administration of amosite in rats, of amosite in hamsters, or of chrysotile in hamsters. There was no evidence of carcinogenicity for pelleted short-range (SR) chrysotile (for rats of both sexes) or for pelleted intermediate-range (IR) fiber length chrysotile for female rats when added to the diet for the lifespan. In the same study, there was a low incidence of benign adenomatous polyps of the large intestine in male rats administered IR chrysotile (NTP 295, 1985). Cocarcinogenesis studies of 1,2-dimethylhydrazine dihydrochloride (DMH) and IR chrysotile were inconclusive for determining whether IR chrysotile had a tumor-enhancing effect, although an increased incidence of neoplasms was observed in the kidneys of female rats exposed to DMH plus IR chrysotile as compared with those exposed to DMH alone (NTP 295, 1985).

An IARC Working Group reported that there is sufficient evidence for the carcinogenicity of asbestos and all commercial forms of asbestos in humans (IARC S.4, 1982). Occupational exposure to chrysotile, amosite, anthophyllite, and mixtures containing crocidolite has resulted in a high incidence of lung carcinomas. Mesotheliomas have been observed after occupational exposure to crocidolite, amosite, and chrysotile asbestos. Gastrointestinal cancers occurred at an increased incidence in groups occupationally exposed to crocidolite, amosite, chrysotile or mixed fibers containing crocidolite, although not all studies are consistent in this respect. An excess of laryngeal cancer has also been observed in some groups of exposed workers. No clear excess of cancer has been associated with the presence of asbestos fibers in drinking water. Mesotheliomas have occurred in individuals living in the neighborhood of asbestos factories and mines and in people living with asbestos workers (IARC S.7, 1987). Both cigarette smoking and occupational exposure to asbestos fibers increase lung cancer incidence independently. When present together, they act multiplicatively (IARC V.2, 1973; IARC V.14, 1977; IARC S.1, 1979; IARC S.4, 1982). A study based upon findings from two asbestos cement manufacturing plants has shown evidence of a greater risk of mesothelioma from exposure to crocidolite than to chrysotile asbestos (Hughes et al., 1987).

PROPERTIES
Asbestos is the generic name given to a class of natural fibrous silicates that vary considerably in their physical and chemical properties. Chrysotile has an idealized chemical composition of $Mg_3(Si_2O_5)(OH)_4$. The composition of chrysotile is typically as follows: SiO_2, 37%-44%; MgO, 39%-44%; FeO, 0%-6.0%; Fe_2O_3, 0.1%-5.0%; Al_2O_3, 0.2%-1.5%; CaO, trace to 5.0%; H_2O, 12.0%-15.0%. Common minerals found in commercial grades include magnetite, chromite, brucite, calcite, dolomite, and awaruite. Chrysotile's

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crystal structure is fibrous and asbestiform. It is white, gray, green, or yellowish, with a silky luster. It is soluble in acid. Amosite has a typical chemical composition of: SiO_2, 49%-53%; MgO, 1%-7%; FeO, 34%-44%; K_2O, 0%-0.4%; Na_2O, trace; and H_2O, 2.5%-4.5%. Amosite has a prismatic, lamellar to fibrous crystal structure. It is ash gray, greenish, or brown with a vitreous, somewhat pearly luster. It is fairly resistant to acids. Anthophyllite's typical chemical composition is as follows: SiO_2, 56%-58%; MgO, 28%-34%; FeO, 3%-12%; Al_2O_3, 0.5%-1.5%; and H_2O, 1%-6%. It has a prismatic, lamellar to fibrous crystal structure. Anthophyllite is gray-white, brown, gray, or green in color, with a vitreous to pearly luster. It is fairly resistant to acids. Crocidolite has the following chemical composition: SiO_2, 49%-53%; MgO, 0%-3%, FeO, 13%-20%; Fe_2O_3, 17%-20%; Al_2O_3, 0%-0.2%; CaO, 0.3%-2.7%; K_2O, 0%-0.4%; Na_2O, 4%-8.5%; and H_2O, 2.5%-4.5%. Crocidolite has a fibrous crystal structure. It is lavender or blue, with a silky dull luster. Crocidolite is fairly resistant to acids.

USE

Domestically used asbestos fibers are technically classified into seven quality categories or grades. Grades 1, 2, and 3 include the longer, maximum-strength fibers and are generally used in the production of textiles, electrical insulation, and pharmaceutical and beverage filters. Grades 4, 5, and 6 are medium-length fibers used in the production of asbestos-cement (A/C) pipe, A/C sheet, clutch facings, brake linings, asbestos paper, packaging, gaskets, and pipe coverings. Grade 7 includes short fibers generally used as a reinforcer in plastics, floor tiles, coatings and compounds, some papers, and roofing felts (OSHA, 1986).

The four commercially important forms of asbestos are chrysotile, amosite, anthophyllite, and crocidolite. Asbestos was consumed in roofing products, 34%, friction products, 23% asbestos-cement 15% and gaskets 8%; and other 20% (USDOI,, 1991). Chrysotile is the most abundant form of asbestos; as such, it is the most commercially important form (IARC V.2, 1973). Chrysotile, amosite, and particularly crocidolite all have extremely high-tensile strengths and are used extensively as reinforcers in cements, resins, and plastics. Chrysotile fibers are soft and flexible, whereas crocidolite and amosite fibers are hard and brittle. Although chrysotile is most adaptable to industrial use, crocidolite and amosite are particularly useful in combination with chrysotile for adding specific properties, such as rigidity (OSHA, 1986). Due to its flexibility and softness, chrysotile can be more readily spun into textiles than the amphiboles (amosite, anthophyllite, and crocidolite) (Kirk-Othmer V.3, 1978). Asbestos has been used in more than 5,000 products, including roofing, thermal and electrical insulation, cement pipe and sheet, flooring, gaskets, friction materials, coatings, plastics, textiles, and paper products. Major research is currently under way to develop and determine suitable substitutes for asbestos.

PRODUCTION

Two firms in California and Vermont produced (in terms of sales) over 44 million lb of asbestos domestically in 1990 (USDOI, 1991). U.S. production increased 18% from that of 1989. Demand for asbestos continued to

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decline as the first phase of the Environmental Protection Agency's (EPA) phaseout of asbestos went into effect. Imports decreased 18%, and exports increased slightly over those of 1989. Apparent consumption decreased 18% from that of 1989. In 1989 two firms produced (in terms of sales) 37.4 million lb of asbestos in the United States (USDOI, 1990). U.S. production in 1988 was 39.6 million lb, and three firms produced (in terms of sales) 114.6 million lbs in 1987 (USDOI, 1990; USDOI, 1988). In 1986 U.S. production was 112.4 million lb and 125.6 million lb in 1985 (USDOI, 1988). About 125.6 million lb of asbestos was produced in 1984 and 154.3 million lb were produced in 1983 (USDOI, 1988). Production of asbestos was reported to be 141.1 million lb in 1982 and 167.5 million lb in 1981 (USDOI, 1985). Domestic production of asbestos was 176.3 million lb in 1980 (USDOI, 1985), the 1979 TSCA Inventory identified one producer of asbestos, with no volume reported, and eight companies that imported 22.6 million lb in 1977 (TSCA, 1979). The CBI Aggregate was between 100 million and 1 billion lb.

U.S. imports of asbestos have declined since 1980. The volumes (in terms of millions of lb) are as follows: 121 (1989), 187 (1988), 216 (1987), 238 (1986), 313 (1985), 462.9 (1984), 432 (1983), 533.4 (1982), 745 (1981), and 721 (1980). (USDOI 1990, 1988, 1987, 1985). U.S. exports of asbestos did not vary as greatly as did U.S. imports (millions of lb): 50 (1989), 70.4 (1988), 127.8 (1987), 103 (1986), 101.4 (1985), 88.2 (1984), 121.4 (1983), 130 (1982), 141.1 (1981), 108 (1980) (USDOI, 1990, 1988, 1987, 1985). The asbestos industry per se had its inception in the 18th century; and by the mid-19th century, both chrysotile and tremolite were mined and processed into commercial products (Kirk-Othmer V.3, 1978).

EXPOSURE

The primary routes of potential human exposure to asbestos are dermal contact, inhalation, and ingestion. Asbestos is used so widely that the entire population is potentially exposed to some degree. The number of workers exposed to asbestos since 1950 has greatly increased, but the intensity of occupational exposure has decreased (McDonald, 1985). Gross pollution in the areas of mines, factories, and shipyards is far less than 30-50 years ago, but general levels of exposure to the fibers in air, water, and food has increased from building construction and demolition and the deterioration and wearing of asbestos-containing materials. Worker exposure is a concern in the mining and milling of asbestos, during the manufacture of all asbestos products, and in the construction and shipbuilding industries. OSHA reported that about 2.5 million workers are estimated to have some potential exposure to asbestos. In addition, worker exposure occurs in asbestos end-product use occupations, e.g., asbestos insulation workers, brake repair and maintenance workers, building demolition workers, asbestos abatement workers, etc. The National Occupational Exposure Survey (NOES) (1981-1983) estimated that 153,937 total workers, including 7,603 women, were potentially exposed to asbestos (NIOSH, 1984). The total estimate was based on actual observations of asbestos (41%) and its use in tradename products (59%). The NOES estimated that 30,594 total

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workers, including 3,410 women, potentially were exposed to chrysotile. The total estimate was based on observations of actual use of chysotile (12%) and its use in tradename products (88%). Asbestos concentrations in industrial air vary from 10 to 100,000 ng/m^3, depending upon the type of occupational exposure (IARC V.14, 1976). The ACGIH has established threshold limit values as 8-hr time-weighted averages (TWAs) of 0.5 fiber/cm^3 for amosite, 2 fibers/cm^3 for chrysotile, 0.2 fiber/cm^3 for crodidolite, and 2 fibers/cm^3 for other forms of asbestos (ACGIH, 1986).

The general population is potentially exposed to asbestos fibers present in air, drinking water, beverages, and foods that come in contact with materials such as adhesives, repeatedly used polyester resins, pharmaceutical and dental preparations, and other asbestos-containing products (ATSDR, 1990a). Average concentrations of asbestos in drinking water ranged from 0.3 to 1.5 μg/l as measured in eastern U.S. river water (IARC V.14, 1976). Dermal absorption is minimal, but contact may lead to secondary ingestion. Exposure to asbestos in dental filling materials is assumed to be very low to practically nonexistent. Families of asbestos workers were potentially exposed to high fiber levels through contaminated clothing brought home for laundering. Asbestos exposure levels ranging from 100 to 500 ng/m^3 were found in houses of workmen (IARC V.14, 1986).

Asbestos fibers are released into the environment from the natural occurrence of asbestos in the earth and as a result of wear and deterioration of asbestos products. Asbestos minerals are emitted into the atmosphere and water systems from the mining and milling of asbestos ores. Concentrations not exceeding 100 ng/m^3, and usually less than 10 ng/m^3, of asbestos fibers are present in the general urban atmosphere (IARC V.14, 1986). Out in the country, away from anthropogenic or natural sources of asbestos, it is estimated that the ambient air concentration of asbestos is < 0.01 ng/m^3 (Chem. Engr. News, 1985a). Applications of asbestos materials to buildings and vehicle brake linings account for a significant amount of emissions to the atmosphere. Demolition of buildings with asbestos insulation or fireproofing may cause high atmospheric concentrations for relatively short periods of time. Disposal of mining and building material wastes in landfills also increases the distribution of asbestos into the environment, but no estimates of the quantity of material released in this manner are available. The Toxic Chemical Release Inventory (EPA) listed 131 industrial facilities that produced, processed, or otherwise used asbestos in 1988 (TRI, 1990). In compliance with the Community Right-to-Know Program, the facilities reported releases of asbestos to the environment which were estimated to total 1.2 million lb.

REGULATIONS

CPSC's banning of asbestos in patching compounds and in gas fireplaces prevented additional possible exposure of several million consumers who may have been exposed to asbestos from these sources. U.S. manufacturers of hand-held hair dryers cooperated with CPSC by voluntarily ceasing to use asbestos liners; this voluntary program resulted in the repair by manufacturers of 2 million dryers. Also, CPSC published an

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intent to further regulate the uses of asbestos, and convened a Chronic Hazard Advisory Panel to assess and, if feasible, to estimate the probable harm to human health that can result from exposure to asbestos. The panel met for the first time in January 1983 and presented a draft report. Public comment was requested, and the final report was published in July 1983. Studies on the release of asbestos from products were completed in FY 1984. Toxicity reviews of major selected asbestos substitutes occurred in FY 1986. CPSC monitored air levels of asbestos in 45 homes, using transmission electron microscopy. The study concentrated on homes with quantities of worn and damaged asbestos materials. The results of this limited study did not show increased indoor levels of asbestos in these homes compared with outdoors. Monitoring on a routine basis is intended to determine whether such materials can present a risk to residents. Testing was done during the winter of 1986 and spring of 1987. An enforcement policy became effective December 23, 1986, requiring labeling of all consumer products containing intentionally added asbestos that, under reasonably forseeable conditions of handling and use, are likely to release fibers. The Commission, in 1989, denied a petition to ban limestone products containing more than 0.1% tremolite because there were no data indicating the presence of asbestiform tremolite in these products and no data indicating that non-asbestiform tremolite is hazardous.

EPA regulates asbestos under the Clean Air Act (CAA), Clean Water Act (CWA), Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), Food, Drug, and Cosmetic Act (FD&CA), Resource Conservation and Recovery Act (RCRA), Safe Drinking Water Act (SDWA), Superfund Amendments and Reauthorization Act (SARA), and Toxic Substances Control Act (TSCA). EPA proposed an asbestos water quality criteria document for the protection of human health under CWA. A reportable quantity (RQ) of 1 lb has been established for asbestos under CERCLA. Under SDWA, EPA has proposed a recommended maximum contaminant level (RMCL) for asbestos. Under TSCA, EPA has proposed to prohibit or phase out the manufacture and use of asbestos in certain products. EPA issued a final rule banning the manufacture, importation, processing, and distribution of most asbestos-containing products. Also under TSCA, EPA has promulgated standards covering asbestos abatement project personnel not covered under OSHA standards. EPA proposed changes in the National Emission Standard for hazardous pollutants. A voluntary EPA program is removing or encapsulating sources of asbestos release in school buildings. EPA published an intent to regulate further the uses of asbestos. Asbestos is subject to reporting requirements under CERCLA, FD&CA, RCRA, SARA, and TSCA.

FDA action concerning asbestos (and talc containing asbestos) restricted the utilization of asbestos filters in the manufacture of parenteral drugs and parenteral drug ingredients. FDA has taken no action to date with regard to asbestos in food because there is no evidence that the ingestion of small amounts of asbestos found in food poses any human health risk.

The OSHA permissible exposure limit (PEL) for asbestos fibers in the

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workplace is 0.2 fibers/cm^3 of air for fibers longer than 5 μm. This standard also requires personal protective equipment, training, medical surveillance, signs and labeling, and engineering controls.

The NIOSH/OSHA Asbestos Work Group recommended that consideration be given to lowering the OSHA PEL to the lowest level detectable. This group stated that the level should be 100,000 fibers/m^3 (greater than 5 μm in length), in a 400-liter air sample, as an 8-hr TWA. The group also recommended the following definition of asbestos:

> "Asbestos is defined to be chrysotile, crocidolite, and fibrous cummingtonites grunerite including amosite, fibrous tremolite, fibrous actinolite, and fibrous anthophyllite. The fibrosity of the above minerals is ascertained on a microscopic level with fibers defined to be particles with an aspect ratio of 3:1 or larger."

OSHA published an Emergency Temporary Standard (ETS) lowering the PEL TWA for ambient asbestos to 0.5 fibers/cm^3. Enforcement of the ETS was stayed by the Fifth Circuit Court of Appeals. OSHA then published a supplemental proposal to the ETS. This supplement contained an additional option for a PEL of 0.2 fibers/cm^3 (5 μm or longer). OSHA regulates asbestos under the Hazard Communication Standard and as a chemical hazard in laboratories.

AZATHIOPRINE
CAS No. 446-86-6

CARCINOGENICITY

There is limited evidence for the carcinogenicity of azathioprine in experimental animals (IARC V.26, 1981; IARC S.4, 1982; IARC S.7, 1987). Suggestive evidence was obtained that lymphomas were induced in mice after intraperitoneal, subcutaneous, or intramuscular injection of azathioprine and that thymic lymphomas and squamous cell carcinomas of the ear duct were induced in rats after oral administration, but there were limitations in the design and reporting of these studies.

An IARC Working Group reported that there is sufficient evidence for the carcinogenicity of azathioprine in humans (IARC S.4, 1982; IARC S.7, 1987). Two large prospective epidemiological studies have shown that renal transplant patients, who usually receive azathioprine as an immunosuppressant, become at high risk for non-Hodgkin's lymphoma, squamous cell cancers of the skin, hepatobiliary carcinomas and mesenchymal tumors. Although this is true for each of the various etiological entities resulting in the need for a transplant, these patients also have in common heavy exposure to foreign antigens. Other patients who have received azathioprine as an immunosuppressant, including those with rheumatoid arthritis, systemic lupus and other 'collagen' disorders, inflammatory bowel disease and certain skin and renal diseases, have also been studied; the same array of malignancies was found to be in excess, although to a lesser extent. For these patients, however, the picture is still not completely clear,

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