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FOURTH ANNUAL REPORT ON CARCINOGENS

1985

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
Public Health Service

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I. EXECUTIVE SUMMARY

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EXECUTIVE SUMMARY

The Fourth Annual Report on Carcinogens, prepared by the National Toxicology Program (NTP), U.S. Public Health Service, is issued by the Secretary of the Department of Health and Human Services (DHHS), pursuant to Public Law 95-622 of November 9, 1978.* This law requires the Secretary to publish an Annual Report which contains "a list of all substances (i) which either are known to be carcinogens or which may reasonably be anticipated to be carcinogens and (ii) to which a significant number of persons residing in the United States are exposed;...." Annual Reports should also provide available information on the nature of exposures, the estimated number of persons potentially exposed, and the extent to which the implementation of Federal regulations decreases the risk to public health from exposure to these substances.

For the purpose of this Report, "known carcinogens" are defined as those substances for which the evidence from human studies indicates that there is a causal relationship between exposure to the substance and human cancer. Substances "which may reasonably be anticipated to be carcinogens" are defined as those for which there is a limited evidence of carcinogenicity in humans or sufficient evidence of carcinogenicity in experimental animals.

Substances in the above categories, for which potential exposure of persons residing in the United States has been demonstrated, are included in the Report. Also included are some substances which have been banned, or the use of which has been restricted, because people previously exposed are potentially at risk, or because some of these substances still remain in the environment. The Fourth Annual Report does not contain all known or reasonably anticipated carcinogens. Additional substances with identified carcinogenic properties as defined above will be included in the subsequent Annual Reports.

Several problems are encountered in developing the information required for the Annual Reports on Carcinogens. Estimating the number of people potentially exposed to a substance and identifying the nature, route, and intensity of this potential exposure are difficult tasks. It is often impossible to obtain accurate production volumes and use patterns for most chemicals. The information that is being collected by the U.S. Environmental Protection Agency under the Toxic Substances Control Act, at least that part which is public record, may assist in obtaining more accurate potential exposure estimates in the future. In addition, the upcoming National Occupational Exposure Survey** will provide new information on the extent and degree of potential exposures or different substances and manufacturing processes.

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* Section 262, Paragraph (4).

** An update of the National Occupational Hazard Survey conducted from 1972 to 1974 by the Centers for Disease Control/National Institute for Occupational Safety and Health (CDC/NIOSH).

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Perhaps the hardest task in preparing the Report is to evaluate the effectiveness of Federal regulations in decreasing the risk to public health. One reason is that virtually all Federal laws concerned with reducing risk have been enacted within the last 15 years. Thus, given the relatively long period between exposure to a carcinogen and the onset of disease, the extent to which the regulations implemented during these 15 years have reduced the risk remains unknown. Another reason is that reliable information on past exposures which could be used as a baseline for estimating future risk reduction is generally not available. Nonetheless, decreasing exposure should be considered as reducing carcinogenic risk even if the reduction cannot be quantified at present.

The Fourth Annual Report lists 150 agents. Included are the entries from the Third Annual Report and 33 additional substances or groups of substances. The new entries were chosen from those designated by the Agencies participating in the preparation of the Report,* from those tested within the National Toxicology Program and the National Cancer Institute Carcinogenesis Bioassay Program,** or from those evaluated by the International Agency for Research on Cancer (IARC), a component of the World Health Organization (WHO), located in Lyon, France.

Of the 150 entries, 24 substances or groups of substances and 7 occupational exposures (etiologic agent(s) unknown) associated with a technological process are listed as "known carcinogens":

Substances

- 4-Aminobiphenyl
- Analgesic mixtures containing phenacetin
- Arsenic and certain arsenic compounds
- Asbestos
- Azathioprine
- Benzene
- Benzidine
- N,N-Bis(2-chlorethyl)-2-naphthylamine (chlornaphazine)
- Bis(chloromethyl)ether and technical grade chloromethyl methyl ether
- 1,4-Butanediol dimethylsulfonate (myleran)
- Certain combined chemotherapy for lymphomas
- Chlorambucil
- Chromium and certain chromium compounds
- Coke oven emissions
- Conjugated estrogens
- Cyclophosphamide
- Diethylstilbestrol
- Melphalan
- Methoxsalen with ultraviolet A therapy (PUVA)
- Mustard gas
- 2-Naphthylamine
- Nickel refining
- Thorium dioxide
- Vinyl chloride

* Centers for Disease Control/National Institute for Occupational Safety and Health (CDC/NIOSH), Consumer Product Safety Commission (CPSC), U.S. Environmental Protection Agency (EPA), Food and Drug Administration (FDA), National Institutes of Health/National Cancer Institute (NIH/NCI), National Institutes of Health/National Institute of Environmental Health Sciences (NIH/NIEHS), National Institutes of Health/National Library of Medicine (NIH/NLM), and U.S. Department of Labor/Occupational Safety and Health Administration (DOL/OSHA).

** Now part of NTP/NIEHS.

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CARCINOGENICITY

The evidence for carcinogenicity of polychlorinated biphenyls (PCBs) in experimental animals is sufficient.[1] Certain mixtures of PCBs (e.g., Kanechlor 500, Aroclor 1254 and 1260) were carcinogenic in mice and rats after administration in the diet, producing liver tumors.[2,3] PCB (1260) was carcinogenic in the female rat, also producing liver tumors.[2]

The evidence for the carcinogenicity of PCBs in humans is inadequate.[1] A slight increase in the incidence of cancer, particularly melanoma of the skin, has been reported in a small group of men exposed occupationally to Aroclor 1254, a mixture of PCBs.[1]

PROPERTIES

PCBs vary in appearance from mobile, oily liquids to white crystalline solids to hard, noncrystalline resins. All forms are insoluble in water.

USE

Since 1974, all uses of PCBs in the United States have been confined to closed systems. Before 1972, PCBs were used in transformer cooling liquids, heat-transfer and hydraulic fluids, vacuum pump fluids, lubricants, plasticizers, fillers in investment casting waxes, surface coatings and sealants, pesticide extenders, and copy paper.

PRODUCTION

The 1979 TSCA Inventory identifies one company producing 35,555,500 pounds of PCBs.[4] PCBs are no longer produced in the United States, except for limited research and development applications; import and export of the compounds has not been permitted since 7/79. Prior to 1977, annual domestic production of PCBs was about 35 million pounds. Domestic production reached a peak volume of 86 million pounds in 1970 and decreased to about 41 million pounds by 1974. PCBs first were produced in the United States in 1929.

EXPOSURE

The release of PCBs from prior industrial uses and the persistence of the compounds in the environment have resulted in widespread contamination of water and soil, with subsequent potential exposure of the general population. Routes of exposure include skin absorption and ingestion; a major source of exposure is through the diet. A 1976 report indicated that fish, cheese, eggs, and contaminated animal feed were the major U.S. commodities in which PCBs were found. The percentage of food samples contaminated with PCBs decreased

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beween 1973 and 1975. Residues of PCBs have been detected in human milk and fat samples collected from the general U.S. population. EPA reports that about 12 million persons within 12 miles of three existing and nine projected commercial incinerators may possibly be exposed to releases of PCBs.

REGULATIONS

In 1970, EPA banned PCBs as a pesticide ingredient and canceled registration of products containing PCBs. EPA promulgated toxic pollutant effluent standards in 1977 and modified the marking and disposal rule in 1979, which was effective in identifying and eliminating some PCB sources. In 1979, EPA issued a ban on manufacturing, processing, and distributing PCBs in commerce; most manufacturing ceased voluntarily before these rules were issued. EPA proposed a water quality criteria document that will protect freshwater, saltwater, and aquatic organisms, as well as human health. EPA recently assessed air pollution sources of PCBs and is considering the need for regulation of emissions from incinerators, the only source for which controls may be essential. Under the Safe Drinking Water Act, EPA is preparing a report to Congress on the nature and extent of PCB contamination, as well as recommendations for further regulatory action, if necessary.

In 1973, FDA established tolerances for PCBs in several foods and in feeds for food-producing animals. In 1979, four of those tolerances were reduced. The tolerances now are 1.5 ppm (fat basis) in milk and manufactured dairy products, 3 ppm (fat basis) in poultry, 0.3 ppm in eggs, 0.2 ppm in finished animal feed, 2 ppm in animal feed components of animal origin, 5 ppm in fish and shellfish (edible portion), and 0.2 ppm in infant and junior foods. FDA has lowered the PCB standard in fish and shellfish from 5 ppm to 2 ppm and has established action levels of 3 ppm (fat basis) in red meat and 10 ppm in paper food-packaging material. OSHA adopted a standard of 1 mg/m^3 (an 8-hour time-weighted average) for PCBs containing 42 percent chlorine, and 0.5 mg/m^3 for PCBs containing 54 percent chlorine; OSHA adopted these standards for toxic effects other than cancer.

REGULATIONS

	Regulatory Action	Effect of Regulation/Other Comments
EPA	FIFRA, 6: PR notice 70-75 sent to all registrants affected. PCBs are banned as active or inert ingredients of pesticides (with polychlorinated terphenyls). Registration of products not reformulated, canceled 10/29/70.	Effectively removed pesticides as source of exposure.

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REGULATIONS

	Regulatory Action	Effect of Regulation/Other Comments
E P A	40 CFR 761.20, 761.40, 761.60; 46 FR 27614. Promulgated 2/17/78. TSCA, 6: Marking and disposal rule. ANPR addressing issues raised by the court order (EDF versus EPA, 79-1580), published 5/20/81.	Sources have been identified. Wastes are being isolated and/or destroyed. Some sources have been eliminated. Rulemaking slated for proposal by 4/23/82. (Actually published 4/22/82.)
	TSCA, 6(e): Regulations required by statute:	
	40 CFR 761, part. Promulgated 2/17/78. Marking and disposal.	
	40 CFR 761 part. Promulgated 8/25/82. Electrical equipment use.	
	40 CFR 761, part. Promulgated 10/21/82. Closed and controlled systems.	
	OTS, personal communication, 6/83. Uncontrolled; inadvertent sources, in development.	Target for proposal, first half of FY 1984.
	40 CFR 761. Promulgated 5/31/79. Ban on manufacturing, processing, and distribution in commerce (including some modifications to marking and disposal rule).	Most manufacturing has been voluntarily discontinued prior to these rules (except for certain R&D applications).
	45 FR 79318. 11/28/80. CWA, 304(a): Water quality criteria published.	Under review for possible revision.
	40 CFR 129.105. Promulgated 2/27/77. CWA, 307(a): Toxic pollutant effluent standard.	

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REGULATIONS

	Regulatory Action	Effect of Regulation/Other Comments
E	40 CFR 117.3, 117.13. Promulgated 8/29/79. CWA, 311: Hazardous spill regulation establishing reportable quantity (10 lb, 4.54 kg) and imposing reporting requirements.	Not based on carcinogenicity. Encourages greater care in handling and shipping of chemicals, and should result in reduction of accidental exposures.
	48 FR 23552. Proposed 5/25/83. CERCLA, 101(14): Designates and establishes reportable quantity of 1 lb. Final rule in OMB review.	Would, if promulgated, provide control over releases of these chemicals into the environment. PCBs (including seven Arochlors) are governed by a CWA 311 hazardous spill regulation, which remains in force until this rule is promulgated.
	43 FR 58946. Promulgated 5/19/80. RCRA, 3001-3004: Proposed rule included six Arochlor compounds in list of toxic wastes, 12/18/78. Designates PCBs as hazardous constituents of waste and subjects them to special handling and report/recordkeeping requirements.	Final rule did not include these, as the TSCA disposal rule addressed PCBs in a more stringent fashion than had been considered.
	40 CFR 257. Promulgated 9/13/79. RCRA, 4004: Prohibition of open burning, use on food, croplands, or open dumping of municipal sludges designated hazardous.	Prohibition on food cropland specifically addresses PCBs.
	OAQPS, personal communication, 1/85. CAA: Assessment of sources and exposures completed 3/85. Under review to determine if regulation is warranted.	Incineration is the only source likely to come under CAA, given TSCA bans.

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REGULATIONS

	Regulatory Action	Effect of Regulation/Other Comments
EPA	ODW, personal communication, 8/80. SDWA: Report to Congress, now in preparation, will document nature and extent of PCB contamination, treatment, and other implications, and establish what, if any, controls may be needed.	
FDA	21 CFR 109.30, 509.30. FD&CA, 406: Tolerances for PCBs as unavoidable contaminants in certain foods and animal feeds established 7/6/73. Four tolerances reduced 6/29/79.	Holds human exposure to lowest practicable level.
	21 CFR 7111.03. Action level of 3 ppm (fat basis) for red meat established 6/10/80.	Holds human exposure to lowest practicable level.
	48 FR 37020. 8/16/83. Permits the use of paper packaging material containing more than 10 ppm if separated from food by a barrier that limits migration to no more than 10 ppm	
	49 FR 21514. 5/22/84. Sets the tolerance for fish and shellfish at 2 ppm.	
NIOSH	NIOSH recommended to OSHA on 9/27/77, that exposure to PCBs be limited to 1.0 microgram/m^3 (10-hour TWA). This recommendation is based on data from studies which have shown PCBs to be carcinogenic and teratogenic in animals, and hence potentially carcinogenic and teratogenic in man. The environmental limit of 1.0 microgram/m^3 is the lowest concentration of PCBs that can reliably be measured.	

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REGULATIONS

Regulatory Action	Effect of Regulation/Other Comments
29 CFR 1910.1000. PEL: 1 mg/m^3 8-hr TWA (42 percent chlorine), 0.5 mg/m^3 8-hr TWA (54 percent chlorine). Potential for skin absorption noted. Standard adopted for toxic effects other than cancer.	Regulatory History: 1952: Walsh-Healey, 1 mg/m^3 maximum allowable concentration. 8/27/71: OSHA Takeover Standard--current limit effective.

REFERENCES

[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. 292 pp. Lyon, France: IARC, 1982, pp. 217-219.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 18. 140 pp. Lyon, France: IARC, 1978, pp. 43-103.

[3]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. 326 pp. Lyon, France: IARC, 1974, pp. 261-289.

[4]Toxic Substances Control Act, Chemical Substance Inventory, 1979: public record.

PROCARBAZINE AND PROCARBAZINE HYDROCHLORIDE

CARCINOGENICITY

There is sufficient evidence for carcinogenicity in humans of intensive chemotherapeutic regimens that include alkylating agents, vinca alkaloids, procarbazine hydrochloride, and prednisone. There is inadequate evidence for carcinogenicity of procarbazine hydrochloride alone in humans.

There is sufficient evidence for the carcinogenicity of procarbazine in experimental animals.[1-3] Laboratory exposure of animals to procarbazine was studied by intraperitoneal injection. In rats, lymph system cancers and cancers of the mammary gland and olfactory nerve were induced in statistically significant numbers. In mice, cancers of the lymph system or leukemia, cancers of the olfactory nerve, pulmonary neoplasms, and cancers of the uterus were induced in statistically significant numbers.[2]

Evidence of carcinogenicity was also found in mice and rats following administration by gavage; in rats following intravenous administration and in one instance following transplacental exposure. Two studies in two species of nonhuman primates suggest that procarbazine hydrochloride may also produce leukemia when administered by multiple routes to the same animal.[1]

PROPERTIES

Procarbazine is a white to pale yellow crystalline powder that is soluble but unstable in water and aqueous solutions.

USE

Procarbazine hydrochloride is used mainly as an antineoplastic agent to treat advanced Hodgkin's disease and oat-cell carcinoma of the lung. FDA approved its use in 1969, indicating that the drug should be used as an adjunct to standard therapy.

PRODUCTION

The 1979 TSCA Inventory reports no production data for procarbazine and its hydrochloride.[4]

EXPOSURE

Possible exposure to procarbazine and it hydrochloride occurs during manufacture of the drug; direct exposure occurs during administration of procarbazine hydrochloride to patients. In 1980, the National Prescription Audit reported 1.5 million prescriptions dispensed for the drug. Some of the metabolites of procarbazine are both carcinostatic and carcinogenic.

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