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Meeting of the IARC working group on the evaluation of carcinogenic risks to humans from occupational exposures to mists and vapors from strong inorganic acids and other industrial chemicals

Carcinogenicity of occupational exposures to mists and vapors from strong inorganic acids, including sulfuric acid, and hydrochloric acid

Strong inorganic acids are used in a wide range of industries for a variety of purposes. In order to evaluate the carcinogenic risk of exposures to strong inorganic acids, studies among workers in the industries in which these acids are used were examined to determine whether common exposures across the industries or across processes are associated with the occurrence of cancers at particular sites. A review was conducted by a working group of experts in carcinogenicity and related fields, which met on 15–22 October 1991 at the International Agency for Research on Cancer (IARC) within the context of the program on the evaluation of carcinogenic risks to humans; the detailed report will appear soon in volume 54 of the IARC monograph series (1).

Occupational exposures are evaluated within the IARC monograph program with the aim of alerting public health officials and others to possible hazards in the workplace. Except in rare instances, however, it is difficult to distinguish the contributions of discrete exposures to a carcinogenic risk observed among workers, many of whom spend their worklives in complex chemical environments.

The observation of excess risks for laryngeal and other cancers of the upper respiratory tract in association with the inhalation of mists and vapors of strong inorganic acids has given rise to the hypothesis that acidity itself might exert a carcinogenic effect. The Working Group on the Evaluation of Carcinogenic Risks to Humans from Occupational Exposures to Mists and Vapours from Strong Inorganic Acids and Other Industrial Chemicals examined the evidence from studies of exposures to mists and vapors from strong inorganic acids in some of the many industries in which they are used. These industries include the manufacture of isopropanol, synthetic ethanol, phosphate fertilizers, lead batteries, soap and detergents, sulfuric acid, and nitric acid and industries in which metals are treated with acids. Sulfuric acid is the principal strong inorganic acid used in these industries. Workers are exposed to acid mists and vapors in industries other than those considered; however, epidemiologic studies on nickel refining, the processing of other basic metals, chromate production, and chromium and nickel plating were thought by the Working Group to be uninformative for evaluating the car-

cinogenic risks of acids, as these processes involve exposures to agents known to be carcinogens.

The degrees of evidence for carcinogenicity in both humans and experimental animals are expressed in the IARC monograph series with standardized wording and groupings (1). The Working Group considered that "there is sufficient evidence that occupational exposure to strong-inorganic-acid mists containing sulfuric acid is carcinogenic." This decision was based on the consistency of reports of cancers of the upper respiratory tract in workers exposed in the manufacture of isopropanol, synthetic ethanol, and soap and detergents and in pickling operations in steel production. Studies of workers involved in the manufacture of phosphate fertilizers, lead batteries, sulfuric acid, and nitric acid were not informative.

An early report indicated an excess of nasal sinus cancer among workers in isopropanol manufacturing using the strong-acid process (2). Studies of a cohort of workers in pickling operations within the United States (US) steel industry showed an excess risk for laryngeal cancer after adjustment for smoking (3). The risk for lung cancer was also increased, higher risks being seen in various subgroups of workers (4). Excess risks for laryngeal cancer were also found in a Swedish study of a cohort of workers in steel pickling (5) and in a nested case-referent study of workers exposed to sulfuric acid in a US petrochemical plant (6). An exposure-response relationship was apparent in the latter study. Two population-based case-referent studies in Canada — one of laryngeal cancer (7) and the other including lung cancer (8) — also showed increased risks associated with exposure to sulfuric acid in particular. The latter suggested an excess risk associated with exposure to mixed inorganic acids as well. In the study of laryngeal cancer, a significant effect was found at the highest exposure level. Supporting evidence was provided by the results of a cohort study in the soap manufacturing industry in Italy (9), which showed an increased risk for laryngeal cancer. In all of these studies, sulfuric-acid mists were the most common exposure.

Although tobacco smoking was not controlled for in most of the studies considered, the finding of increased risks for laryngeal cancer in the absence of increased risks for lung cancer meant that smoking could be ruled out as a major confounder. In many studies, the increased risks for cancer of the larynx and lung were still found after adjustment had been made for

smoking in the statistical analysis. The overall categorization by the Working Group was thus group 1.

Hydrochloric acid is also used in pickling and cleaning steel and other metals, in the production of many inorganic and organic chemicals, in food processing, in the cleaning of industrial equipment, in the extraction of metals, and for many other purposes. It is formed when hydrogen chloride dissolves in water. The epidemiologic studies in which exposure to this acid could be evaluated, from among those considered in the evaluation of exposures to strong-acid mists in general, were confined to one cohort study of steel pickling workers (4), which showed an excess risk for cancer of the lung in workers exposed primarily to hydrochloric acid; a Canadian population-based case-referent study, which showed an increased risk for oat-cell carcinoma of the lung but not for other histological types; and three industry-based case-referent studies, none of which showed an association between exposure to hydrogen chloride and cancers of the lung, brain, or kidney.

The epidemiologic studies were considered to provide inadequate evidence for the carcinogenicity of hydrochloric acid to humans. Two studies on rats, in which the compound had no effect on tumor incidence when given alone and in which hydrogen chloride enhanced the effect of formaldehyde only when the two gases were premixed before administration and not when given concomitantly, provided inadequate evidence for the carcinogenicity of hydrochloric acid in experimental animals. Hydrochloric acid was therefore considered to be unclassifiable as to its carcinogenicity to humans (group 3).

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Carcinogenicity of exposures to 1,3-butadiene

The recent publication of a follow-up of cohort studies of cancer in relation to exposure to 1,3-butadiene in Canada and the United States (1, 2) and of a case-referent study nested within one of these studies (3, 4) prompted a review of the evidence pertaining to the carcinogenicity of this compound. The review and an evaluation were made by a working group of experts in carcinogenicity and related fields, which met on 15-22 October 1991 at the International Agency for Research on Cancer (IARC) within the context of the program on the evaluation of carcinogenic risks to humans; the detailed report will appear shortly in volume 54 of the series *IARC Monographs on Carcinogenic Risks to Humans* (5). 1,3-Butadiene has been produced on a large scale since the 1930s. It is used to manufacture a wide range of polymers and copolymers, including styrene-butadiene rubber, polybutadiene, nitrile rubber, acrylonitrile-butadiene-styrene resins, and styrene-butadiene latexes. The rubber industry (ie, the manufacture of finished rubber goods, in which there is potential exposure to 1,3-butadiene and a wide range of other chemicals) has been evaluated previously within the IARC monograph program (6, 7).

A cohort study of workers who manufactured 1,3-butadiene monomer (2) showed a significantly increased risk for lymphosarcoma and reticulosarcoma. Although there was no overall risk for leukemia, a subgroup of workers with "nonroutine" exposure to 1,3-butadiene had a nonsignificant excess of leukemia. In a study of styrene-butadiene rubber manufacturing (8), the risk for leukemia appeared to be increased in one of the two plants studied, but no increase in risk was seen for other cancers of the lymphatic and hematopoietic system. In an earlier case-referent study of the rubber industry (9), a large excess of lymphatic and hematopoietic cancers, including lymphatic leukemia, was found among workers employed in styrene-butadiene rubber production.

In the most recent study of workers at eight styrene-butadiene polymer plants in Canada and the United States (1), there was no overall increase in risk for leukemia or other cancers of the lymphatic system, but production workers, presumed by the authors to be those with the highest exposure to 1,3-butadiene, showed significantly increased risks for leukemia among black production workers and for other lymphatic cancers among all production workers. In a case-referent study nested within this cohort (3, 4), a large excess of leukemia was found to be associated with exposure to 1,3-butadiene, which could be distinguished from the risk associated with styrene by use

of a cumulative ranked exposure index for butadiene and styrene separately. The relative risk for exposure to 1,3-butadiene, adjusted for exposure to styrene, was above 7.

One study thus specifically related an increased risk for leukemia to exposure to 1,3-butadiene and not to styrene. In other studies, the increased risks for leukemia and other lymphatic cancers occurred among workers whose exposure had been in the manufacture of 1,3-butadiene or of styrene-butadiene rubber. The IARC Working Group, after considerable discussion, decided that this information required confirmation and constituted only limited evidence for the carcinogenicity to humans of 1,3-butadiene.

The results of experimental studies on this compound showed quite clearly, however, that it is a potent carcinogen. Tumors were induced in mice and rats exposed by inhalation at all concentrations tested. 1,3-Butadiene induced tumors at multiple organ sites in animals of each sex and of both species, including tumors of the hematopoietic system and an uncommon neoplasm of the heart in male and female mice. Neoplasms occurred in multiple organs in mice after only 13 weeks of exposure. Many of the increased incidences were dose-related.

The evidence was further supported by the suggestion from studies in vitro that the metabolism of 1,3-butadiene is qualitatively similar in humans and experimental animals. The compound is metabolized in mammals to epoxy metabolites which interact with deoxyribonucleic acid. It induces base-substitution mutations in bacteria, and similar mutations in the *K-ras* oncogene have been reported for tumors induced in mice exposed to 1,3-butadiene (10).

The combined evidence from epidemiologic and experimental studies thus led the Working Group to the conclusion that 1,3-butadiene is probably carcinogenic to humans (group 2A).

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