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Meeting of the IARC working group on some industrial chemicals

Many of the industrial chemicals considered by the latest working group convened by the International Agency for Research on Cancer (IARC), for evaluation in the IARC program for the preparation of the series *Monographs on the Evaluation of Carcinogenic Risks to Humans*, have considerable commercial importance as the building blocks for widely used polymers and copolymers. Several of the chemicals are characterized by unsaturated chemical bonds, which are necessary for their polymerization. These bonds can also be the targets for metabolic reactions in which epoxides are formed. Some of the latter are industrially important chemicals in their own right and were also evaluated by the group that met in Lyon on 15-22 February 1994. (See the list of participants at the end of this article.) Although many of the compounds had been evaluated previously within the monograph series, modifications to the procedure made on the basis of advice from experts in all areas of cancer research (1) mean that data on aspects other than cancer, such as genetic and related effects, metabolism, and kinetics, are now considered in the evaluation of carcinogenicity.

Ethylene is, chemically, the simplest compound of those considered. It is the petrochemical produced in largest volume worldwide. Although it is used mainly as an intermediate in the production of polymers and other industrial chemicals, workers can also be exposed during its use to promote the ripening of fruits and vegetables. Ethylene is also introduced into the environment from natural and man-made sources, including emissions from vegetation, and as a product of burning organic material (including cigarettes) and the incomplete combustion of fossil fuels. Surprisingly, the carcinogenicity of ethylene has been addressed in only one epidemiologic study, one of workers involved in the manufacture of ethylene oxide. That information was considered inadequate to evaluate the carcinogenicity of ethylene in humans. Its carcinogenicity in experimental animals has also been addressed in only one study, which showed no effect. Ethylene was therefore considered to be unclassifiable as to its carcinogenicity in humans (group 3).

Ethylene oxide, in contrast, has been studied in several epidemiologic and experimental studies. It is used in largest volume in the production of other industrial chemicals, but the greatest opportunity for exposure occurs during its use in the sterilization of medical instruments and supplies in hospitals, in industry, and in the fumigation of spices. In epidemiologic studies of exposure to ethylene oxide, the

most frequently reported association has been with lymphatic and hematopoietic cancers. Nonsignificant excesses were seen in all four studies of workers involved in sterilization, and in the largest and most informative of these studies, conducted in the United States, a significant trend was found, especially for lymphatic leukemia and non-Hodgkin's lymphoma, in relation to estimated cumulative exposure to ethylene oxide. The results of the studies of chemical workers are compatible with those of the studies of sterilization personnel. These studies were considered to provide limited evidence for the carcinogenicity of ethylene oxide in humans. Ethylene oxide is, however, consistently carcinogenic in studies in experimental animals and is overwhelmingly active in tests for genetic and related effects. Applying the principle stated in the preamble to the monograph series that "Exceptionally, an agent (mixture) may be placed in Group 1 when evidence in humans is less than sufficient but there is sufficient evidence of carcinogenicity in animals and strong evidence in exposed humans that the agent (mixture) acts through a relevant mechanism of carcinogenicity," the working group placed ethylene oxide in group 1 (carcinogenic to humans). The working group based their decision on the fact that ethylene oxide is a directly acting alkylating agent that (i) induces a sensitive, persistent dose-related increase in the frequency of chromosome aberrations (and sister chromatid exchange) in peripheral lymphocytes and micronuclei in bone-marrow cells from exposed workers, (ii) has been associated with malignancies of the lymphatic and hematopoietic system in both humans and experimental animals, (iii) induces a dose-related increase in the frequency of hemoglobin adducts in exposed humans and dose-related increases in the numbers of adducts in both DNA [deoxyribonucleic acid] and hemoglobin in exposed rodents; (iv) induces gene mutations and heritable translocations in germ cells of exposed rodents, and (v) is a powerful mutagen and clastogen at all phylogenetic levels.

Propylene is used mainly in the preparation of alkylates for gasoline. Like ethylene, however, its carcinogenicity has surprisingly not been studied. No epidemiologic data were available, and the data from studies in experimental animals were inadequate. Propylene could not, therefore, be classified as to its carcinogenicity in humans (group 3).

Propylene oxide, which is used as a chemical intermediate and, to a less extent, in foods, was studied only in one case-referent study, which does not

allow any conclusion with respect to carcinogenicity. It is, however, clearly carcinogenic in experimental animals and gives positive results in a wide range of tests for genetic and related effects. It was considered to be possibly carcinogenic to humans (group 2B).

Styrene is one of the most widely produced monomers in the world; it is used mainly in the production of polystyrene, acrylonitrile-butadiene-styrene resins, styrene-butadiene rubbers and latexes, and unsaturated polystyrene resins. Exposure to styrene is particularly high in the manufacture of fiber glass-reinforced polyester products. Epidemiologic studies have been carried out in the production of glass-reinforced plastic products, the production of styrene monomer and styrene polymerization, and the production of styrene-butadiene rubber. The malignancies observed in excess are generally of the lymphatic and hematopoietic system. The two largest, most informative but partially overlapping studies of workers in the reinforced plastics industry, where there is less opportunity for confounding than in other industries, have certain features that are suggestive of a cancer hazard. In one, risk increased with average intensity of exposure and with time since first exposure. In the other, risk was the greatest for men employed at times when the highest exposures occurred. The studies do not, however, indicate an increase in risk with increasing cumulative exposure to styrene, and there is no overall increase in risk for lymphatic and hematopoietic cancer.

Studies on experimental animals provide only limited evidence for carcinogenicity, but styrene is metabolized to styrene-7,8-oxide, which binds covalently to DNA and is active in various tests for genetic effects. The genetic and related effects of styrene are therefore associated with its oxidation, which also occurs, for example, in cultured whole blood from humans, in which styrene at low concentrations induces dose-related chromosome damage. Styrene-7,8-oxide is detected in the blood of workers exposed to styrene. Adducts in hemoglobin and DNA, DNA single-strand breaks, and alkali-labile sites, as well as significant increases in the frequency of chromosome damage, have been found in workers exposed to styrene in the reinforced plastics industry. Positive results are associated with higher overall styrene levels and negative results with decreasing exposures to styrene. Although the role of other contaminants cannot be excluded in studies of workers, their occurrence is variable and their concentrations are very low in comparison with that of styrene. Styrene was therefore considered by the working group to be possibly carcinogenic to humans (group 2B).

Styrene-7,8-oxide is used mainly in the preparation of fragrances and as a reactive diluent in epoxy resin formulations. No epidemiologic data were available to the working group. It produced benign and malignant tumors of the forestomach in mice and

rats after administration by gavage. In making the overall evaluation to classify the compound into group 2A (probably carcinogenic to humans), the working group also took into consideration the fact that styrene-7,8-oxide (i) forms covalent adducts with DNA in humans, rats, and mice; (ii) induces gene mutation in bacteria and in rodent cells in vitro, (iii) induces chromosome aberrations, micronuclei, and sister chromatid exchange in human cells in vitro, and (iv) induces chromosome aberrations and sister chromatid exchange in mice in vivo.

Epidemiologic studies on the carcinogenicity of acrylamide have shown either no or nonsignificant increases in risk. In experimental animals, however, acrylamide showed clear carcinogenic activity, and both acrylamide and its epoxide glycidamide are active in tests for genetic and related effects. Thus, although inadequate evidence in humans and sufficient evidence in experimental animals would previously have meant that acrylamide was categorized into group 2B, it was placed in group 2A (probably carcinogenic to humans) on the basis of supporting evidence that (i) acrylamide and its metabolite glycidamide form covalent adducts with DNA in mice and rats, (ii) acrylamide and glycidamide form covalent adducts with hemoglobin in exposed humans and rats, (iii) acrylamide induces gene mutation and chromosome aberrations in germ cells of mice and chromosome aberrations in germ cells of rats and forms covalent adducts with protamines in germ cells of mice in vivo, (iv) acrylamide induces chromosome aberrations in somatic cells of rodents in vivo, (v) acrylamide induces gene mutation and chromosome aberrations in cultured cells in vitro, and (vi) acrylamide induces cell transformation in mouse cell lines.

Two further acrylic compounds, N-methyloacrylamide and 2-ethylhexyl acrylate, could not be classified as to their carcinogenicity in humans. Neither could methyl methacrylate be classified as to its carcinogenicity. Occupational exposures have been measured during its production and during its use in polymers, as a component of surgical bone cement, in denture fabrication, and in the preparation of artificial fingernails. One epidemiologic study of workers in acrylic sheet manufacturing showed a significant increase in mortality from colon cancer in one plant and a nonsignificant increase in another, especially among workers with the highest exposure. However, the workers were also exposed, to a less degree, to other compounds. In a study of workers in methyl methacrylate manufacture and polymerization, no significant increase in cancer deaths was found. One experiment with mice and one experiment with rats exposed by inhalation showed no increase in tumor incidence. A further study of oral administration to rats was inadequate for evaluation. The working group considered that the experimental data provided evidence suggesting lack of carcinogenicity in experimental animals.

A similar situation was found for the monomer vinyl toluene. No epidemiologic data were available, but no increase in the incidence of tumors was observed in one experiment with mice and one experiment with rats, in which vinyl toluene was given by intragastric intubation or in experiments in which mixed isomers of the compound were administered to mice and rats by inhalation. The evidence was again considered to provide evidence suggesting a lack of carcinogenicity in experimental animals. The overall evaluation was that vinyl toluene could not be classified as to its carcinogenicity in humans (group 3).

Isoprene, used mainly in the production of isoprene rubber (used in vehicle tires), block polymers containing styrene (used as thermoplastic rubbers), pressure-sensitive adhesives and butyl rubber, has not been studied for its carcinogenicity in humans. It was carcinogenic to experimental animals and was therefore placed in group 2B (possibly carcinogenic to humans).

4-Vinylcyclohexene is produced by catalytic dimerization of 1,3-butadiene and has been used in flame retardants, flavors, and fragrances and other uses. Although neither compound has been studied epidemiologically, they are clearly carcinogenic in experimental animals. They were therefore both classified as possibly carcinogenic to humans (group 2B).

Reference

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