Carcinogenicity of perfluorooctanoic acid, tetrafluoroethylene, dichloromethane, 1,2-dichloropropane, and 1,3-propane sultone

In June, 2014, 20 experts from nine countries met at the International Agency for Research on Cancer (IARC; Lyon, France) to assess the carcinogenicity of perfluorooctanoic acid (PFOA), tetrafluoroethylene (TFE), dichloromethane (DCM), 1,2-dichloropropane (1,2-DCP), and 1,3-propane sultone (1,3-PS). These assessments will be published as volume 110 of the IARC Monographs.1,2 1,2-DCP is a synthetic chlorinated solvent, and a byproduct of the production of epichlorhydrin. It is used mainly as a chemical intermediate in the production of other organic chemicals such as propylene, carbon tetrachloride, and tetrachloroethylene, and in paint stripping, and was used as an ink-removal agent in the printing industry in Japan from the mid-1990s until 2012. 1,2-DCP was classiﬁed as carcinogenic to humans (Group 1), on the basis of sufﬁcient evidence in humans that exposure to 1,2-DCP causes cholangiocarcinoma (biliary-tract cancer). The most important human evidence regarding carcinogenicity comes from studies of workers in a small offset printing plant in Osaka, Japan, where a very high risk of cholangiocarcinoma was reported.3,4 Additional cases were later identiﬁed from several other printing plants. The major challenge in assessing the occurrence of cancer in the Japanese printing plants was to establish whether the observed excess of cholangiocarcinoma could be attributed to a speciﬁc agent. Although workers were exposed to more than 20 different chemicals, exposure to 1,2-DCP was common to all except one of the 24 patients with cholangiocarcinoma, and six of the patients had no known exposure to DCM (used together with 1,2-DCP in this industry). The working group considered the rarity of cholangiocarcinoma, the very high relative risk, the young ages of the patients, the absence of non-occupational risk factors, and the intensity of the exposure as indications that the excess of cholangiocarcinoma was unlikely to be the result of chance, bias, or non-occupational confounding. Sufﬁcient evidence for carcinogenicity has also been reported in experimental animals, with malignant lung and hepatocellular tumours observed in exposed mice.5 On the basis of this evidence, most of the working group concluded that 1,2-DCP was the causative agent responsible for the large excess of cholangiocarcinoma in the exposed workers. However, a minority concluded that the association between 1,2-DCP and cholangiocarcinoma was credible, but the role of other agents, mainly DCM, could not be separated with complete conﬁdence. The working group members also noted that most of the evidence came from reports in just one plant.

DCM has been used in the manufacture of polycarbonate plastics, hydroﬂourocarbons, synthetic ﬁbres, and photographic ﬁlms, as an aerosol propellant, for paint stripping, metal cleaning, and printing-ink removal, and as an extraction solvent for some foods. DCM was classiﬁed as probably carcinogenic to humans (Group 2A), on the basis of sufﬁcient evidence in experimental animals with a striking and atypical pattern of tumours. Speciﬁcally, neoplasms at several sites and with very high incidence were noted in male and female rodents after exposure to TFE (mice: liver haemangiosarcoma, hepatocellular carcinoma, and histocytic sarcoma; rats: renal cell adenoma or carcinoma, hepatocellular carcinoma, monocellular cell leukaemia, and the rare liver haemangiosarcoma [in female rats only]).6–8

1,3-PS has been used as an intermediate in the manufacture of other chemicals and a range of products including detergents, pesticides, pharmaceuticals, and photographic materials. Major industrial use has been largely terminated, but use in manufacturing lithium batteries has been reported recently. 1,3-PS was classiﬁed as probably carcinogenic to humans
(Group 2A), on the basis of inadequate evidence in humans and sufficient evidence in experimental animals, with a mechanistic upgradation supported by strong evidence of genotoxicity. 1,3-PS causes malignant tumours of the skin and lymphohaematopoietic system in mice and malignant glioma in rats. 1,3-PS is an alkylating agent that reacts directly with DNA and protein. DNA reactivity was evident in various genotoxicity assays, including in animals and in human cells in vitro. Because 1,3-PS does not require metabolic activation and acts directly with DNA and other macromolecules, the working group concluded that this mechanism probably operates both in animals and humans.

PFOA and its salts are used in the production of fluoropolymers and in many industrial and commercial products, notably in producing non-stick cookware, waterproof clothing, and paper coatings used in food packaging. PFOA is persistent in the environment and has been detected worldwide at low concentrations in the general population. Additionally, communities near some production facilities have been highly exposed to PFOA as a result of emissions to air and water. On the basis of limited evidence in humans that PFOA causes testicular and renal cancer, and limited evidence in experimental animals, the working group classified PFOA as possibly carcinogenic to humans (Group 2B). Increased risk of kidney cancer with a statistically significant exposure-response trend was reported in workers in a fluoropolymer production plant in West Virginia, USA, and in an exposed community near the plant (relative risk 2.0, 95% CI 1.0–3.9). 13,14 Increases of about threefold in the risk of testicular cancer were reported in the most highly exposed residents of communities near the same plant. 15,16 The working group considered the evidence regarding mechanisms of PFOA-associated carcinogenesis to be moderate, which did not lead to a change in the overall classification of PFOA.

We declare no competing interests.

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16 Solvents Industry Group, Shell, and Concawe (the oil industry association for environment, health, and safety). Representatives M Blisson, for INERIS (Institut National de l’Environnement Industriel et des Risques, France); Observers J Arts, for the REACH Chlorsolv Consortium and the European Chlорinated Solvent Association and the Halogenerated Solvent Industry Alliance (Netherlands); J L Butenho, for the PlasticsEurope Fluoropolymers Group (USA); J Carretier, for the Léon Bérard Centre (France); A Forrest, for the United Fire Fighters of Winnipeg (Canada); G W Olsen, for the Center for Advancing Risk Assessment Science and Policy of the American Chemistry Council (USA); J M Symons IV, for the PlasticsEurope Fluoropolymers Group (USA). Declaration of interests JA is employed by AkzoNobel. LB is retired but employed (part-time) by JM; receives a pension, benefits, and travel support from JM; and holds stock in 3M. GW is employed by JM; receives travel support from JM; and holds stock in 3M. JWS is employed by DuPont.
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