Carcinogenicity of 1,1,1-trichloroethane and four other industrial chemicals

In October, 2021, a Working Group of 20 scientists from 12 countries met remotely at the invitation of the International Agency for Research on Cancer (IARC) to finalise their evaluation of the carcinogenicity of five agents: 1,1,1-trichloroethane, 1,2-diphenylhydrazine, diphenylamine, *N*-methylolacrylamide, and isophorone. These assessments will be published in Volume 130 of the *IARC Monographs*.[1]

1,1,1-Trichloroethane was classified as "probably carcinogenic to humans" (Group 2A) on the basis of "limited" evidence of carcinogenicity in humans and "sufficient" evidence in experimental animals. All other agents were classified as "possibly carcinogenic to humans" (Group 2B) on the basis of "sufficient" evidence of carcinogenicity in experimental animals.

The evidence for carcinogenicity in experimental animals was "sufficient" because all agents, except *N*-methylolacrylamide, increased the incidence of malignant neoplasms or an appropriate combination of benign and malignant neoplasms in two species. *N*-Methylolacrylamide caused the aforementioned increase in both sexes of a single species in a Good Laboratory Practice (GLP) study. Evidence regarding cancer in humans was "inadequate" for agents other than 1,1,1-trichlorethane because few or no data were available. For all agents, the mechanistic evidence was "limited".

1,1,1-Trichloroethane was used extensively until the 1990s as a solvent, metal degreaser, chemical intermediate, and in numerous other applications. Since the Montreal Protocol on Substances that Deplete the Ozone Layer, production and use have dwindled[2] and it is now mostly used as a chemical feedstock in closed systems and for "essential uses"—eg, medical devices and aviation safety. Poorly documented non-essential uses might occur in low-income and middle-income countries.

The association between occupational exposure to 1,1,1-trichloroethane and cancer risk was investigated in 23 cohort, nested case-control, and case-control studies. The largest number of studies evaluated the risk of lymphatic and haematopoietic malignancies; fewer studies were available for other cancers, including those of the kidney, urinary bladder, breast, brain, and nervous system.

The Working Group concluded that there was "limited" evidence of carcinogenicity in humans for multiple myeloma. Some evidence of positive associations with 1,1,1-trichloroethane was observed in the three available studies on multiple myeloma. Positive, but statistically imprecise associations with ever-exposure to 1,1,1-trichloroethane were observed in two cohort studies (one was only among women) with small numbers of exposed cases.[3,4] A case-control study reported a positive association between ever-exposure and multiple myeloma, with an odds ratio of 1·8 (95% CI 1·1–2·9).[5] The association remained similar in magnitude in a sensitivity analysis evaluating potential exposure misclassification. Positive associations were observed across most categories of exposure duration and cumulative exposure, with no indication of a positive trend in risk. Overall, the Working Group concluded that a causal association between exposure to 1,1,1-trichloroethane and multiple myeloma was credible. However, in view of the small numbers of exposed participants and the potential influence of selection bias and exposure misclassification, chance and bias could not be ruled out with reasonable confidence. Evidence for other cancer types was "inadequate"; there were few positive findings and available studies in humans were not sufficiently informative to permit a conclusion to be drawn about a causal association.

In multiple species, including humans, 1,1,1-trichloroethane is absorbed and distributed into the brain and adipose tissue, metabolised by cytochrome P450 enzymes to trichloroethanol and trichloroacetic acid, and eliminated as the parent compound in breath or metabolites in urine, or both. In rodents, inhaled 1,1,1-trichloroethane caused splenic lymphoma and bronchioloalveolar carcinoma in male mice; bronchioloalveolar adenoma or carcinoma (combined) in female mice; and peritoneal mesothelioma in male rats.[6] The mechanistic evidence across different experimental systems, including human cells in vitro, was suggestive but incoherent for genotoxicity, and suggestive for oxidative stress and other key characteristics of carcinogens based on a small set of studies.

1,2-Diphenylhydrazine was primarily used as an intermediate in the manufacture of benzidine dyes, which ceased in the past several decades in the USA and EU, although production might occur elsewhere. Additional uses include as an intermediate in drug manufacture. Exposure data were sparse. 1,2-Diphenylhydrazine is absorbed and excreted as the parent compound or metabolites, or both, in urine of rodents; the evidence for aniline or benzidine as metabolites was suggestive but inconclusive. In mice, dietary exposure to 1,2-diphenylhydrazine caused hepatocellular carcinoma in females. In rats, dietary exposure to 1,2-diphenylhydrazine caused

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All Working Group members declare no competing interests.

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All representatives declare no competing interests.

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M Batoon is employed by a company that formulates products with diphenylamine.

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hepatocellular carcinoma, squamous cell carcinoma of the Zymbal gland, squamous cell papilloma or carcinoma (combined) of the ear canal, Zymbal gland, or skin of the ear (combined), and benign or malignant (combined) adrenal pheochromocytoma in males; and mammary adenocarcinoma in females.[7] The mechanistic evidence across different experimental systems was suggestive but incoherent for genotoxicity, and there was a paucity of data for other key characteristics.

Diphenylamine is a high production volume (HPV) chemical and intermediate used in lubricants, hydraulic and metal-working fluids, dyes and textile treatments, and agrochemicals to prevent fruit scalding. The latter application is prohibited in the EU, but ongoing in the USA and elsewhere. Occupational exposures likely occur during synthesis and agricultural application, and population exposures occur through fruit consumption in some countries. Exposure data were sparse. Diphenylamine is absorbed as the parent compound or metabolites, or both, and excreted in urine of multiple species, including humans. After dietary exposure, diphenylamine caused haemangioma or haemangiosarcoma (combined) of the liver, spleen, and all organs (combined) in male mice; uterine histiocytic sarcoma in female mice;[8] haemangiosarcoma of the spleen and all organs (combined), and fibroma or fibrosarcoma (combined) of the subcutis in male rats; and uterine adenocarcinoma and spleen mononuclear cell leukaemia in female rats.[9] The mechanistic evidence across different experimental systems, including human cells in vitro, was suggestive but incoherent for genotoxicity, and suggestive for oxidative stress and other key characteristics of carcinogens based on a small set of studies.

N-Methylolacrylamide is an HPV chemical and intermediate used for adhesives, sealants, inks, resins, paints, plastics, and paper and textile finishes. Exposure data were sparse. Documented worker exposure involved the use of grout containing *N*-methylolacrylamide in tunnel construction in Norway and Sweden, and as a sealant in window manufacture. *N*-Methylolacrylamide is distributed, glutathione-conjugated, and excreted as the parent compound or metabolites, or both, in urine and faeces of mice. Data on conversion to acrylamide or glycidamide were scarce. In a GLP gavage study in mice, *N*-methylolacrylamide caused bronchioloalveolar carcinoma in males and females; hepatocellular carcinoma in males; and Harderian gland adenoma or carcinoma (combined) in females.[10] The mechanistic evidence across different experimental systems was suggestive but incoherent for genotoxicity, and suggestive for other key characteristics based on a small set of studies.

Isophorone is an HPV chemical used widely as a solvent and intermediate in the manufacture of lacquers, polymers, inks and paints, agrochemicals, nitrocellulose finishes, and cleaning products. Isophorone has been detected in numerous polymer-based products from food packaging to aquatic inflatables, and in food items, possibly because of agrochemical contamination or migration from packaging. Exposure data were sparse and mostly from historical studies of screen printers. Isophorone is absorbed and excreted as the parent compound or metabolites, or both, in urine of rodents and rabbits. When administered by gavage, isophorone caused fibrosarcoma of the subcutis, mesenchymal tumours (fibroma, fibrosarcoma, neurofibrosarcoma, or sarcoma; combined) of the skin or subcutis, hepatocellular adenoma or carcinoma (combined), and malignant lymphoma of the haematopoietic system in male mice; and preputial gland carcinoma, and tubular cell adenoma or adenocarcinoma (combined) of the kidney in male rats.[11] The mechanistic evidence across different experimental systems was suggestive but inconsistent for genotoxicity, and suggestive for other key characteristics based on a small set of studies.

We declare no competing interests.

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