Carcinogenicity of chemicals in industrial and consumer products, food contaminants and flavourings, and water chlorination byproducts

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Monograph Working Group Members

D DeMarini—Chair (USA); M Baril (Canada); F Le Curieux (Finland); D W Lachenmeier (Germany); C Leclercq (Italy); H Tsuda (Japan); R A Woutersen (Netherlands); C M Villanueva (Spain); J C Caldwell, M F Cesta, J C Corton, J K Dunnick, M D Friesen, R A Herbert, R M Lunn, R Melnick, F E Mirer, I Rusyn (USA)

Conflicts of interest
None

Invited specialists
None

In October, 2009, the International Agency for Research on Cancer (IARC) completed a review of the more than 100 agents classified as "carcinogenic to humans" (Group 1). These assessments will be published in six parts as Volume 100 of the IARC Monographs (Volumes 100A–F).

The IARC Monographs Programme has now resumed its regular schedule and in February, 2011, 18 scientists from eight countries met to assess the carcinogenicity of 18 chemicals present in industrial and consumer products or food—as natural constituents, contaminants, or flavourings—or occurring as water chlorination byproducts (table). Some of these agents are discussed in more detail below. These assessments will be published as Volume 101 of the IARC Monographs.[1]

For most of the substances reviewed, there were many sources of exposure, including complex mixtures at the workplace, food, drinking water, consumer products, and the environment. For example, diethanolamine is one of many constituents of metalworking fluids to which workers are exposed, and bromochloroacetic acid, dibromoacetic acid, and dibromoacetonitrile are three of the many chlorination byproducts present in drinking water and swimming pools. For this reason, there were no or very few epidemiological studies assessing agent-specific exposure.

In view of the limited agent-specific information from epidemiological studies, our assessments relied mainly on carcinogenicity bioassays. The relevance to humans of the tumours reported in these studies was discussed with regard to mechanisms of carcinogenesis—eg, genotoxicity or other effects, such as peroxisome proliferation and PPARalpha activation, alpha$_{2u}$-globulin nephropathy, and metabolism via CYP2F enzymes. For several of the compounds, similar tumour types, with low spontaneous incidences, were observed. For all 18 agents, the Working Group concluded that there was "sufficient evidence of carcinogenicity in experimental animals", leading to an overall evaluation—in the absence of adequate epidemiological information—of "possibly carcinogenic to humans" (Group 2B). The only exception was 2-nitrotoluene (Group 2A).

Occupational exposure to 2-nitrotoluene occurs during production of dyes, rubber chemicals, agricultural chemicals, and explosives. In a Good Laboratory Practice (GLP) feeding study, 2-nitrotoluene caused an unusually high incidence of tumours in rats, including fibrosarcomas of the skin, malignant mesotheliomas, mammary gland fibroadenomas (also in male rats), and cholangiocarcinomas. Even short exposures of 13 or 26 weeks caused cancer in rats. In mice, unusually high incidences of carcinomas of the caecum and haemangiosarcomas were noted.[2] In rodents, metabolism of 2-nitrotoluene results in formation of an electrophilic DNA-reactive compound that forms adducts in the liver.[3] A similar pathway is likely to exist in humans. Indeed, workers exposed to a mixture of nitrotoluenes, including 2-nitrotoluene, had mutagenic urine and increased levels of chromosome aberrations in circulating blood lymphocytes. The adduct 2-methylaniline-haemoglobin (specific for 2-nitrotoluene exposure) was also found in exposed workers.[4] In rats, this biomarker correlated with liver–DNA adducts.[3] Moreover, mutations were found in *Catnb*, *p53*, and *K-Ras* in tumours of the caecum

	Use, occurence	Group
2-nitrotoluene*	Dye precursor	2A
1-amino-2,4-dibromoanthraquinone	Dye precursors	2B
Anthraquinone		2B
Cumene	Industrial chemical	2B
Di(2-ethylhexyl)phthalate*	Present in consumer products (plasticiser), food contaminant	2B
Diethanolamine*	Present in consumer products, additive in metalworking fluids	2B
Coconut oil diethanolamine condensate	Present in consumer products	2B
Benzophenone	Industrial chemicals, food flavourings, natural occurrence in food, present in consumer products	2B
2,4-hexadienal		2B
Methyleugenol		2B
Methyl isobutyl ketone		2B
1,3-dichloro-2-propanol	Food processing contaminants	2B
3-monochloro-1,2-propanediol		2B
2-methylimidazole	Industrial chemical	2B
4-methylimidazole	Food contaminant, industrial chemical	2B
Bromochloroacetic acid	Water disinfection byproducts	2B
Dibromoacetic acid		2B
Dibromoacetonitrile*		2B

*Previously evaluated as "not classifiable as to its carcinogenicity to humans" (Group 3).

Table: **Agents assessed by the IARC Monograph Working Group**

in mice, which are common features of human colon cancer.[5] In view of these mechanistic considerations, and of the extraordinarily early onset and high tumour incidences reported, 2-nitrotoluene was placed in Group 2A, "probably carcinogenic to humans".

The general population is exposed to 4-methylimidazole through its presence in class-III and class-IV caramels, which are widely used colourants, particularly in beverages. 4-Methylimidazole was tested for carcinogenicity in mice and rats in a GLP feeding study, and caused increased incidences of alveolar and bronchiolar carcinomas in male and female mice, and of mononuclear cell leukaemia in female rats.[6] The mechanisms of carcinogenesis were not elucidated.

Di(2-ethylhexyl)phthalate (DEHP) is widely used as a plasticiser. The general population is exposed to DEHP through leaching from plastic medical devices, such as blood bags and medical tubing, and as a contaminant of food packaged in DEHP-containing materials. DEHP was tested for carcinogenicity by oral (feed) exposure in mice and rats; hepatocellular adenomas and carcinomas were consistently increased in both species. Additional studies found an increased incidence of pancreatic acinar-cell adenomas in male rats,[7] and an increased incidence of Leydig-cell tumours in rats.[8] DEHP was previously evaluated as "not classifiable as to its carcinogenicity to humans" (Group 3). The previous Working Group argued that DEHP caused liver tumours in rats and mice by a non-DNA-reactive mechanism involving peroxisome proliferation, which was considered not relevant to humans.[9] Since then, additional mechanistic information has become available, including studies with DEHP in peroxisome proliferator-activated receptor alpha (*PPARalpha*)-null mice,[10] studies with several transgenic mouse strains carrying human *PPARalpha* or with hepatocyte-specific constitutively activated PPARalpha,[11,12] and a study in humans exposed to DEHP from the environment.[13] Indeed, activation of *PPARalpha* and the subsequent downstream events are an important mechanism of DEHP-induced carcinogenesis in rats and mice. Data from these new studies suggest that many molecular signals and pathways in several cell types in the liver, rather than a single molecular event, contribute to cancer development in rodents. Thus, the Working Group concluded that the human relevance of the molecular events leading to DEHP-induced cancer in several target tissues (eg, liver and testis) in rats or mice could not be ruled out, resulting in the evaluation of DEHP as a Group-2B agent, rather than Group 3.

For agents with "sufficient evidence of carcinogenicity in experimental animals" and no or limited epidemiological data, rigorous consideration of molecular mechanisms is needed to inform cancer-hazard classification. Thorough studies of molecular changes induced in relevant animal models and in human tissue samples were influential for the overall evaluations in this Working Group meeting.

Yann Grosse, Robert Baan, Béatrice Secretan-Lauby, Fatiha El Ghissassi, Véronique Bouvard, Lamia Benbrahim-Tallaa, Neela Guha, Farhad Islami, Laurent Galichet, Kurt Straif, on behalf of the WHO International Agency for Research on Cancer Monograph Working Group
International Agency for Research on Cancer, Lyon, France

We declare that we have no conflicts of interest.

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