GENERAL REMARKS

This hundred-and-first volume of the *IARC Monographs* contains evaluations of the carcinogenic hazard to humans of some chemicals present in industrial and consumer products, food contaminants and flavourings, and water chlorination by-products. Among these, dibromoacetonitrile (Volume 71), 2-nitrotoluene (Volume 65), diethanolamine and di(2-ethylhexyl) phthalate (Volume 77) had been evaluated previously. A summary of the findings of this volume appears in *The Lancet Oncology* (Grosse *et al.*, 2011).

Assessment, quantification and relative contributions of sources of exposure

Human exposures to potentially carcinogenic agents may result from complex mixtures in the air, water, food and certain occupations, which make the assessment of their risk for cancer difficult, as exemplified by several agents evaluated in this volume.

Most of the agents reviewed in this volume of *IARC Monographs* do not have a single source and humans may be exposed occupationally, or through food, drinking-water and the environment. Quantitative determination of the most important sources of human exposure is relevant, and has been attempted by the Working Group when valid information was available in the scientific literature. For a few agents, however, quantitative information on many — if not all — sources of exposure was lacking or inconclusive. An example is methyleugenol, for which the daily estimates of dietary exposure from a given source (e.g. basil) varied over three orders of magnitude from the microgram to the milligram per kilogram of body weight range, and thus complicated relative comparisons with other sources.

Several of the substances reviewed in this volume may be contained in foods and beverages. They may either occur naturally (e.g. methyleugenol, 2,4-hexadienal, methyl isobutyl ketone or benzophenone), be formed as a contaminant during food processing (e.g. 3-monochloro-1,2-propanediol, 1,3-dichloro-2-propanol or 2,4-hexadienal), migrate from packaging materials (e.g. di(2-ethylhexyl) phthalate or benzophenone) or be added directly (e.g. as flavouring compounds such as methyleugenol, 2,4-hexadienal, methyl isobutyl ketone or benzophenone) or occur indirectly as natural constituents of or contaminants in food additives (e.g. 4-methylimidazole in caramel colouring). The Working Group noted either the general absence of data on occurrence in food (e.g. 2-methylimidazole) or the availability of only comparatively old data (e.g. 4-methylimidazole). For some agents, large sets of data from food surveys are available (e.g. 3-monochloro-1,2-propanediol and

1,3-dichloro-2-propanol) but these may not reflect the current situation of the market, because the surveys were often conducted before regulatory limits came into force or before measures to mitigate exposure were implemented by industry.

Epidemiology of complex exposures

In this volume of *IARC Monographs*, the evaluation of the risk for cancer attributed to specific agents was limited by the paucity of epidemiological studies specific for those chemicals. One study was identified that evaluated urinary metabolites of di(2-ethylhexyl) phthalate, but was limited by its cross-sectional design: exposure was assessed at the time of disease. Prospective studies linking biomarkers of exposure to di(2-ethylhexyl) phthalate with cancer risk may be feasible in view of current efforts to collect population data. For other substances (e.g. 2-nitrotoluene, anthraquinone, diethanolamine, bromochloroacetic acid, dibromoacetic acid and dibromoacetonitrile), studies of workers or people exposed to the substances were available but were limited by a lack of a chemical-specific exposure assessment or by the fact that exposure was to a mixture of chemicals. For example, workers exposed to 2-nitrotoluene are exposed to other carcinogens, such as *ortho*-toluidine, or mutagens, such as tri- and dinitrotoluenes. The use of mechanistic data and molecular epidemiological approaches should help in the evaluation of complex mixtures, and to disentangle the effects of cancer risks from a specific substance when people are exposed to that substance in conjunction with known or suspected carcinogens.

Metalworking fluids

This volume of *IARC Monographs* evaluated the carcinogenicity of diethanolamine (IARC *Group 2B*) and coconut oil diethanolamine condensate (IARC *Group 2B*). These constituents of metalworking fluids, which are used to lubricate, cool and flush chips in the machining, cutting and grinding of metal to manufacture items such as engine blocks, gears, transmissions, chassis parts and other metal products. The four major categories of metalworking fluids are: straight oils (generally mineral oils), soluble oils, semi-synthetic (straight oils diluted with water and additives) and synthetic (additives and water without oils). Ethanolamines — either diethanolamine or triethanolamine — are commonly added to soluble, semi-synthetic or synthetic metalworking fluids. Diethanolamine may also be present as an unintended impurity of intended triethanolamine or fatty-acid diethanolamide additives. Workers are exposed by inhalation of aerosols or skin contact. Since the mid-1940s, water-based fluids have been increasingly used in high-production operations, such as those in the automobile industry. The proportion of water-based fluids that contain diethanolamine and that of processes that used water-based fluids over time cannot be estimated precisely from the available literature. However, it appears that most workers in modern machining plants probably had some exposure to diethanolamine (NIOSH, 1998).

The carcinogenicity of diethanolamine and the epidemiological literature on metalworking fluids have been reviewed previously (IARC, 2000), when a few cohort studies of workers exposed to water-based fluids were identified. The most prominent was a large cohort study of workers in the automobile

parts manufacturing industry in the United States of America from which several nested studies were conducted (Eisen *et al.*, 1992). The current Working Group identified an update of this cohort (Eisen *et al.*, 2001) from which another series of substudies was conducted, as well as an update of another cohort of automobile industry workers (Kazerouni *et al.*, 2000) and a population-based case–control study (Colt *et al.*, 2011). Associations with an increased incidence of cancer at various tumour sites were noted in the majority of these studies (Mirer, 2003, 2010; Savitz, 2003).

In this volume of *IARC Monographs* and the previous *Monograph* (IARC, 2000), the Working Groups concluded that evidence from this body of literature could not be used for a specific evaluation of the carcinogenicity of diethanolamine because of the potential presence of other agents such as *N*-nitrosodiethanolamine (IARC *Group 2B*), poorly refined mineral oils and chlorinated paraffins. The Working Group did not evaluate the carcinogenicity of metalworking fluids as an exposure circumstance. The Advisory Group meeting that discussed future priorities for the *IARC Monographs* Programme (IARC, 2008) recommended that the evaluation of metalworking fluids should have medium priority.

Disinfection by-products

Various disinfection by-products, some of which are evaluated in this volume of *IARC Monographs*, are also encountered almost exclusively through the drinking of, and swimming, showering and bathing in disinfected water.

Disinfection of drinking-water is one of the major public health interventions in history, and has reduced mortality from waterborne infectious diseases. Disinfection of drinking-water and water used in swimming pools is a necessity. However, disinfectants are highly reactive chemicals that, besides inactivating microorganisms, react with organic matter to form undesired by-products. Chlorine, in the form of chlorine gas or hypochlorite solution, has been the most widely used disinfectant worldwide. By-products of chlorination, and specifically trihalomethanes, were first detected in the early 1970s. Four trihalomethanes (chloroform [IARC *Group 2B*], bromodichloromethane [IARC *Group 2B*], dibromochloromethane [IARC *Group 3*] and bromoform [IARC *Group 3*]), together with nine bromine- and chlorine-based haloacetic acids, are the main by-products of chlorination on a weight basis. The chlorine-bromine speciation depends on the bromine content of the raw water. Trihalomethanes and haloacetic acids are regulated in the European Union, the USA and other countries.

Chlorine is being progressively replaced by alternative disinfectants to meet these regulations. Although the use of alternatives, including ozone, chlorine dioxide and chloramines, reduces the formation of the regulated trihalomethanes and haloacetic acids, other disinfection by-products are formed. For example, when raw water contains bromine, bromate is formed by ozonation. Chlorate and chlorite are by-products of disinfection with chlorine dioxide, and the use of chloramines may result in the formation of iodinated trihalomethanes and nitrogenated by-products, such as *N*-nitrosodimethylamine (IARC *Group 2A*). The potential health impact of these alternative disinfection by-products is mainly unknown.

No epidemiological studies have evaluated exposure specifically to bromochloroacetic acid, dibromoacetic acid or dibromoacetonitrile, the three disinfection by-products evaluated in this volume.

Human exposure to these chemicals always occurs in mixtures; other disinfection by-products in chlorinated drinking-water and chlorinated swimming pool water include more than 700 chemicals. The physical properties of these chemicals differ and determine their routes of exposure. Inhalation of volatile disinfection by-products, such as trihalomethanes, occurs in showers and swimming pools. Dermal absorption of trihalomethanes and other skin-permeable compounds may occur in showers, baths and swimming pools. However, ingestion is the main pathway of exposure for other disinfection by-products, such as haloacetic acids, because of their low volatility and skin permeability. Due to the complexity of the mixtures and exposure scenarios, future evaluations of the effects of disinfection by-products in humans should reflect actual exposure situations rather than isolating individual chemicals.

Several studies have been conducted during the last three decades to evaluate the risk for cancer associated with disinfection by-products. Because the characteristics of raw water and the types of treatment used are the main determinants of the concentration of disinfection by-products formed, many epidemiological studies have used such variables as surrogates of exposure to these compounds (e.g. chlorinated surface versus non-chlorinated water). The most recent studies quantified exposure to trihalomethanes as a proxy for the whole mixture. These have been reviewed in the Introduction to the *Monographs* on Bromochloroacetic acid, Dibromoacetic acid and Dibromoacetonitrile. However, evidence in humans is insufficient to attribute the observed effects to a single agent. Other disinfection by-products evaluated by the *IARC Monographs* programme are shown in Table 1.

The use of biomarkers has been limited in epidemiological studies of cancer that evaluated the effects of exposure to disinfection by-products. These compounds do not accumulate in the body, and no biomarkers of internal dose that reflect long-term exposure have been identified. Studies that evaluate molecular markers of genetic susceptibility may help to disentangle the mechanisms and effects of specific disinfection by-products.

Using data on genotypes and other molecular analyses, some of the components of complex mixtures may be identified as a contributing factor in the causation of cancers associated with exposure to these compounds. For example, in a case–control study of urinary bladder cancer in Spain, Cantor *et al.* (2010) showed that the risk for bladder cancer increased sixfold after exposure to drinking-water, primarily through showering, bathing and swimming, among people who had both the glutathione *S*-transferase T-1 genotype, which metabolizes brominated trihalomethanes to mutagens, and a particular single-nucleotide polymorphism in glutathione *S*-transferase Z genotype, which metabolizes haloacetic acids. This type of molecular epidemiology pointed to brominated trihalomethanes and haloacetic acids as critical components with a potential causative role in bladder cancer associated with exposure to drinking-water.

The interpretation of the occurrence of rare tumours

The Working Group noted that several of the chemicals evaluated in this volume of *IARC Monographs* induced several unusual (rare) neoplasms in animal studies, including: hepatoblastomas in mice, histiocytic sarcomas in mice, mammary gland tumours in male rats, neuroendocrine tumours of the glandular stomach in mice and rats, urinary bladder tumours in rats, large intestinal tumours in mice and rats, glandular stomach adenomas in male rats, squamous-cell papillomas and

Table 1 Evaluations of chlorinated drinking-water, some chemicals used in the chlorination of drinking-water and some chlorination by-products, from this and previous *IARC Monographs* volumes

Agent	Degree of evidence of carcinogenicity		Overall evaluation of carcinogenicity to humans	*IARC Monographs* volume (year)
	Humans	Experimental animals		
Chlorinated drinking-water	I	I	3	Volume 52 (1991)
Some chemicals used in the disinfection of drinking-water				
Sodium chlorite	ND	I	3	Volume 52 (1991)
Hypochlorite salts	ND	I	3	Volume 52 (1991)
Chloramine	I	I	3	Volume 84 (2004)
Disinfection by-products				
Trihalomethanes				
Chloroform	I	S	2B	Volume 73 (1999)
Bromodichloromethane	I	S	2B	Volume 52 (1991)
Dibromochloromethane	I	L	3	Volume 52 (1991)
Bromoform	I	L	3	Volume 52 (1991)
Haloacetic acids				
Dichloroacetic acid	I	S	2B	Volume 84 (2004)
Trichloroacetic acid	I	L	3	Volume 84 (2004)
Bromochloroacetic acid	I	S	2B	Volume 101 (this volume)
Dibromoacetic acid	I	S	2B	Volume 101 (this volume)
Halogenated acetonitriles				
Bromochloroacetonitrile	ND	I	3	Volume 52 (1991)
Chloroacetonitrile	ND	I	3	Volume 52 (1991)
Dibromoacetonitrile	ND	I	3	Volume 52 (1991)
Dichloroacetonitrile	ND	I	3	Volume 52 (1991)
Trichloroacetonitrile	ND	I	3	Volume 52 (1991)
Dibromoacetonitrile	ND	S	2B	Volume 101 (this volume)
Chloral hydrate	I	L	3	Volume 84 (2004)
3-Chloro-4-(dichloromethyl)-5-hydroxy-2(5*H*)-furanone (MX)	I	L	2B*	Volume 84 (2004)
Potassium bromate	I	S	2B	Volume 73 (1999)

*Other relevant data were used to upgrade the overall evaluation.
I, inadequate evidence; L, limited evidence; ND, no data; S, sufficient evidence; for definition of the degrees of evidence and evaluations, see the Preamble

carcinomas of the tongue and oral cavity in rats, squamous-cell carcinomas of the tongue in male mice, squamous-cell papillomas and carcinomas of the forestomach in mice and rats, mesotheliomas in male rats, renal mesenchymal tumours in female rats, and adenomas of the respiratory epithelium of the nose in rats.

Several chemicals evaluated in this volume induce the above relatively rare neoplasms and are also mutagenic. Although each evaluation is for a specific chemical, there were similarities in the mutagenicity and carcinogenicity profiles among several members of the group that are structurally related, such as bromochloroacetic acid and dibromoacetic acid, which both induce hepatoblastomas in mice and mesotheliomas in rats. The consistency of these rare tumours lends biological plausibility to the findings and raises concerns of potential human carcinogenicity. To dismiss the occurrence of rare tumours would seem to be unwise. This observation supports the criteria in the Preamble that "a single study in one species and sex might be considered to provide *sufficient evidence of carcinogenicity* when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites."

The IARC criteria regarding *sufficient evidence of carcinogenicity* in experimental animals may, under some circumstances, require a judgement call on the "appropriate combination of benign and malignant neoplasms" when an increase in the incidence of malignant tumours only is not observed. The Working Group felt that the rarity of the incidence of the tumour may also be taken into account, meaning that a rare neoplasm observed as the combination of some benign and a few malignant tumours could demonstrate the progression to cancer.

Dose differences between rodent studies and human exposures

For several chemicals considered in this volume, data showed that the chemical in question induced tumours in rodents at quite high doses; however, biomonitoring or feeding studies in humans showed that the typical or maximum doses to which humans are exposed are considerably lower than those used in rodent studies. For example, such analyses showed that the lowest dose of methyleugenol used in rodent studies that induced tumours is 10 000 times higher than the average or highest dose observed in humans in biomonitoring or feeding studies. Thus, the question arises whether the doses to which humans are exposed are sufficient to present a risk for cancer. An additional complication is that, for some agents, there was little evidence of mutagenicity. Thus, do low doses of non-genotoxic rodent carcinogens induce tumours in humans? The Working Group considered this to be an issue of potency or risk and not relevant to hazard identification. Thus, despite the differences in exposure, a chemical could be evaluated as a cancer-causing agent at some level in humans, although the actual risk might be quite low.

Single mode-of-action hypotheses

Several chemicals evaluated in this volume induced tumours in experimental animals that were associated with α2u-globulin nephropathy, activation by pulmonary cytochrome P450 2F or peroxisome proliferation. However, advances in molecular biology have revealed that, subsequent to exposures, alterations in multiple processes lead to environmental or occupational carcinogenesis.

The potential roles of various cellular and molecular activities were considered in the evaluations of mechanistic events that underlie the carcinogenicity of the agents reviewed. For chemicals that elicit genotoxicity, this response cannot be excluded as a major contributing factor to the cancer outcome. For some chemicals, commonly used activation systems may not be adequate to detect genotoxic effects, e.g. the need for nitroreductase activity to convert 2-nitrotoluene to a mutagenic intermediate. For chemicals that do not show genotoxicity in a large battery of screening assays, it is frequently noted that multiple signalling pathways contribute to an altered phenotype. Single mode-of-action hypotheses require extensive testing, because a narrow focus on single pathways may result in oversimplified interpretations of the complex multiple pathways that lead to tumour induction.

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