GENERAL REMARKS

This one-hundred-and-fifteenth volume of the *IARC Monographs* contains evaluations of the carcinogenic hazard to humans of seven industrial chemicals (*N,N*-dimethylformamide, 2-mercaptobenzothiazole, hydrazine, tetrabromobisphenol A, 1-bromopropane, 3-chloro-2-methylpropene, and *N,N*-dimethyl-*p*-toluidine) to which workers or the general population are or can be potentially exposed. All seven agents were accorded high or medium priority for evaluation in the *IARC Monographs* programme by an Advisory Group that met in 2014 (Straif et al., 2014). 3-Chloro-2-methylpropene was evaluated previously in Volume 63 of the *IARC Monographs* (IARC, 1995) as *not classifiable as to its carcinogenicity to humans* (Group 3). Hydrazine was evaluated previously as *possibly carcinogenic to humans* (Group 2B) and *N,N*-dimethylformamide as *not classifiable as to its carcinogenicity to humans* (Group 3) in Volume 71 of the *IARC Monographs* (IARC, 1999). Since the previous evaluations, new data have become available. A summary of the findings of this volume appears in *The Lancet Oncology* (Grosse et al., 2016).

High production volume chemicals and exposure measurement data

Four "high production volume" chemicals (*N,N*-dimethyl-*p*-toluidine, 2-mercaptobenzothiazole, tetrabromobisphenol A, and *N,N*-dimethylformamide) were evaluated. The Working Group noted that for two of these (*N,N*-dimethyl-*p*-toluidine and 2-mercaptobenzothiazole) no data on exposure measurement were available in occupational settings or the general population.

Data on exposure measurement were also lacking for two other chemicals evaluated in the present volume (3-chloro-2-methylpropene and hydrazine).

Isoniazid

Hydrazine is a metabolite of isonicotinic acid hydrazide (isoniazid), which was evaluated in Supplement 7 of the *IARC Monographs* as *not classifiable as to its carcinogenicity to humans* (Group 3) (IARC, 1987). Data on hydrazine and its metabolites from studies on isoniazid and isoniazid metabolites are included in Section 4 of the monograph on hydrazine, but isoniazid was not re-evaluated.

Disruption of the thyroid hormone pathway

The regulation of thyroid hormone action is perhaps more complex than the regulation of action of other hormones that act on nuclear receptors. This is because the predominant hormone in the blood, thyroxine (T_4), must be actively transported across membranes. In the central nervous system, T_4 must be taken up by glial cells, converted to T_3, and then be transported to neurons (Bernal et al., 2015). The conversion of T_4 to T_3 itself represents another regulated step in the control of thyroid hormone action. This complexity is difficult to account for when considering the impact of environmental chemicals such as tetrabromobisphenol A on thyroid hormone action. In addition, the effect of chemicals on the thyroid hormone receptor itself probably depends on the receptor isoform (TRα or TRβ), as well as the DNA motif to which it is bound (Gilbert et al., 2012). This is important because the measures of thyroid "disruption" in humans are a measure of hormone levels in the blood, which may not faithfully capture the impact of chemical exposures on thyroid hormone action (Bansal et al., 2014). Moreover, while the concentration of thyroid hormone in the blood is maintained within a relatively narrow range under normal conditions, there is significant variation among individuals in the set-point around which hormone levels are maintained (Andersen et al., 2002, 2003). Thus it is to be expected that there will be variation between studies – in humans and in vitro – employing different cell lines, different receptor isoforms, and different strategies for evaluating the impact of a particular chemical on the thyroid system. Finally, and because disruption of pathways involving the thyroid hormone receptor is closely associated with the development of specific cancers (Rosen & Privalsky, 2011), the effects of chemical exposures on thyroid hormone receptor should not be ignored.

Evaluation of data on the mechanisms of cancer

In its evaluation of data on mechanisms of carcinogenesis, the Working Group used the procedures first introduced in Volume 112 of the *IARC Monographs* for assessing the strength of evidence with respect to 10 key characteristics of carcinogens (Smith et al., 2016) and for reviewing data from large-scale toxicity testing programmes (IARC, 2017).

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