GENERAL REMARKS

This one-hundred-and-twelfth volume of the *IARC Monographs* contains evaluations of the carcinogenic hazard to humans of five pesticides: diazinon, glyphosate, malathion, parathion, and tetrachlorvinphos.

Most uses of the insecticide diazinon have been restricted in the USA, Canada, and the European Union, and parathion has been severely restricted globally since the 1980s. Tetrachlorvinphos is banned in the European Union, but continues to be used in the USA and elsewhere as an insecticide on animals, including in pet flea collars. Exposures to the insecticide malathion may occur through its continued use in agriculture, residential, or public-health applications, notably mosquito control. The herbicide glyphosate is structurally similar to other organophosphate pesticides, but is toxicologically distinct and does not inhibit cholinesterase activity. Glyphosate has the highest production volumes of all herbicides and is currently used worldwide in agriculture, forestry, urban, and home applications.

The organophosphate insecticides are part of the grouping of "non-arsenical insecticides," that in 1991 were classified as Group 2A (*probably carcinogenic to humans*) (IARC, 1991). This classification applies to the group of chemicals as a whole, and not necessarily to all individual chemicals within the group. Regarding the individual agents, malathion, parathion, and tetrachlorvinphos were previously evaluated by a Working Group in 1987 and were assigned to Group 3 (*not classifiable as to its carcinogenicity to humans*). The *IARC Monographs* programme had not previously evaluated glyphosate or diazinon. In light of the new data published since any prior evaluations, especially on cancer epidemiology and cancer mechanisms, organophosphate pesticides were accorded priority for evaluation by the *IARC Monographs* during 2015–2019 (Straif et al., 2014). A systematic and objective approach using chemoinformatics, database integration, and automated text mining (Guha et al., 2016) informed selection of agents evaluated in Volume 112. A summary of the findings of this volume appears in *The Lancet Oncology* (Guyton et al., 2015).

Use of systematic review approaches and tools

The principles for evaluating studies and integrating evidence for the *IARC Monographs* are outlined in the Preamble. An Advisory Group to recommend Priorities for *IARC Monographs* during 2015–2019 (Straif et al., 2014) endorsed these principles and encouraged the *Monographs* programme to explore use of new systematic review tools in a manner consistent with them, particularly with respect to the evaluation of mechanistic data. The Advisory Group's report noted "the need for systematic identification of mechanistic data with transparent selection of publications was recognized, in order to clarify mechanistic processes" (Straif et al.,

2014). Accordingly, several new practices were implemented starting from Volume 112 of the *Monographs*, as documented in the "Instructions for authors" of the *IARC Monographs*. In particular, the evaluation introduced a new approach for objectively and systematically collating and analysing mechanistic information based on 10 key characteristics of carcinogens. An expert Working Group convened by IARC concluded that carcinogens in Group 1 (*carcinogenic to humans*) commonly show one or more of these 10 key characteristics (Smith et al., 2016).

In addition, this volume of the *Monographs* made systematic use of large-scale toxicity screening data that are publicly available from government databases for the first time. Specifically, high-throughput screening (HTS) data generated by the Tox21 and ToxCast research programmes of the government of the USA (Kavlock et al., 2012; Tice et al., 2013) were analysed to inform evaluations about the in-vitro bioactivity of the chemicals included in *IARC Monographs* Volume 112. Such data were used to provide supporting information and to fill data gaps in the determination on whether several of the chemicals under evaluation (diazinon, malathion, parathion, and tetrachlorvinphos) may act through the key characteristics of known human carcinogens (Smith et al., 2016).

Finally, the "Instructions to authors" (IARC, 2014) outline the literature search strategy, inclusion and exclusion criteria, databases, tools and other elements of the systematic reviews. These practices are also consistent with other authoritative recommendations on the conduct of systematic literature reviews, such as those from the United States National Research Council panels on formaldehyde (National Research Council, 2011) and Integrated Risk Information System (IRIS) process (National Research Council, 2014).

Critical review of exposure assessment methods

Section 1 of this volume includes a critical review of the exposure assessment methods used in the pertinent epidemiological studies (see Section 1.4.2 of Malathion). Assessment of exposure to the agents considered here is challenging due to the predominant role of dermal exposure in occupational settings, correlated exposures to multiple pesticides, and the lack of persistent biological markers of long-term exposure. The Working Group considered the strengths and limitations of the exposure assessment methods used in each study and took these into account in its evaluations.

Studies of cancer in humans

The epidemiological database for evaluating the carcinogenicity to humans of the agents considered here is relatively sparse, and there are no studies of workers manufacturing these pesticides. Several major studies, all conducted in North America, provided data for several of the agents evaluated in this volume (see the Monograph on Malathion, Table 2.1). All except one of the cohort studies investigated the occurrence of cancer among agricultural or pest-control workers or their families. Case–control studies in the USA, Canada, Sweden, and France, most population-based, also provided pertinent data. One of these studies assessed pesticide exposures using a job-exposure matrix, while the others used questionnaires. Although these studies investigated associations involving a diverse range of cancers, the largest body of data available for evaluation concerned non-Hodgkin lymphoma and other lympho-haematopoietic cancers. A meta-analysis of the associations between non-Hodgkin lymphoma and exposure to malathion, diazinon, or glyphosate was also taken into account in considering the evidence for those pesticides.

Studies in experimental systems

In the interests of transparency, IARC evaluations rely only on data that are in the public domain and available for independent scientific review. The evaluation of glyphosate by the Working Group included any industry studies that met these criteria. However, they did not include data from summary tables in online supplements to published articles, which did not provide enough detail for independent assessment. This was the case for some of the industry studies of cancer in experimental animals.

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