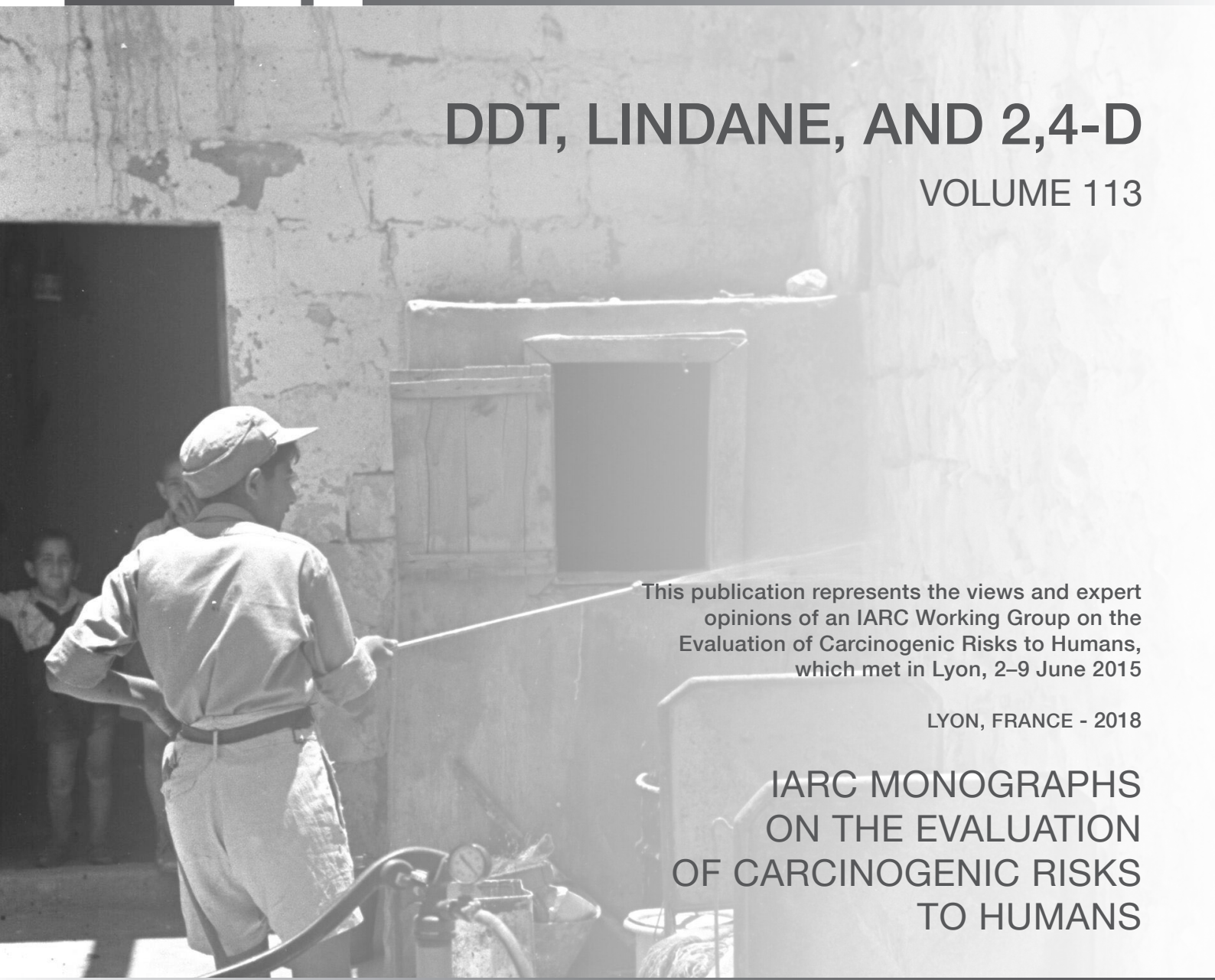
IARC MONOGRAPHS



DDT, LINDANE, AND 2,4-D

VOLUME 113

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IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer

World Health Organization

GENERAL REMARKS

This one-hundred-and-thirteenth volume of the *IARC Monographs* contains evaluations of the carcinogenic hazard to humans of three pesticides: DDT, lindane, and 2,4-D. DDT (1,1′-(2,2,2-trichloro-ethylidene)bis(4-chlorobenzene)) and lindane (γ-hexachlorocyclohexane) belong to the family of organochlorine insecticides and 2,4-D (2,4-dichlorophenoxyacetic acid) is a chlorophenoxy herbicide. Organochlorine pesticides were accorded priority for evaluation in the *IARC Monographs* programme by an Advisory Group that met in 2014 (Straif et al., 2014). A systematic and objective approach using chemoinformatics, database integration, and automated text mining (Guha et al., 2016) also informed selection of the agents evaluated in this volume. A summary of the findings of this volume appears in *The Lancet Oncology* (Loomis et al., 2015).

DDT and lindane

DDT is one of the best known and most studied chemicals of environmental concern. It was introduced as an insecticide in the 1940s and came into widespread use for disease vector control and agriculture after the Second World War. DDT was an important tool in national and international efforts to eradicate malaria, including the WHO Global Programme for Malaria Eradication; spraying with DDT has been credited with helping to reduce the worldwide burden of malaria. However, by the 1960s concerns began to emerge because of the environmental persistence of DDT and its adverse effects on wildlife, and by the 1970s experimental data from studies in experimental animals began to suggest that organochlorine pesticides, including DDT, might have carcinogenic activity. Based largely on these data, the carcinogenicity of DDT was reviewed by the Working Group early in the history of the *IARC Monographs* in Volume 5, *Some organochlorine pesticides* (IARC, 1974), and again in Supplement 7 and Volume 53 (IARC, 1987; 1991). In these evaluations, data from experimental animals provided *sufficient evidence* of carcinogenicity, while the data from humans provided *inadequate evidence* (IARC, 1987; 1991), resulting in a classification of *possibly carcinogenic to humans* (Group 2B). Most uses of DDT other than limited indoor spraying for malaria control are now severely restricted because of its persistence and environmental effects. Nevertheless, DDT is still detectable in the environment, in food, and in the blood and adipose tissue of people and animals worldwide.

Lindane is the γ isomer of hexachlorocyclohexane; it is the only isomer of that series with insecticidal properties, although other forms, notably the more stable α and β isomers, can be present in technical-grade lindane and are sometimes measured as surrogate indicators of exposure to lindane. Like DDT, lindane was

commercialized as an insecticide in the 1940s and is now largely banned due to its toxicity. It was used mainly in agriculture, with use peaking in the 1950s. Lindane was first evaluated for carcinogenicity in Volume 5 of the *IARC Monographs*, and was re-evaluated in Volume 20 and Supplement 7; in all of these evaluations, lindane was considered within the class of hexachlorocyclohexanes, which were classified as *possibly carcinogenic to humans* (Group 2B).

Although active use of DDT and lindane has greatly diminished, research into their carcinogenicity has continued, and new epidemiological and mechanistic data have become available since these compounds were last evaluated by the Working Group. This new research and continuing exposure to DDT justify re-evaluation of the carcinogenicity of both pesticides.

2,4-D

Like the other pesticides evaluated in this volume, 2,4-D was introduced in the 1940s and saw increasing use in the ensuing decades. By the 1960s, it was one of the most widely used herbicide active ingredients. Besides its use in agriculture, during the war in Viet Nam 2,4-D was mixed with another chlorophenoxy herbicide, 2,4,5-T (2,4,5-trichlorophenoxyacetic acid) to produce agent orange that was used extensively as a defoliant by the United States military. 2,4-D continues to be used in substantial quantities, primarily in agriculture, and mixtures of 2,4-D and other active ingredients, including glyphosate, have recently been approved for use to combat weeds that are resistant to other herbicides.

The carcinogenicity of 2,4-D was first evaluated by the Working Group in Volume 15 of the *IARC Monographs* (IARC, 1977) and in Supplement 4 (IARC, 1982), when the evidence for carcinogenicity in humans and animals was found to be *inadequate*. When next evaluated in Volume 41 and Supplement 7 (IARC, 1986; 1987), 2,4-D was considered with the class of chlorophenoxy herbicides, which included several other compounds in addition to 2,4-D and 2,4,5-T. By that time, it had been recognized that commercial preparations of chlorophenoxy herbicides, particularly 2,4,5-T, were frequently contaminated with dibenzodioxins and dibenzofurans, so the evaluations of the chemical class were largely focused on the dioxins, which were subsequently classified as *carcinogenic to humans* (Group 1). Since those evaluations, the dioxin content of chlorophenoxy herbicide formulations has been reduced and epidemiological studies of 2,4-D independently from dioxin and related herbicides have been conducted. In the present re-evaluation the Working Group sought to use the available data on 2,4,-D to disentangle its effects from those of associated agents. Data on 2,4,5-T, dioxin or the class of chlorophenoxy herbicides alone were therefore not considered.

Evaluation of pesticides

In evaluating the agents in this volume, the Working Group took into account several challenges that are particular to research on the carcinogenicity of pesticides.

As intentionally toxic substances, pesticides are subject to licensing and regulation, and these are generally directed towards active pesticide ingredients. For this reason, most experimental studies of pesticides evaluate these active ingredients as single substances. However, many pesticides, including lindane and 2,4-D, are marketed as commercial formulations that contain other substances in addition to the active ingredients. Consequently, epidemiological studies on pesticides almost always concern people who have been occupationally or environmentally exposed to commercial products, rather than to single substances. The Working Group considered such differences in the epidemiological and experimental data in reaching an overall evaluation.

The assessment of exposure to pesticides presents further challenges. The epidemiological studies reviewed in this volume included both studies of cancer among workers exposed occupationally to pesticides and studies of cancer risks associated with pesticide exposures in the population at large. These exposures may be assessed using one of two general approaches based either on questionnaires or on quantitative measurement of pesticides or their metabolites in biological samples from study subjects. Both types of exposure data were available for DDT and lindane, while only questionnaire-based assessments were available for 2,4-D. Although biologically based measurements are objective and quantitative, they are not necessarily superior to traditional methods, as they are potentially subject to bias related to inter- and intra-individual variability. The Working Group took both types of data into account in its evaluations.

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

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