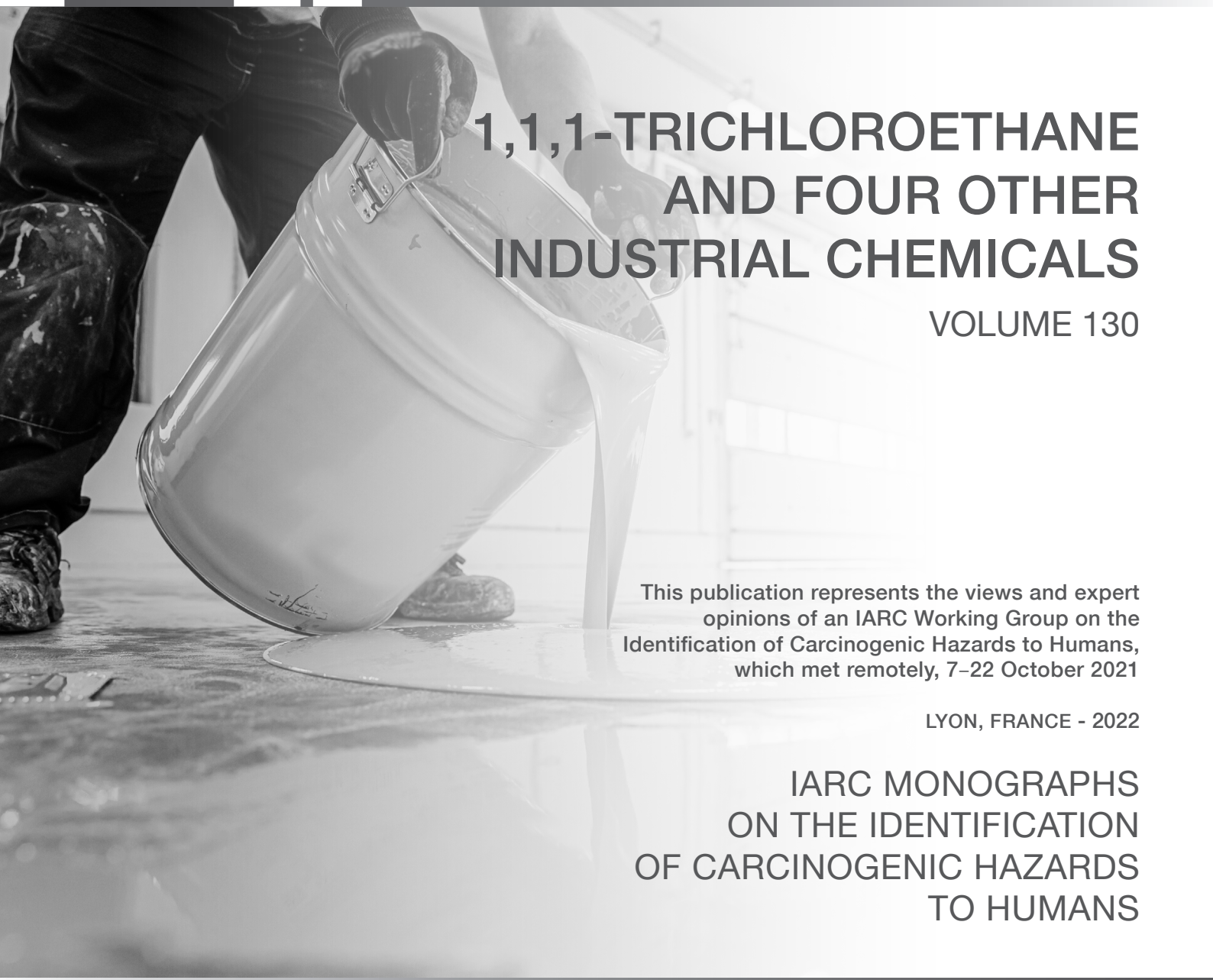
IARC MONOGRAPHS



1,1,1-TRICHLOROETHANE AND FOUR OTHER INDUSTRIAL CHEMICALS

VOLUME 130

This publication represents the views and expert opinions of an IARC Working Group on the Identification of Carcinogenic Hazards to Humans, which met remotely, 7–22 October 2021

LYON, FRANCE - 2022

IARC MONOGRAPHS ON THE IDENTIFICATION OF CARCINOGENIC HAZARDS TO HUMANS

International Agency for Research on Cancer

World Health Organization

GENERAL REMARKS

This one-hundred-and-thirtieth volume of the *IARC Monographs* contains evaluations of the carcinogenic hazard to humans of five industrial chemicals: 1,1,1-trichloroethane, 1,2-diphenylhydrazine, diphenylamine, *N*-methylolacrylamide, and isophorone. Due to the coronavirus disease (COVID-19) pandemic, this meeting was held remotely.

1,1,1-Trichloroethane was considered previously by the *IARC Monographs* programme in 1978 (IARC, 1979), 1987 (IARC, 1987), and most recently in 1998, when it was evaluated as *not classifiable as to its carcinogenicity to humans (Group 3)* (IARC, 1999). *N*-Methylolacrylamide was considered previously by the *IARC Monographs* programme in 1994 and was also evaluated as *not classifiable as to its carcinogenicity to humans (Group 3)* (IARC, 1994). 1,2-Diphenylhydrazine, diphenylamine, and isophorone have not been evaluated previously by the *IARC Monographs* programme.

The Advisory Group to Recommend Priorities for the *IARC Monographs* that met in 2019 recommended that 1,1,1-trichloroethane be evaluated with high priority; 1,2-diphenylhydrazine, diphenylamine, and *N*-methylolacrylamide with medium priority; and isophorone with low priority (IARC, 2019a; Marques et al., 2019). A summary of the findings of this volume appears in *The Lancet Oncology* (Belpoggi et al., 2021).

Occupational exposure in the past

National surveys and epidemiological studies indicate that 2–6% of North American and European populations (e.g. Silvestri et al., 1983; Talibov et al., 2014) were occupationally exposed to 1,1,1-trichloroethane in the 1980s and 1990s, although extreme reductions in use have occurred since the adoption of the Montreal Protocol on Substances that Deplete the Ozone Layer, in 1987 (UNEP, 2021). The substantial use of 1,1,1-trichloroethane in the past may have an enduring impact on cancer incidence rates for cancer types with long latency. Historical groundwater contamination with 1,1,1-trichloroethane could also remain a source of exposure in the future (Palau et al., 2016).

Availability of epidemiological data

There was a paucity of epidemiological data for agents other than 1,1,1-trichloroethane. Information on use of this agent is more limited in low- and middle-income countries than in high-income countries. Given the large number and variety of chlorinated organic solvents in commercial use, many human cancer studies only described the group or class of compounds under assessment (e.g. chlorinated aliphatic hydrocarbons), and did not name 1,1,1-trichloroethane explicitly in the abstract of their

publication. This made the identification of relevant studies in the literature search challenging. As a result, multiple literature search terms were used in title and abstract searches to capture various chemical class names in addition to the agent name. Full-text literature searches were also conducted to identify studies that did not state the agent name in the title or abstract, but that reported analyses specific to 1,1,1-trichloroethane in the body of the article. This feature of the agent is likely to be a challenge for future monographs investigating individual chemicals that belong to a broader class of compounds.

The human cancer studies investigating epidemiological associations between 1,1,1-trichloroethane exposure and cancer risk were primarily limited by challenges in the assessment of exposure. Studies with assessment of biomarkers of exposure to 1,1,1-trichloroethane were a notable research gap, as only one such study was identified. There was one study on transgenerational effects of exposure, which was another notable research gap. More generally, the number of studies per cancer site was small, and there were only two cohort studies of workers occupationally exposed to the agent.

For diphenylamine, information was available about occupations known to have a high probability of exposure; however, there was very little epidemiological research about cancer risk among exposed workers.

Data from high-throughput screening assays

The analysis of the in vitro bioactivity of all evaluated agents, except *N*-methylolacrylamide, was informed by data from high-throughput screening assays generated by the Toxicity Testing in the 21st Century (Tox21) and Toxicity Forecaster (ToxCast) research programmes of the government of the USA (Thomas et al., 2018). Three compounds (i.e. 1,2-diphenylhydrazine, diphenylamine, and isophorone) were considered active in low numbers of assay end-points mapped to the following key characteristics of carcinogens (Smith et al., 2016): "is genotoxic", "induces oxidative stress", "modulates receptor-mediated effects", and "alters cell proliferation, cell death, or nutrient supply". Specifically, 1,2-diphenylhydrazine was considered active in four assay end-points for "is genotoxic", four assay end-points for "induces oxidative stress", seven assay end-points for "modulates receptor-mediated effects", and nine assay end-points for "alters cell proliferation, cell death, or nutrient supply"; diphenylamine was considered active in six assay end-points for "modulates receptor-mediated effects", and eight assay end-points for "alters cell proliferation, cell death, or nutrient supply"; and isophorone was considered active in five assay end-points for "modulates receptor-mediated effects", and two assay end-points for "alters cell proliferation, cell death, or nutrient supply". The results were generated with the software "kc-hits" (key characteristics of carcinogens – high-throughput screening discovery tool) (available from: https://gitlab.com/i1650/kc-hits). The mapping of assay end-points to each key characteristic follows that described in *IARC Monographs* Volume 123 (IARC, 2019b). All ToxCast/Tox21 data were obtained from the United States Environmental Protection Agency CompTox Chemicals Dashboard 10th Release (US EPA, 2021) at the time of the evaluations performed for the *IARC Monographs* Volume 130 in October 2021. These programmes are constantly being improved and new assays are added over time. However, at present, the general lack of metabolic activation and the small number of genotoxicity assays in these high-throughput screening programmes restrict their value in determining whether a chemical is genotoxic as part of an assessment of carcinogenicity.

Scope of systematic review

Standardized searches of the PubMed database (NCBI, 2021) were conducted for the agent and for each outcome (cancer in humans, cancer in experimental animals, and mechanistic evidence, including the key characteristics of carcinogens). The literature trees for the agent, including the full set of search terms for the agent name and each outcome type, are available online.[1]

References

Belpoggi F, Cattley RC, Reisfeld B, Stewart P, Turner MC, Audebert M, et al.; IARC Monographs Vol 130 group (2021). Carcinogenicity of 1,1,1-trichloroethane and four other industrial chemicals. *Lancet Oncol.* 22(12):1661–2. doi:10.1016/S1470-2045(21)00659-8 PMID:34774220

IARC (1979). 1,1,1-Trichloroethane. In: Some halogenated hydrocarbons. *IARC Monogr Eval Carcinog Risk Chem Hum*. 20:1–609. Available from: https://publications.iarc.fr/38 PMID:296120

IARC (1987). Overall evaluations of carcinogenicity: an updating of IARC Monographs volumes 1 to 42. *IARC Monogr Eval Carcinog Risks Hum Suppl*. 7:1–440. Available from: https://publications.iarc.fr/139 PMID:3482203

IARC (1994). Some industrial chemicals. *IARC Monogr Eval Carcinog Risks Hum*. 60:1–560. Available from: https://publications.iarc.fr/78 PMID:7869568

IARC (1999). Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide (Part 1, Part 2, Part 3). *IARC Monogr Eval Carcinog Risks Hum*. 71:1–1586. Available from: https://publications.iarc.fr/89 PMID:10507919

IARC (2019a). Report of the Advisory Group to Recommend Priorities for the IARC Monographs during 2020–2024. Lyon, France: International Agency for Research on Cancer. Available from: https://monographs.iarc.who.int/wp-content/uploads/2019/10/IARCMonographs-AGReport-Priorities_2020-2024.pdf, accessed 25 September 2020.

IARC (2019b). Some nitrobenzenes and other industrial chemicals. *IARC Monogr Eval Carcinog Risks Hum*. 123:1–213. Available from: https://publications.iarc.fr/584

Marques MM, Berrington de Gonzalez A, Beland FA, Browne P, Demers PA, Lachenmeier DW, et al.; IARC Monographs Priorities Group (2019). Advisory Group recommendations on priorities for the IARC Monographs. *Lancet Oncol*. 20(6):763–4. doi:10.1016/S1470-2045(19)30246-3 PMID:31005580

NCBI (2021). PubMed [online database]. Bethesda (MD), USA: National Library of Medicine. Available from: https://pubmed.ncbi.nlm.nih.gov/.

Palau J, Jamin P, Badin A, Vanhecke N, Haerens B, Brouyère S, et al. (2016). Use of dual carbon-chlorine isotope analysis to assess the degradation pathways of 1,1,1-trichloroethane in groundwater. *Water Res.* 92:235–43. doi:10.1016/j.watres.2016.01.057 PMID:26874254

Silvestri GT, Lukasiewicz JM, Einstein M (1983). Occupational employment projections through 1995. Monthly labor review November 1983. Available from: https://www.bls.gov/opub/mlr/1983/11/art4full.pdf, accessed 15 November 2021.

Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, et al. (2016). Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. *Environ Health Perspect*. 124(6):713–21. doi:10.1289/ehp.1509912 PMID:26600562

Talibov M, Lehtinen-Jacks S, Martinsen JI, Kjærheim K, Lynge E, Sparén P, et al. (2014). Occupational exposure to solvents and acute myeloid leukemia: a population-based, case-control study in four Nordic countries. *Scand J Work Environ Health*. 40(5):511–7. doi:10.5271/sjweh.3436 PMID:24840289

Thomas RS, Paules RS, Simeonov A, Fitzpatrick SC, Crofton KM, Casey WM, et al. (2018). The US Federal Tox21 Program: A strategic and operational plan for continued leadership. *Altern Anim Exp*. 35(2):163–8. doi:10.14573/altex.1803011 PMID:29529324

UNEP (2021). About Montreal Protocol. Paris, France: United Nations Environment Programme, OzonAction. Available from: https://www.unep.org/ozonaction/who-we-are/about-montreal-protocol, accessed 19 December 2021.

US EPA (2021). CompTox Chemicals Dashboard. 10th release. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://comptox.epa.gov/dashboard/, accessed October 2021.

[1] The literature trees for the present volume are available at: https://hawcproject.iarc.who.int/assessment/661/ (1,1,1-trichloroethane), https://hawcproject.iarc.who.int/assessment/658/ (1,2-diphenylhydrazine), https://hawcproject.iarc.who.int/assessment/662/ (diphenylamine), https://hawcproject.iarc.who.int/assessment/659/ (*N*-methylolacrylamide), and https://hawcproject.iarc.who.int/assessment/663/ (isophorone).