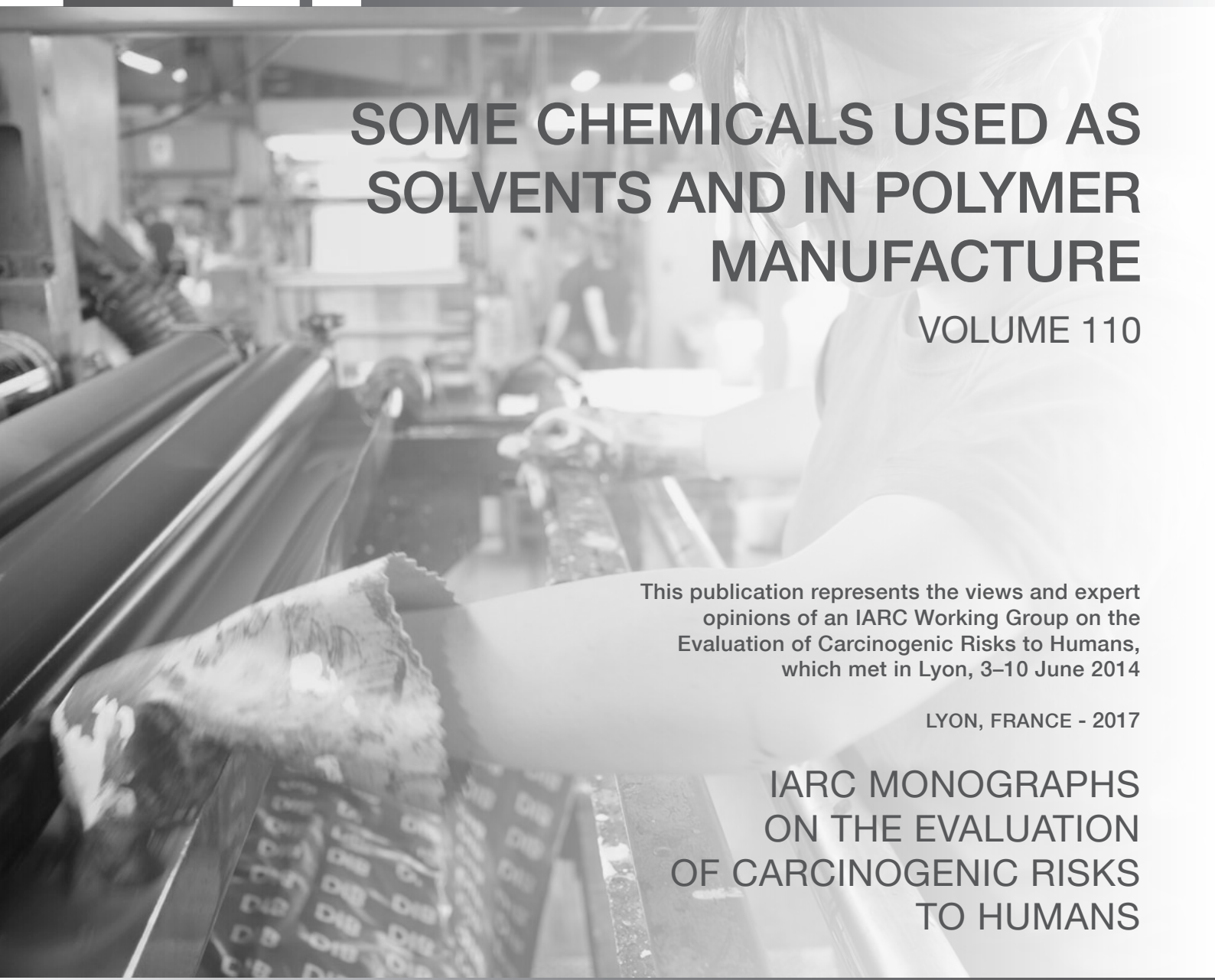
IARC MONOGRAPHS



SOME CHEMICALS USED AS SOLVENTS AND IN POLYMER MANUFACTURE

VOLUME 110

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, which met in Lyon, 3–10 June 2014

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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-tenth volume of the *IARC Monographs* contains evaluations of the carcinogenic hazard to humans of perfluorooctanoic acid, tetrafluoroethylene, 1,2-dichloropropane, dichloromethane, and 1,3-propane sultone. Exposure measurements and biomonitoring studies have shown that workers and the general population are exposed to these agents. All except one of these agents, perfluorooctanoic acid, were evaluated previously in Volume 71 of the *IARC Monographs* (IARC, 1999), when the Working Group classified three (tetrafluoroethylene, dichloromethane, and 1,3-propane sultone) as *possibly carcinogenic to humans* (Group 2B) and one (1,2-dichloropropane) as *not classifiable as to its carcinogenicity to humans* (Group 3). Since the previous evaluations, new data have become available, and the Preamble to the *IARC Monographs* has been modified to permit more explicit consideration of mechanistic data. A summary of the findings of this volume appears in *The Lancet Oncology* (Benbrahim-Tallaa et al., 2014).

Perfluorooctanoic acid

Interference with steroidogenic enzymes is a putative mechanism that may result in testicular carcinogenesis. The evidence that perfluorooctanoic acid could cause cancer of the testis was considered credible by the Working Group and unlikely to be explained by bias and confounding, but this cancer is rare and the conclusion was based on small numbers of cases. Taking into account the data in humans and experimental animals, and the mechanistic data on perfluorooctanoic acid, a plausible hypothesis for perfluorooctanoic acid-related carcinogenesis in the testes involves perturbation of molecular pathways related to testosterone, estradiol, and estrogen receptor, including during development. However, the lack of strong data precludes the establishment of a causal relationship between perturbation of these pathways and increased risk of cancer, with respect to human testicular cancer in general, as well as perfluorooctanoic acid-induced cancers in particular. If established, causal relationships between sex-hormone perturbations and specific cancers in humans could have implications for identifying the causes of hormone-related cancer based on mechanistic data.

1,2-Dichloropropane and dichloromethane

Biomonitoring studies have shown that workers and the general population are exposed to 1,2-dichloropropane and dichloromethane. The Working Group noted that a reported cluster of cancers of the biliary tract in workers at small

printing plants in Japan was very unusual, given the rarity of the outcome, the young ages at diagnosis, the absence of other known risk factors among the cases, and the very high relative risk, as well as the specificity and the intensity of the exposures (Kumagai et al., 2013; Kumagai, 2014). The Working Group recalled a previously reported cluster of four cases of angiosarcoma in workers exposed to vinyl chloride in a single chemical plant in the USA in January 1974. That cluster was extremely unusual in that the incidence of angiosarcoma at that time in the USA was only about 25 cases per year. An IARC Working Group determined later that the association between angiosarcoma and exposure to vinyl chloride was causal, based on investigation of this cluster in the USA and others elsewhere, and an earlier study in experimental animals (IARC, 2008).

1,2-Dichloropropane and dichloromethane are used as chemical intermediates and in paint stripping, but their use in the cleaning of printing presses in Japan resulted in exposure to both agents at remarkably high concentrations. The use of 1,2-dichloropropane for printing-press cleaning was reported to be widespread in Japan in the mid-1990s after the decline in use of 1,1,1-trichloroethane (although no specific statistics were available). Offset printing machines at typical small and medium-sized printing firms located in urban areas in Japan tended to be installed in small rooms with poor ventilation. When printers wiped the machines with cleaning cloths imbibed with volatile agents, the agents evaporated fully into the room to create high concentrations in the air. The sensitive control of room temperature and moisture to ensure product quality prevented air circulation, which resulted in much higher concentration of the agents near the breathing zone of the worker. This unique work environment and usage had not been observed previously. No information was available to the Working Group on whether 1,2-dichloropropane was used similarly in the 1990s in countries other than Japan; to date, this specific exposure setting has not been reported elsewhere.

In the cluster of cancers of the biliary tract in Japan, the Working Group noted the rapid work of the Japanese investigators and the Japanese government to confirm the cluster, and to provide epidemiological data on the exposed cohort that enabled estimation of the relative risk for those exposed to 1,2-dichloropropane only; this evidence played an important role in the decision of the Working Group regarding the evidence for carcinogenicity of 1,2-dichloropropane in humans. The Working Group also noted that there is a need for further epidemiological studies of those exposed occupationally either to dichloromethane alone (without 1,2-dichloropropane), or 1,2-dichloropropane alone (without dichloromethane), at different levels, with a focus on detecting cancers of the biliary tract. There is also the question of whether the combination of 1,2-dichloropropane and dichloromethane is synergistic, such that the exposure to both is more potent than exposure to either one separately. Furthermore, the Working Group noted that past cohort studies of printers might be re-examined in more detail with regard to exposure to dichloromethane and 1,2-dichloropropane, and separating out cancers of the biliary tract from the combined category of liver and biliary tract. In addition, further experimental studies are needed to understand the mechanisms of co-exposure to 1,2-dichloropropane and dichloromethane.

1,3-Propane sultone

In making its evaluation, the Working Group took into consideration the data demonstrating that 1,3-propane sultone is a strong, direct-acting alkylating agent that reacts with DNA and protein. A comprehensive review of agents

with similar direct alkylating activity, including those previously evaluated for carcinogenicity by IARC, may be warranted to identify agents with similar carcinogenic potential.

References

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