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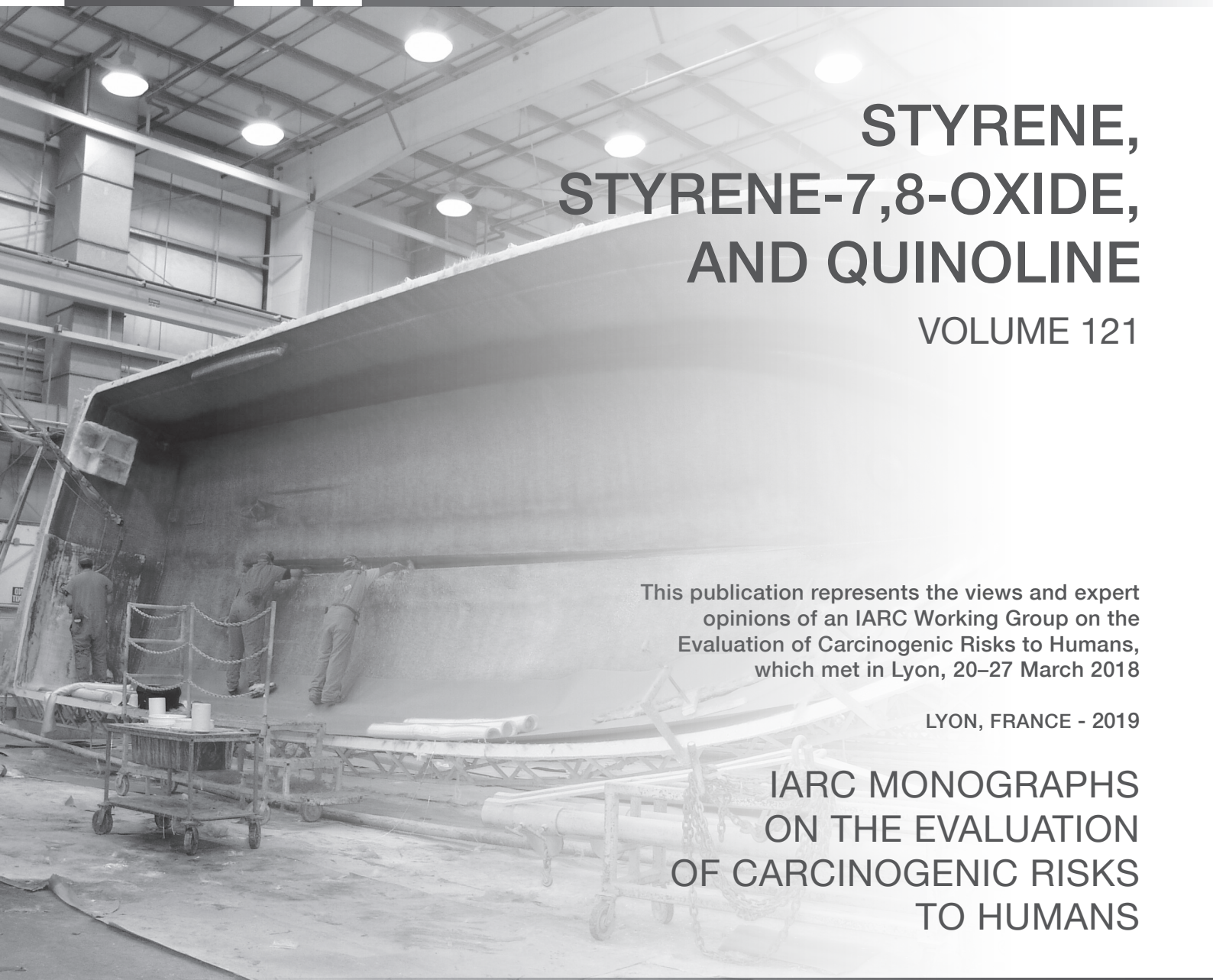

STYRENE, STYRENE-7,8-OXIDE, AND QUINOLINE

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peroxidation at concentrations that sufficiently depleted tissue glutathione levels, but results with *N*-acetylcysteine or buthionine sulfoximine pre-treatment were not supportive. For styrene-7,8-oxide, the available studies covered disparate end-points; the evidence that styrene-7,8-oxide induces oxidative stress is therefore *weak*.

There is *moderate* evidence that both styrene and styrene-7,8-oxide induce immunosuppression. Single studies of workers exposed to styrene reported the impairment of various measures of innate immune function ex vivo, in addition to the inhibition of lymphocyte proliferation. Several studies of workers exposed to styrene reported alterations in peripheral blood leukocyte populations. In several studies in rodents, each of which evaluated different end-points, subchronic exposure to styrene inhibited resolution of infection, and affected bone marrow progenitor cell populations, peripheral leukocyte populations, and/or splenic cellularity. For styrene-7,8-oxide, no in vivo data were available. In studies in human whole-blood cells conducted in vitro, and in mouse or rat lymphocytes, proliferation was inhibited. Murine natural killer cell lytic activity was decreased in a dose-responsive manner, and interferon response to viral infection was inhibited in murine embryonic fibroblasts.

There is *weak* evidence that styrene induces chronic inflammation. In multiple studies of workers exposed to styrene, alterations in immune cell populations consistent with pro-inflammatory responses were observed. In human lung carcinoma cells in vitro, non-cytotoxic concentrations of styrene induced a number of inflammatory responses. Inflammation was not consistently increased after long-term exposure in numerous studies in mice and rats. In several studies in mice, each of which evaluated different end-points, styrene stimulated different allergic or adaptive immune responses after short-term exposure. Data are sparse for styrene-7,8-oxide; the evidence that styrene-7,8-oxide induces chronic inflammation is *weak*.

Respiratory disease, haematological effects, altered liver function, and neurotoxicity have been reported in exposed workers. In rats and mice, styrene given by various exposure routes induced respiratory tract toxicity and hepatotoxicity. Although fewer data are available for styrene-7,8-oxide, the effects reported are similar; in addition, forestomach irritation was reported in rats after chronic oral exposure.

Results were largely null or negative in the Toxicity Forecaster and Toxicity Testing in the 21st Century high-throughput testing programmes of the United States government, and high-content gene expression studies were uninformative.

6. Evaluation

6.1 Cancer in humans

There is *limited evidence* in humans for the carcinogenicity of styrene. Positive associations have been observed between exposure to styrene and lymphohaematopoietic malignancies.

There is *inadequate evidence* in humans for the carcinogenicity of styrene-7,8-oxide.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of styrene.

There is *sufficient evidence* in experimental animals for the carcinogenicity of styrene-7,8-oxide.

6.3 Overall evaluation

Styrene is *probably carcinogenic to humans (Group 2A)*.

Styrene-7,8-oxide is *probably carcinogenic to humans (Group 2A).*

6.4 Rationale

In making this overall evaluation, the Working Group noted that the mechanistic and other relevant data support the classification of styrene in Group 2A.

In making its overall evaluation, the Working Group took account of the mechanistic and other relevant data in classifying styrene-7,8-oxide (the major metabolite of styrene) in Group 2A. Styrene-7,8-oxide is an electrophile. There is strong evidence in human systems that it forms DNA adducts and is genotoxic. This mechanism can also operate in humans.

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