



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

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TO HUMANS**

GENERAL REMARKS

This one-hundred-and-twenty-first volume of the *IARC Monographs* contains evaluations of the carcinogenic hazard to humans of quinoline, styrene, and styrene-7,8-oxide.

Styrene was previously considered by *IARC Monographs* Working Groups in February 1978 ([IARC, 1979](#)), March 1987 ([IARC, 1987](#)), February 1994 ([IARC, 1994](#)), and February 2002 ([IARC, 2002](#)). Styrene-7,8-oxide was considered by *IARC Monographs* Working Groups in February 1976 ([IARC, 1976](#)), February 1978 ([IARC, 1979](#)), June 1984 ([IARC, 1985](#)), and February 1994 ([IARC, 1994](#)). New data have become available since these previous evaluations, and these have been included and considered in the present volume. Quinoline had not been previously evaluated by the *IARC Monographs* programme.

A summary of the findings of this volume appears in *The Lancet Oncology* ([Kogevinas et al., 2018](#)).

Quinoline

Quinoline is present in air pollution and in tobacco smoke. It is a high production volume chemical that is used to produce various drugs and dyes. Potential human exposures to quinoline in occupational settings are not well understood, with significant gaps in knowledge with respect to exposures occurring during the production and use of quinoline-derived drugs, the use of quinoline as an industrial solvent, and new uses of quinolinium as an ionic liquid crystal

solvent. Other data relevant to the carcinogenicity of quinoline to humans are also sparse. No data were available on cancer in humans, or on absorption, distribution, metabolism, or excretion in humans. Furthermore, no data were available on carcinogen mechanisms in humans or in human cells. Quinoline is carcinogenic in mice and in rats, inducing rare tumours of various embryological origins. Malignant tumours were induced with a high incidence at the lowest dose tested, occurred with short latency, and caused early deaths. There was also strong evidence that quinoline is genotoxic in experimental systems, inducing mutations and chromosomal damage in rodents and in vitro upon metabolic activation.

Styrene-7,8-oxide and styrene

Styrene-7,8-oxide is primarily used to produce epoxy resins. Human exposure during the manufacture of styrene-7,8-oxide, or during the production or use of epoxy resins, is not well understood. Occupational exposure has been documented in the reinforced plastics industry, where styrene 7,8-oxide co-occurs with styrene, at concentrations that are typically 3 orders of magnitude lower than those of styrene. Styrene-7,8-oxide and its albumin and haemoglobin adducts have been detected in the blood in

occupationally exposed populations and the general population. In the reinforced plastics industry, styrene exposures are apparently decreasing, with likely concomitant reductions in styrene-7,8-oxide exposures.

Human exposure to styrene is better characterized, but breathing-zone air concentration data for occupational exposures throughout the production and use of styrene are sparse, particularly in low- and middle-income countries. The sources of styrene in indoor air have also not been quantitatively characterized. Population-based data are also not available, such as to inform the relative importance of different sources of styrene exposure (including occupational exposures, cigarette smoking, and indoor and outdoor air). Short-term, high-level exposure was the focus of many investigations of styrene in humans. A variety of exposure metrics are available, but the selection has not always been informed by consideration of the biological rationale.

In humans, there was *inadequate evidence* for the carcinogenicity of styrene-7,8-oxide. For styrene, the epidemiological studies provided *limited evidence* for carcinogenicity, based on positive associations with lymphohaematopoietic malignancies. For solid tumours, including lung cancer, the evidence was sparse or inconsistent. There was an increase in the incidence of sinonasal adenocarcinoma, a rare cancer, in one large cohort of workers in the reinforced plastics industry (Nissen et al., 2018), but cases were few and chance and confounding could not be discounted. In the studies of cancer in humans, inconsistency in the classification by haematopoietic subtypes was noted. Incidence-based studies, and pooling of data from large studies concerning rare cancers, may help to clarify gaps.

In experimental animals, there was *sufficient evidence* of carcinogenicity for styrene. There was also *sufficient evidence* of carcinogenicity for styrene-7,8-oxide. The overall evaluation of styrene-7,8-oxide as *probably carcinogenic*

to humans (Group 2A) took into account the mechanistic and other relevant data pertinent to the key characteristics of carcinogens (Smith et al., 2016). Because styrene-7,8-oxide is the major metabolite of styrene, these mechanistic data also provided independent support of the classification of styrene as *probably carcinogenic to humans* (Group 2A). Styrene-7,8-oxide is an electrophile and reacts directly with DNA. Styrene-7,8-oxide and styrene are genotoxic. Styrene-7,8-oxide-derived DNA adducts were found in the blood (Rappaport et al., 1996) and urine of exposed workers. However, for other indicators of genotoxicity, the results were mixed. In human cells in vitro, styrene-7,8-oxide as well as styrene induced DNA damage, gene mutations, chromosomal aberrations, micronucleus formation, and sister-chromatid exchanges (Bastlová et al., 1995); similar findings were seen in various experimental systems. In rodents exposed to styrene-7,8-oxide or styrene, results were equivocal for cytogenetic effects, but positive for DNA damage in multiple tissues.

Other mechanistic data were also relevant to the evaluation of styrene. In particular, the human relevance of the styrene-induced lung tumours in mice was considered, and data pertinent to a proposed rodent-specific mechanism were reviewed. This proposed mechanism involves metabolism of styrene to 4-vinylphenol by CYP2F2, cytotoxicity in club (Clara) cells, and regenerative epithelial proliferation in the terminal bronchioles (Cruzan et al., 2012). Styrene induced cytotoxicity, lung cell proliferation, and bronchial hyperplasia in both CD-1 and C57BL/6 mice, but not in C57BL/6 *Cyp2f2*^(-/-) mice or in a C57BL/6 *Cyp2f2*^(-/-) humanized CYP strain (Cruzan et al., 2017). However, lung tumours developed only in CD-1, and not in C57BL/6, mice (Cruzan et al., 2017). Furthermore, no in vivo metabolism data were available in C57BL/6 strains, and the observed increases in lung cell proliferation did not persist beyond the short term, even with continuous

exposure. Overall, it was concluded that the mechanistic events for lung tumour induction by styrene in CD-1, B6C3F₁, and O20 mice have not been established.

The factors that may influence individual susceptibility to the carcinogenicity of styrene or styrene-7,8-oxide, including sex and life-stage differences, are not well understood.

Although high-throughput data were available for styrene, styrene-7,8-oxide, styrene glycol, and 2-phenylethanol, as well as quinoline, these data were not influential in the overall evaluations in this volume. High-throughput data streams have certain strengths, and may afford opportunities to fill gaps in evidence and to support mechanistic conclusions. However, there are also limitations to the applicability and utility of such data to IARC Monographs evaluations (see also [Chiu et al., 2018](#); [Guyton et al., 2018](#)), because large-scale screening programmes were designed to aid prioritization of large chemical libraries for additional toxicity testing rather than to identify hazards of a specific chemical or chemical group.

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