Carcinogenicity of quinoline, styrene, and styrene-7,8-oxide

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M Kogevinas (Spain)—Meeting Chair; M Sim (Australia); M E Parent (Canada); G M Calaf (Chile), J Mráz, P Vodicka (Czech Republic); A A Jensen, H Kolstad (Denmark); K Hemminki (Germany); C Colosio (Italy); S Fukushima, T Suzuki (Japan); J P Texeira (Portugal); D H Phillips (UK); S J Bertke, J M Fritz, W M Gwinn, D Kriebel, S Nesnow, L A Nylander-French, M Sandy, S L Smith-Roe, G Stoner (unable to attend) (USA)

Declaration of interests

All working group members declare no competing interests.

Invited specialists

R Tornero-Velez (USA)

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R Tornero-Velez was invited to a workshop with significant travel costs paid by the American Chemistry Council.

Representative

M Sarpa de Campos Mello, for the Ministry of Health, Brazil (unable to attend)

Declaration of interests

All representatives declare no competing interests.

Observers

M I Banton, for the Styrene Information and Research Center (SIRC), USA; T Chachibaia for the NGO 'Ammonium Nitrate Safe Governance Initiative', Georgia (unable to attend); H-P Gelbke, for PlasticsEurope, Belgium; L Vodickova, for the Charles \

In March, 2018, a Working Group of 23 scientists from 12 countries met at the International Agency for Research on Cancer (IARC) in Lyon, France, to finalise their evaluation of the carcinogenicity of quinoline, styrene, and styrene-7,8-oxide. This assessment will be published in Volume 121 of the IARC Monographs.[1]

Quinoline is an azaarene that is present in tobacco smoke and air pollution. Quinoline occurs in petroleum and shale oil processing, and is found in groundwater and soil at coal tar and creosote-contaminated sites. A high production volume chemical, quinoline is used to produce a variety of drugs and dyes. No data were available on cancer in humans, or on exposure, absorption, or distribution of quinoline in humans. In mice and rats, quinoline induced 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. In both sexes of Crj:BDF1 mice, drinking water exposure to quinoline increased the incidences of liver histiocytic sarcoma, and in various organs, haemangioma and haemangiosarcoma.[2] Additionally, hepatocellular carcinoma incidence was increased in male mice. Quinoline administered by intraperitoneal injection in CD-1 mice induced lymphoma in females and hepatocellular carcinoma in males.[3] In male and female F344/DuCrj rats, drinking water containing quinoline increased the incidences of haemangiosarcoma (in various organs), and hepatocellular adenoma and carcinoma. Nasal cavity sarcoma, nasal esthesioneuroepithelioma, and mediastinal sarcoma were increased in male rats.[2] In three feeding studies,[4] quinoline increased the incidence of liver haemangiosarcoma in male rats of various strains. There was strong evidence that quinoline is genotoxic in experimental systems, inducing mutations[5] and chromosomal damage in rodents and in vitro (upon metabolic activation), but no human data on cancer mechanisms were available. The Working Group classified quinoline as "possibly carcinogenic to humans", Group 2B, based on sufficient evidence of carcinogenicity in experimental animals.

Styrene is present in tobacco smoke and air pollution. A high production volume chemical, styrene is primarily used to produce polystyrene polymers. Styrene and styrene-7,8-oxide, the principal metabolite of styrene in humans, are found in workplace air, particularly in the reinforced plastics and rubber industries.[6] Styrene-7,8-oxide is primarily used to produce epoxy resins.

The most informative epidemiological studies of cancer were in large occupational cohorts (of >100 000 workers) in the reinforced plastics industry, where styrene exposure levels are highest, in Europe,[7] the UK,[8] Denmark,[9] across the USA,[10] and Washington state. The Working Group assessed the overall pattern of the findings for lymphohaematopoietic malignancies as a whole, noting increased incidence or mortality of subtypes of leukaemia and lymphomas in several studies, with greater consistency for leukaemia, and in particular myeloid leukaemia. The incidence of acute myeloid leukaemia increased strongly with increasing cumulative styrene exposure for a latency period of 15 years in the most informative study.[9] Increased myeloid leukaemia (acute and chronic combined) mortality was reported in the US study for the highest cumulative styrene exposure category.[10] There was no overall increased mortality of myeloid leukaemias (acute and chronic combined) in the European cohort, but an increase was observed with increasing mean intensity of exposure in a ten-year lag analysis. The incidence of sinonasal adenocarcinoma, a rare cancer, was increased in one large cohort of reinforced plastics workers,[11] but cases were few and chance and confounding could not be discounted. Evidence for solid tumours, including lung cancer, was sparse or inconsistent. Overall, the epidemiological studies provide credible evidence that exposure to styrene causes lymphohaematopoietic malignancies, but confounding, bias, or chance cannot be ruled out.

In CD-1 mice, inhalation exposure to styrene increased the incidence of bronchioloalveolar carcinoma in males,[12] and in females in a separate study,[13] in which bronchioloalveolar adenoma or carcinoma (combined) was also increased in both sexes. In 020 mice, transplacental exposure followed by gavage increased the incidences of lung carcinoma in females, and lung adenoma or carcinoma (combined) in males and females.[14] In B6C3F1 mice, exposure to styrene by gavage increased the incidence of bronchioloalveolar adenoma or carcinoma (combined) in males, and hepatocellular adenoma in females. In one of two inhalation studies, styrene exposure increased the incidence of malignant mammary tumours in female rats.[15]

The Working Group classified styrene in Group 2A, "probably carcinogenic to humans" based on limited evidence in humans and sufficient evidence in experimental animals for carcinogenicity. Strong evidence of a mechanism that also operates in humans supported the Group 2A classification of styrene. Styrene is rapidly absorbed, widely distributed to adipose tissues, and extensively metabolised in humans and experimental systems. Approximately 60% of excretion products formed from inhaled styrene come from its metabolism to styrene-7,8-oxide. Styrene-7,8-oxide is an electrophile and reacts directly with DNA. There was strong evidence that styrene

and styrene-7,8-oxide are genotoxic. In exposed workers, styrene-7,8-oxide-derived DNA adducts were found in the blood[6] and urine, while results were mixed for other indicators of genotoxicity. In human cells in vitro, styrene as well as styrene-7,8-oxide induced DNA damage, gene mutations, chromosomal aberrations, micronucleus formation, and sister-chromatid exchanges;[16] similar findings were seen in various experimental systems. In rodents exposed to styrene or styrene-7,8-oxide, results were equivocal for cytogenetic effects, but positive for DNA damage in multiple tissues.

There was also strong evidence that styrene modulates receptor-mediated effects in exposed human subjects, based on studies reporting increased serum prolactin. Additionally, there was strong evidence that styrene and styrene-7,8-oxide alter cell proliferation. Styrene reduced cell proliferation in cultured human lymphocytes, and styrene and styrene-7,8-oxide increased proliferation in various rodent tissues. In considering the human relevance of the styrene-induced mouse lung tumours, the Working Group reviewed data relevant to a proposed rodent-specific mechanism involving metabolism of styrene to 4-vinylphenol by CYP2F2, cytotoxicity in club (Clara) cells, and regenerative epithelial proliferation in the terminal bronchioles.[17] 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(-/-) humanised CYP strain.[12] However, lung tumours developed only in CD-1, and not in C57Bl/6, mice.[12] 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. Thus, the Working Group concluded that the mechanistic events for lung tumour induction by styrene in CD-1, B6C3F1, and O20 mice have not been established.

For styrene-7,8-oxide, there was inadequate evidence of carcinogenicity in humans. In B6C3F1 mice, gavage exposure to styrene-7,8-oxide increased the incidences of forestomach squamous cell papilloma and carcinoma in males and females, and hepatocellular adenoma or carcinoma (combined) in males. Gavage exposure to styrene-7,8-oxide increased the incidences of forestomach squamous cell papilloma and carcinoma in Sprague-Dawley and Fischer 344/N rats of both sexes,[15,18] and mammary benign or malignant (combined) tumours in male Sprague-Dawley rats.[15] In BDIV rats, transplacental exposure to styrene-7,8-oxide followed by gavage increased the incidences of forestomach papilloma in males and forestomach carcinoma in males and females.[19] The Working Group classified styrene-7,8-oxide as "probably carcinogenic to humans" (Group 2A) based on sufficient evidence of carcinogenicity in experimental animals and strong evidence that styrene-7,8-oxide, an electrophile, forms DNA adducts and is genotoxic, a mechanism that also operates in humans.

Rogelio Tornero-Velez was invited to a workshop with significant travel costs paid by the American Chemistry Council. All other authors declare no competing interests.

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University, Czech Republic; M Wilde, for the University of Kent, UK; J Williamson, for the University of Kent, UK

Declaration of interests
M I Banton is employed by a company that manufactures styrene. Her expenses for attendance at the IARC Monograph Meeting were paid by an industry group with an interest in styrene (Styrene Information and Research Center [SIRC]). H-P Gelbke works as a consultant to the Styrenics Steering Committee (SSC) of PlasticsEurope of the European Chemical Industry Council (CEFIC) and receives funds for it. J Williamson receives research funding from the UK Arts and Humanities Research Council. All other observers declare no competing interests.

IARC Secretariat
L Benbrahim-Tallaa (unable to attend); V Bouvard; T Driscoll; M Foerster; F El Ghissassi; Y Grosse; N Guha; KZ Guyton; A Hall; C Jaillet; H Mattock; D Middleton; K Straif; M Talibov; N Vilahur

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