

**COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD,
CONSUMER PRODUCTS AND THE ENVIRONMENT**

Mechanism of carcinogenicity of 1, 3-dichloropropan-2-ol (1,3-DCP).

Introduction

- 1) At its meeting in November 2003 the COC considered the need to revise its opinion on the carcinogenicity of 1, 3 –DCP in the light of a revised opinion from the COM. This was in response to new data being provided on the mutagenicity of the compound. The COM had considered that the negative results in an in-vivo bone marrow assay for clastogenicity, and in an in-vivo liver assay had provided adequate re-assurance that the mutagenic activity seen in-vitro was not expressed in-vivo. Background to the COC consideration is given in paper CC/03/42
- 2) The COC considered the possible non-genotoxic mechanisms whereby 1, 3 –DCP could induce the tumours seen in the animal bioassays. They re-affirmed their earlier view that the tumours of the kidney and thyroid could have been secondary to sustained cell proliferation. With regard to the liver tumours they agreed that there was evidence of a hepatotoxic effect at doses below those producing a significant increase in combined hepatocellular adenoma and carcinoma. They agreed that in view of this, and the fact that negative results were obtained in the liver UDS assay, it could be concluded that the liver tumours were induced by a non-genotoxic mechanism.
- 3) Thus the Committee agreed that the induction of tumours in the liver, kidney and thyroid could be explained by a non-genotoxic mechanism, which would be consistent with the COM view that 1, 3 –DCP did not have any significant genotoxic potential in-vivo. The Committee then considered the tumours induced by 1, 3 –DCP in the tongue. There was no increase in such tumours in the low dose, nor in the mid dose in the males, and the low incidence (2%) at this level in the females may not have been treatment related. There was a clear increase in papillomas and carcinomas of the tongue in the high dose group in both sexes, although the dose level used clearly exceeded the MTD, resulting in treatment related mortality. The Committee agreed that 1, 3 –DCP was an irritant, and that a plausible mechanism could be chronic irritation of the tongue in the bioassay, since the compound had been given in the drinking water. However, no data were available on the potential of 1, 3 –DCP to produce irritancy of the tongue since at the time of the bioassay it was not routine to examine the tongue histologically. Members noted that there was evidence suggesting that bacteria metabolised 1, 3 –DCP to

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epichlorohydrin a genotoxic carcinogen. It was suggested that one possible mechanism for the induction of tumours in the tongue was due to bacterial action on 1, 3 –DCP in the oral cavity producing epichlorohydrin.

- 4) Members considered that further work was needed before a genotoxic mechanism of action could be completely discounted for the tongue tumours in the rat. It was suggested that this could be investigated by 32P-post-labelling studies with suitably high doses of 1, 3 –DCP.
- 5) In view of the difficulties in carrying out such studies, it was felt that a review of the carcinogenicity of epichlorohydrin should be performed to ascertain whether any data were available to support, or discount, the ability of this compound to induce tumours in the tongue in chronic bioassays in the rat.

Carcinogenicity of Epichlorohydrin

- 6) The carcinogenicity of epichlorohydrin was last reviewed by IARC in 1999. A copy is attached at Annex A. It was concluded that there was sufficient evidence in experimental animals for the carcinogenicity of epichlorohydrin. The overall evaluation was Group 2A (probably carcinogenic to humans).
- 7) Results from 2 bioassays were available in rats using the oral route.
- 8) In one case animals were given up to 1500 ppm in the drinking water for 81 weeks at which time the experiment was terminated. Group size was small (18). A clear dose-related increase in forestomach hyperplasia, papilloma and carcinoma was however seen. The only comment regarding cancers of the oral cavity was that squamous cell carcinomas of the oral cavity were seen in 2/12 (16.7%) of the surviving rats from the high dose group. There is no mention of cancers of the tongue.
- 9) In a larger study female rats (group size 50) were given epichlorohydrin by gavage 5 days a week for 2 years. The only site at which an increase in tumours was seen was the forestomach. There was no increase in tumours in the oral cavity or the tongue. However, compound was administered by gavage rather than in the drinking water.
- 10) In an inhalation study in rats (group size 100) lifetime exposure, the only treatment related increase in tumours was in the nasal cavity (ie site of initial contact).
- 11) A copy of the publications relating to the bioassays using the oral route is given in Annex B.

Advice from the COC

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12)The Committee is asked to consider whether these data on epichlorohydrin warrant any reconsideration of the advice relating to the need for a ³²P postlabelling study in the tongue, and whether any alternative approaches could be used such as investigating whether epichlorohydrin was formed in the oral cavity.

Secretariat
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ANNEX A

IARC REVIEW OF THE CARCINOGENICITY OF EPICHLOROHYDRIN

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ANNEX B

ORAL CARCINOGENICITY BIOASSAY STUDIES ON EPICHLOROHYDRIN