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Scientific Committee on Food

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OPINION

OF THE

SCIENTIFIC COMMITTEE ON FOOD

ON

3-MONOCHLORO-PROPANE-1,2-DIOL (3-MCPD)

UPDATING THE SCF OPINION OF 1994

adopted on 30 May 2001.

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Terms of Reference

To re-examine the opinion of the SCF expressed on 16 December 1994, that 3-MCPD is a genotoxic carcinogen in the light of the new study reports.

Background

3-Monochloro-propane-1,2-diol (3-MCPD) is a member of a group of contaminants known as chloropropanols, which includes known genotoxic animal carcinogens such as 1,3-dichloropropan-2-ol. 3-MCPD is a by-product in soy sauce and in hydrolysed vegetable protein produced through acid hydrolysis, usually present in trace amounts (< 1 mg/kg), although individual samples may contain high levels (up to a few hundred mg/kg). It can be also present as a contaminant in some food additives, in epichlorohydrin/amine copolymers used as flocculants or coagulant aids in water treatment, and may be present in drinking water (Sunahara *et al*., 1993). Other occurrences have also been reported. A task within the framework of scientific co-operation by Member States (SCOOP) aims at the collection and collation of data on levels of 3-MCPD in foodstuffs (European Commission, 2000).

The SCF issued an opinion on 3-MCPD on 16 December 1994 concluding *inter alia* as follows:

> *"The Committee noted that several of the above described gaps of information had not been filled since it's first evaluation of 3-MCPD. However, based on the results of the recent carcinogenicity study and other available data, the Committee is now of the opinion that there is sufficient evidence for carcinogenicity of 3-MCPD in rats. In addition, 3-MCPD is mutagenic in the Ames test causing base pair substitutions in S. typhimurium TA 1535, positive in the mouse lymphoma TK locus assay, and possibly the Chinese hamster V79 HPRT test in vitro, and causes sister chromatid exchanges in V79 cells. In view of the clearly demonstrated in vitro genotoxicity and the tumorigenic effect in rats, 3-MCPD must be regarded as a genotoxic carcinogen. It also causes malignant transformations in mouse fibroblasts. While the role of nephrotoxicity and hormonally mediated effect of 3-MCPD cannot be ruled out, conclusive evidence for the significance of such (secondary) hormonal mechanisms has not been provided. A safe threshold dose cannot be determined and 3-MCPD should be considered as an undesirable contaminant in food. Therefore residues of 3-MCPD in food products should be undetectable by the most sensitive analytical method".*

The SCF re-considered its previous opinion in the light of the CANTOX report "Safety evaluation of 3-monochloropropanediol" dated September 4, 1996. On 13 June 1997 it concluded that

> *"The Contaminants Working Group has reviewed the safety evaluation of 3-monochloro-propandiol (3-MCPD) prepared by CANTOX INC for the International Hydrolysed Protein Council. This document does not present any new evidence. The conclusions drawn by CANTOX are based on a different*

interpretation of the same studies, which had been reviewed by the SCF before its opinion was expressed in 1994. All data quoted by CANTOX including negative results of in vivo genotoxicity tests, data on metabolic pathways and indications for hormonal mediated carcinogenesis had been considered during the preparation of the SCF opinion.

Therefore, it was concluded that there is no reason for the Committee to change its opinion on 3-MCPD as expressed on 18 December 1994".

Recently, two new studies were commissioned by the UK Drinking Water Inspectorate on the *in vivo* genotoxicity of 3-MCPD:

- 3-MCPD: Measurement of unscheduled DNA synthesis in rat liver using an *in vivo*/*in vitro* procedure (Fellows, 2000);

- 3.MCPD: Induction of micronuclei in the bone marrow of treated rats (Marshall, 2000).

On the basis of these study reports the UK Committee on Mutagenicity (COM) and UK Committee on Carcinogenicity (COC) issued statements (COM 2000, COC 2000).

In addition a paper by Frei and Würgler (1997) on a mutation/somatic recombination assay in *Drosophila melanogaster* (SMART test) was evaluated, which had not been considered previously by the Committee.

In vivo genotoxicity

- 3-MCPD (purity 98.5%) did not induce unscheduled DNA synthesis (UDS) in the liver of male Han Wistar rats using the *in vivo/in vitro* test protocol. The substance was given by two single oral administrations; 40 and 100 mg/kg bw. The UDS was evaluated by autoradiography (Fellows, 2000).

- 3-MCPD (purity 99.2%) was found negative in the bone marrow micronucleus test in male Han Wistar rats treated by gavage once daily on two consecutive days at doses of 0, 15, 30 and 60 mg/kg bw. Animals were sacrificed 24 hours after the second treatment. A dose-related decrease in the PCE/NCE ratio was observed, indicating that this substance and/or its metabolites reached the target cells (Marshall, 2000).

- A mutation/somatic recombination assay in *Drosophila melanogaster* (SMART test) showed no evidence of genotoxicity for 3-MCPD as well as for the parent compounds 2-chloro-1,3-propanediol (2-CPD) and 1,3-dichloro-2-propanol (Frei and Würgler, 1997).

Evaluation

The Committee agreed that both the *in vivo* mammalian genotoxicity assays (the rat bone-marrow micronucleus test and the rat liver UDS) carried out to acceptable standards as well as the mutation/recombination *Drosophila* SMART test were negative, providing adequate evidence that the genotoxic activity observed *in vitro* was not expressed *in vivo*. The same conclusion was reached by the UK COM (COM, 2000). The additional information also supports the view that the increase in benign tumours observed in the long-term carcinogenicity assay in rats is the result of non-genotoxic mechanisms, either through chronic hormonal imbalance (mammary gland fibromas, Leydig cell tumours) or sustained cytotoxicity and chronic hyperplasia (renal tumours). This conclusion was also reached by the UK COC (COC, 2000).

Conclusions

Taking into account the lack of genotoxicity *in vivo* and the likely secondary mechanisms of the tumorigenic effects seen in the chronic toxicity/carcinogenicity study in the rats the Committee considered that a threshold-based approach for deriving a Tolerable Daily Intake (TDI) would be appropriate. The Committee noted that at the lowest dose (1.1 mg/kg bw/day) in the above-mentioned rat study there are some indications of adverse effects in several organs, which attain statistical significance at higher doses. Despite of the lack of statistical significance at the lowest dose, the Committee considered this to be a LOAEL, being close to a NOAEL. Taking also into account other limitations in the database (e.g. lack of reproduction/developmental toxicity studies) an overall uncertainty factor of 500 was used by the Committee to derive a TDI of 2 µg/kg bw.

References

COC (2000). Carcinogenicity of 3-monochloro propane 1,2- diol (3-MCPD). UK Committee on Carcinogenicity, Statement COC/00/S5 (Update of COC/99/S5), - December 2000. http://www.doh.gov.uk/mcpd1.htm.

COM (2000). Mutagenicity of 3-monochloro propane 1,2-diol (3-MCPD). UK Committee on Mutagenicity, Statement COM/00/S4, October 2000. http://www.doh.gov.uk/mcpd2.htm.

European Commission (2000). Commission Decision 2000/669/EC of 18 October 2000 amending Decision 94/652/EC establishing the inventory and distribution of tasks to be undertaken within the framework of co-operation by Member States in the scientific examination of questions relating to food. Official Journal L 279, 01/11/2000 p. 49 – 51.

Fellows M (2000). 3-MCPD: Measurement of Unscheduled DNA synthesis in rat liver using an *in vivo/in vitro* procedure. Covance Laboratories Limited, Harrogate, UK.

Report Number 1863/1-D5140, July 2000, prepared for the Drinking Water Inspectorate, London, UK.

Frei H and Würgler, FE (1997). The vicinal chloroalcohols 1,3-dichloro-2-propanol (DC2P), 3-chloro-1,2-propanediol (3-CPD) and 2-chloro-1,3-propanediol (2-CPD) are not genotoxic in vivo in the wing spot test of *Drosophila melanogaster*. Mutation Research, 394, 59-68.

Marshall RM (2000). 3-MCPD: Induction of micronuclei in the bone-marrow of treated rats. Covance Laboratories Limited, Harrogate, UK. Report No 1863/2-D5140, July 2000, prepared for the Drinking Water Inspectorate, London, UK.

Sunahara G, Perrin I, and Marchessini M (1993). Carcinogenicity study on 3-monochloro propane 1,2-diol (3-MCPD) administered in drinking water to Fischer 344 rats. Report No RE-SR93003, Nestec Ltd, Research and Development, Switzerland.