

DRAFT

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

**1,3-DICHLOROPROPAN-2-OL (1,3 DCP) and
2,3 -DICHLOROPROPAN-1-OL (2,3 DCP)**

INTRODUCTION

1 1,3-Dichloropropan-2-ol (1,3-DCP) and 2,3 dichloropropan-1-ol (2,3 DCP) are members of a group of chemicals called chloropropanols, which also includes 3-chloro-1,2-propanediol (3-MCPD). Chloropropanols are contaminants of some foodstuffs and of polyamine flocculants used in the treatment of drinking water.

2 3-MCPD was considered by COM and COC during 2000 and statements from both committees have been issued. 3-MCPD was considered by COC to be non-genotoxic *in vivo*.

3 1,3-DCP was reviewed by COC in 1991 (CC/91/4) who considered it to be an *in-vitro* mutagen from summary data, and also that it would be prudent to regard it as genotoxic *in vivo*. The COC agreed that the "limited information available suggested that 1,3-DCP was genotoxic and carcinogenic" and stated that it "wished to see more detailed information from the relevant studies". Copies of CC/91/4 and relevant extracts from the minutes (CC/MIN/91/1) are provided in Annexes A and B respectively.

4 In light of the recent evaluations of 3-MCPD, and the availability of additional mutagenicity data for 1,3 DCP since the 1991 appraisal by COC, the genotoxicity of 1,3 DCP and 2,3 DCP was reviewed by COM in 2001. The additional data for 1,3 DCP (mainly *in vitro* studies), confirmed the earlier (1991) COC view that 1,3 DCP should be regarded as having genotoxic potential *in vivo*. COM also took the opportunity to review a companion substance, 2,3 DCP, for which there are much less data, and advised that it would be prudent also to regard this substance as having genotoxic potential *in vivo*.

5 This paper deals mainly with 1,3 DCP. Apart from the additional genotoxicity studies with 1,3 DCP, and apart from some additional acute toxicity and metabolic information generated following human poisoning incidents in Japan in the 1990's, there are no additional carcinogenicity data available for 1,3 DCP. In 1991, the COC asked to see additional data from the carcinogenicity study but it has not been possible at this stage to obtain full access to the study data, but attempts are continuing.

6 The objective of this paper is to

- make COC aware of the recent opinion of the COM on 1,3 DCP and 2,3 DCP, and
- ask the COC to consider and update, if necessary, the 1991 opinion of the COC on 1,3 DCP and produce a statement

7 Additionally, for completeness, COC are also invited to consider available data for 2,3 DCP. While there are no carcinogenicity data for this substance, there are some carcinogenicity data available on the brominated analogue, 2,3-dibromopropano-1-ol (2,3 DBP) which may provide some useful background information.

BACKGROUND: PUBLIC HEALTH ISSUES

Water

8 In light of earlier (1999) COC advice on 3-MCPD, the Drinking Water Inspectorate (DWI) restricted the dosing of water with approved polyamine flocculants, (which contain 3-MCPD and also other chloropropanols as contaminants) to a maximum of 2.5mg flocculant /l. Maximum levels of 3-MCPD in the flocculants were set at 40ppm to achieve maximum level of 0.1µg 3-MCPD/l in treated drinking water. (nb these maximum levels of 3-MCPD in flocculants are now being reviewed following revised opinions by COC and COM in 2000 on the lack of *in-vivo* genotoxicity of this substance and the possibility of setting an ADI for this substance). However no mandatory levels for other chloropropanols (i.e. 1,3-DCP or 2,3-DCP) have been set by the DWI. At the current maximum flocculant dosage rates and impurity levels in flocculants, concentrations in drinking water may theoretically be in the 2-3µg/litre range (although no measurements in drinking water have been carried out). Levels in 1991 when 1,3 DCP was first considered by COC were estimated to be 16µg/litre. Following COM/COC advice, the DWI may decide to identify a maximum contaminant level in flocculants for the each of the monochloropropanols.

Foodstuffs

9 1,3 DCP is a process contaminant formed as a result of the action of hydrochloric acid on vegetable protein. It is therefore a potential contaminant of any food where acid-hydrolysed vegetable protein (acid-HVP) has been used as an ingredient. Of particular concern are soy and similar oriental sauces, where the addition of acid-HVP, a flavour enhancer, is often used to speed up the otherwise lengthy fermentation process this being the traditional production method. There are some published data on levels of 1,3 DCP in soy sauces but little else has been investigated. In a recently reported short study (Crews et al, 2000), the range of levels of 1,3 DCP observed was <0.005 – 4.28 mg/kg. There could be a potential dietary exposure risk for ethnic groups, since the recommended amount for a single serving is 15 ml of soy sauce. (ie upto 68µg per serving). There is very little information on levels of 2,3 DCP in foods.

Regulatory aspects

10 In 1993 the FAO/WHO Expert Committee on Food Additives (JECFA) concluded that, because of its carcinogenicity, 1,3-DCP is an undesirable contaminant in food and that levels in hydrolysed vegetable proteins should be reduced to as low as technologically achievable (Olsen, 1993). As JECFA are reviewing 3-MCPD in the

summer of 2001, they are also likely also to review 1,3 DCP. There are no plans for JECFA to review 2,3 DCP

11 A draft European (CEN) standard for polyamine flocculants in water treatment proposes maximum contaminant levels for 1,3 DCP of 500ppm and for 2,3 DCP of 1000ppm. There is no published toxicological basis for these values, which appear to be transcribed from established water industry standards in the USA. At the maximum dosage rates for flocculants set by DWI, levels in of 1,3 DCP in drinking water could be 1.25µg/litre. (nb new UK Drinking Water Quality Regulations control genotoxic contaminants of water treatment chemicals eg epichlorhydrin and acrylamide to be within a maximum drinking water level of 0.1µg/litre). When COC reviewed 1,3 DCP in 1991, theoretical levels in drinking water were considered to be 16 µg/l.

1,3-DCP : SUMMARY OF TECHNICAL AND TOXICOLOGICAL DATA

12 Relevant chemical, physical and toxicological data for 1,3 DCP have been submitted in 1991 to COC (CC/91/4 para 11 to 24, see Annex A) and more recently to COM (MUT/01/06 para 9 to 24; see Annex C).

13 Key points from the data are

- a) Apart from the 104-week carcinogenicity/toxicity study, there are limited repeat-dose studies with 1,3 DCP. These have all been conducted by oral gavage and comprise;
 - 9-day dose-ranging study in rats, with a maximum dose of 75 mg/kg/d (see para 9, Annex A)
 - 13-week (5d/wk) study in Sprague-Dawley rats, maximum dose of 100 mg/kg/d (see para 19 to 24, Annex A)
 - 14-day reproductive study in male rats, maximum dose 60 mg/kg/d (see para 23, Annex C).
- b) A consistent finding is evidence of liver and kidney damage. Additionally in the 13-week study, stomach lesions, characteristic of gastric irritation were observed in males. Nasal lesions (olfactory region of the nasal mucosa) were observed consistently in all high dose group animals (100 mg/kg/d). From the 13-week repeat dose study, a NOAEL of 1 mg/kg/d was identified.
- c) Available, albeit limited, metabolic information indicates that 1,3 DCP may be metabolised to form epichlorohydrin, which may, via glycidol, be conjugated to form mercapturic acid derivatives (Jones and Fakouri 1979). More recent in vitro investigations with hepatocyte cultures indicate a pathway through CYP2E1 to dichloroacetone (a directly acting cytotoxic compound) followed by glutathione depletion (Hammond et al., 1996, Hammond and Fry 1997, 1999; Garle et al., 1997, Fry et al., 1999).

1,3-DCP : GENOTOXICITY STUDIES

14 Tables 1 and 2 summarise the currently available data on the genotoxicity of 1,3-DCP. Data considered previously by COC in 1991 are identified by asterisk (*) in the tables. COC opinion on the genotoxicity data as recorded in the minutes of the meeting of March 12th 1991 is provided in Annex B.

15 The results of mutagenicity studies with bacteria and mammalian cells suggest that 1,3-DCP is mutagenic *in vitro*. It has been suggested by Hahn et al (1991) that the *in-vitro* genotoxicity of 1,3-DCP is due to the chemical formation of epichlorohydrin.

16 Some inconsistency was found with regards to the effects of metabolic activation. Von der Hude et al (1987) reported the genotoxicity of 1,3-DCP to be reduced by S9 mix in the SCE test. Gold et al (1978) found this chemical to be mutagenic (*S typhimurium* TA 100) only after metabolic activation. Nakamura et al (1979) described an increase in the direct mutagenicity by S9 mix for the strains TA 100 and TA 1535. Stolzenburg & Hine (1980), in contrast, observed a reduction of TA 100 revertants with the addition of S9 mix. Lynn et al (1981) found 1,3-DCP to be mutagenic in TA 100 without liver metabolic activation and Silhankova et al (1982) reported the test compound to produce base substitutions in TA 1535 both with and without metabolic activation.

17 1,3 DCP was negative in a SMART assay in *Drosophila*.

18 There are no data from *in vivo* studies in mammalian cells.

19 In reviewing these data the COM concluded that it would be prudent to regard 1,3-DCP (and 2,3-DCP) as potentially genotoxic *in vivo* and agreed that both compounds should be tested for genotoxicity *in vivo* using the approach set out in the COM guidelines

Table 1 Summary of <i>S Typhimurium</i> results with 1,3-DCP				
Test system	Test object	Doses	Results (+activation/-activation)	Reference
In vitro bacterial Mutation assay	S Typhimurium TA 1535	2-200 µmole/plate	+/+	*Silhankova et al., 1982
In vitro bacterial Mutation assay	S Typhimurium TA1537,TA1538,TA98	2-200 µmole/plate	-/-	*Silhankova et al., 1982
In vitro bacterial Mutation assay	S Typhimurium TA100	10-1,000 µmole/plate	+/+	*Stolzenberg and Hine, 1980
In vitro bacterial Mutation assay	S Typhimurium TA100, TA1535	100-6,666 µmole/plate	+/+	Zeiger et al., 1988
In vitro bacterial Mutation assay	S Typhimurium TA97, TA98	100-6,666 µmole/plate	+/-	Zeiger et al., 1988
In vitro bacterial Mutation assay	S Typhimurium TA100, TA1535	3-300 µmole/plate	+/+	*Nakamura et al., 1979
In vitro bacterial Mutation assay	S Typhimurium TA100	Responses reported at ≤ 500	+/nt	Majeska and Matheson, 1983
In vitro bacterial Mutation assay	S Typhimurium TA100	1.0-62.8 µmole/plate	+/+	Hahn et al., 1991
In vitro bacterial Mutation assay	S Typhimurium TA1535	1.0-78.6 µmole/plate	+/+	Hahn et al. 1991
In vitro bacterial Mutation assay	S Typhimurium TA100, TA1535	Up to 1,250 µg/plate	+/+	Ohkubo et al., 1995
In vitro bacterial Mutation assay	S Typhimurium TA98	Up to 1,250 µg/plate	Nt/-	Ohkubo et al., 1995
In vitro bacterial Mutation assay	S Typhimurium TM677	Up to 100 µg/plate	+/+	Ohkubo et al., 1995
In vitro bacterial Mutation assay	S Typhimurium TA100	10-100µg/plate	+/-	*Gold et al., 1978
In vitro bacterial Mutation assay	S Typhimurium TA100	100-1000µg/plate	Nt/+	*Lynn et al., 1981

* indicates study previously considered by COC in 1991

Table 2 Summary of other genotoxicity results with 1,3-DCP				
Test system	Test object	Doses	Results (+activation/-activation)	Reference
In vitro bacterial Mutation assay	E.coli TM930	2-200 µmole/plate	+/-	*Silhankova et al., 1982
In vitro SOS chromotest assay	E.coli PM21; GC4798	2.5-30µmole/sample	+/-	Hahn et al., 1991
In vitro mammalian mutation assay	Mouse lymphoma TK locus	2-9 mg/ml	+/+	Henderson et al., 1987
In vitro mammalian mutation assay	Mouse lymphoma TK locus	Details not available	+/+	*San & Blanchard 1990
In vitro mammalian SCE assay	Chinese hamster V79 cells	0.12-3.3 mM	Weak +/+	*Von der Hude et al., 1987
In vitro mammalian SCE assay	CHO cells SCE	Details not available	+/+	*Putman & Morris 1990
In vivo somatic mutation (wing spot test)	<i>Drosophila melanogaster</i>	0.05-10mM	-	Frei and Wurgler, 1997

* indicates study previously considered by COC in 1991

1,3 -DCP : CARCINOGENICITY DATA

1991 COC evaluation

20 The 104- week study with 1,3 DCP in Wistar rats (Hercules 1986) is summarised in paras 31-37 and tables 6 and 7 taken from CC/91/4 below (nb this section reproduced directly from relevant pages of CC/91/4 in Annex A). Additional information and comment on the study follows in paragraphs 21-24 . It should be noted that in the description reproduced below, that the oncogenicity study was conducted in Switzerland by RCC with Wistar KFM-Han rats (outbred: SPF quality). Of the 80 animals per sex per group, only 50 per sex per group were treated for the 104 week duration. Interim sacrifices of 10 animals per sex per group were performed at 26, 52 and 78 weeks and laboratory investigations carried out. Of the 50 males and 50 females at the high dose (group 4), laboratory investigations were conducted on 10 per sex per group. Necropsy was carried out on all rats

21 The Secretariat are endeavouring to retrieve the full report of the above carcinogenicity study, but have at present been able only to locate the summary report pages (pages 1-38; full report = 1308 pages) . These provide some additional information that was not considered by COC in 1991

Onset of tumours

22 Regarding the onset of oncogenic lesions, the following findings were reported at interim sacrifice (understood to be 10 animals/sex/ group at interim sacrifice cf 50/sex/group at termination)) ;

Liver

- at 26 weeks a 10% incidence of hepatocellular adenomas in males of group 3 (80mg/l), but none in the other groups
- at 52 weeks of treatment, a 10% incidence of hepatocellular adenomas and a 10% incidence of carcinomas were observed in females of group 4 (240mg/l)
- after 78 weeks of treatment, hepatocellular carcinomas were observed in 70% of females and 30% of males in group 4 (nb rates at termination of study 72% females ; 16 % males ; nb in females of this group at termination, 25% of carcinomas metastasised to the lungs).

Kidney

- after 78 weeks renal tubular adenomas were observed in 10% males of group 4 (nb rates at termination 18% males ; 2% females)

Tongue

- after 78 weeks, lingual papilloma were observed in 10% of males in group 3 and lingual carcinomas were observed in 10% males of group 4. At termination, a

single papilloma was encountered on the tongue in one male in group 2 (27mg/l) (not shown in table 7 above) as well as an incidence of 14.3% in males and 12% in females at the top dose, but with 0% incidence in group 3. The authors comment that

"it cannot be decided from this study whether or not the single papilloma observed in the tongue of one male in group 2 reflects an oncogenic effect of the test article or whether it is a spontaneous finding. Historical data reveal that papillomas and carcinomas of the tongue have rarely occurred spontaneously in the Wistar rat strain used by RCC"

Thyroid

- after 78 weeks thyroid follicular adenomas were observed in 10 % males in group 3. An increased incidence (unspecified in time and extent) of thyroid follicular hyperplasia was observed in males of group 4

Treatment unrelated tumours

23 A number of other neoplastic lesions were observed ; their type, incidence and distribution were considered by the authors of the report to be similar in both control and treated rats. After 104 weeks, the majority of neoplastic lesions were encountered in endocrine organs ; ie pituitary (up to 93.6%) and thyroid glands (up to 12 %) and also in hormone dependent organs such as mammary gland (upto 50%), uterus (upto 8%) and testes (up to 10.5%). Poteracki and Walsh (1998) in their review of the spontaneous neoplasms in control Wistar rats (CrI(WI)BR) report an incidence of endocrine tumours of 39.1% in males and 62.8% in females.

Other tumours

24 One papilloma was encountered in the forestomach of one female in group 4 after 78 weeks of treatment . The significance of this finding is unclear, but the authors comment that these tumours have rarely occurred spontaneously in the Wistar rat strain used by RCC.

Conclusions

25 The study showed that 1,3 DCP was carcinogenic to the rat at doses of 6mg/kg/day (ie 80mg/l in drinking water) and greater. Given the doubtful significance of the papillary tumour of the tongue in a one female animal in the low dose group, a no-effect level for induction of tumours would appear to be 27mg/l in drinking water, equivalent to 2mg/kg/d in male rats and 3mg/kg/d in females

26 In 1991 COC commented that this study showed a definite increase in the incidence of liver tumours at the highest dose in both sexes. A treatment related increase in tumours at other sites were noted, particularly the tongue and possibly the kidney. The Committee also considered that there was a very steep dose-response relationship for the hepatic carcinomas.

2,3 DCP ; SUMMARY OF DATA AND COM VIEW

27 There are very few toxicological data for 2,3 DCP. Carcinogenicity studies have not been carried out. However, a no-effect level of 10mg/kg/d has been determined from a 13 week oral rat study. Limited genotoxicity studies have been carried out

28 There are also very little data on the absorption, distribution, and excretion of 2,3-DCP. Theoretically, 2,3 DCP could be metabolised to produce epichlorohydrin (and subsequently glycidol) and therefore has structural alerts for genotoxicity and carcinogenicity. Additionally, a pathway to 3-MCPD is possible with potential effects upon the kidney and male reproductive performance

29 COM have recently considered 2,3 DCP and while there is evidence of genotoxicity *in vitro*, no studies have been performed *in vivo*. COM concluded that it would be prudent to regard 2,3-DCP (*and 1,3 DCP*) as potentially genotoxic *in vivo* and agreed that both compounds should be tested for genotoxicity *in vivo* using the approach set out in the COM guidelines. In the first instance this should be in the *in-vivo* bone marrow micronucleus assay.

COMPARISONS BETWEEN 1,3 DCP AND 2,3 DCP

30 2,3 DCP is considered to be less toxic than 1,3 DCP. In studies carried out subsequent to the reported human poisonings in the mid 1990's, 1,3 DCP but not 2,3 DCP, was shown to cause fulminant liver injury with submassive necrosis after ip administration to rats (Shiozaki et al 1994). *In vitro* studies reported by Hammond and co-workers (Hammond et al, 1996, Hammond and Fry 1997, 1999, Garle et al 1999, Fry et al 1999) have given some insight into the possible explanations for the differential toxicity of these two isomers. The data indicate that the hepatotoxicity of 1,3 dichloropropanol may be mediated through CYP2E1 to yield dichloroacetone (a potent cytotoxin), with subsequent involvement of S-glutathione transferases, resulting in depletion of glutathione, loss of mitochondrial function and cytotoxicity. In culture systems, 2,3 DCP is not as hepatotoxic as 1,3 DCP, but its toxicity is increased by induction of CYP2E1 (by isoniazid). These studies also indicate that 2,3 DCP is metabolised to an aldehyde (rather than a ketone) intermediate, which depletes glutathione at high concentrations, but under basal metabolic conditions appears to be effectively detoxified by aldehyde dehydrogenase. Increased CYP2E1 activity or decreased aldehyde dehydrogenase activity (eg by inhibition by cyanamide) promotes the accumulation of the aldehyde metabolite of 2,3 DCP and thereby increases glutathione depletion and toxicity.

BROMOPROPANOLS

2,3 Dibromopropan-1-ol

31 While there are no carcinogenicity studies available for 2,3DCP, IARC (2000) have recently evaluated the brominated analogue 2,3 dibromo-propanol (2,3 DBP) and considered that "there is sufficient evidence in experimental animals for the

carcinogenicity of 2,3 dibromo propanol-1-ol” and in their overall evaluation commented “2,3-Dibromopropan-1-ol is possibly carcinogenic to humans (Group 2B)” (see Annex D).

32 Animal carcinogenicity data related to skin application in mice and rats. In mice it produced tumours of the skin at the site of application and forestomach in both males and females, and tumours of the liver in males. In rats it produced tumours of the skin at the site of application and of the digestive tract, including the mouth, oesophagus, forestomach and intestines, nasal mucosa and zymbal gland in both males and females, and tumours of the liver mammary gland and clitoral gland in females.

Comparisons to chloropropanols (in vitro studies)

33 In vitro toxicity studies in 3T3 mouse fibroblasts and in rat hepatocytes has shown that the cytotoxicity of dichloropropanols (1,3 DCP and 2,3 DCP) were dependent upon cytochrome P450 (CYP2E1) and also glutathione. However the cytotoxicity of 1,3 dibromopropanol was largely *independent* of P450 (Hammond et al 1999), but is likewise dependent upon glutathione depletion. In these assays, bromopropanols were found to be more toxic than their chlorinated counterparts; a finding consistent with the known reactivity of organohalides:ie the toxicity of halopropanols, increases as electronegativity increases and/or ease of homolytic cleavage increases (Hammond et al 1996). Hammond and colleagues have rationalised that unlike the chloropropanols, 1,3 dibromopropanol may be a direct substrate for glutathione-S-transferase.

34 These findings indicate that findings for dibromopropanols may not readily be applied to their chlorinated counterparts. Substrate specificity for CYP2E1 and glutathione-S-transferase appear to be important factors which may be responsible for differential toxicity both between the isomers and the different halogenated species

COC DISCUSSION

35 Members are asked to consider the data provided above and in the Annexes, and in the light of the recent COM conclusions are asked to comment on the carcinogenicity of 1,3 DCP. While some additional information on genotoxicity has been produced since 1991, only limited additional information on the carcinogenicity study with 1,3 DCP has been retrieved. Nevertheless, opinion is sought as to whether the view expressed by COC in 1991, that “the limited information available suggested that 1,3 DCP was genotoxic and carcinogenic” is still appropriate and whether in the circumstances, it would be prudent to reduce exposures to 1,3 DCP to as low a level as technologically feasible

36 There are no specific data on the carcinogenicity of 2,3 DCP. In vitro evidence points to metabolic differences between the brominated and chlorinated propanols, and there are differences in toxicity of the chlorinated isomers themselves. This indicates that evidence of carcinogenicity of 2,3 dibromopropanol, while raising an alert, may not indicate similar potential for 2,3 DCP, particularly in view of

absence of evidence of the genotoxicity of 2,3 DCP in vivo. However opinion is sought whether in the circumstances it would be prudent to regard 2,3 DCP as possessing genotoxic activity in vivo and that exposures to 2,3 DCP be reduced to as low a level as technologically feasible.

DRAFT CONCLUSIONS

37 It is prudent to assume the that 1,3 DCP is a genotoxic carcinogen and that exposures to this compound should be reduced to as low a level as technologically feasible

38 It is prudent to assume that 2,3 DCP possesses genotoxic activity in vivo. Although no carcinogenicity data are available, it would however be prudent to reduce exposures to this compound to as low a level as technologically feasible

**Secretariat
March 2001**

ANNEXES

- ANNEX A CC/91/4: 1,3-Dichloropropan-2-ol
- ANNEX B Extract from COC minutes CC/MIN/91/1 (Item 5: 1,3-Dichloropropanol CC/91/4)
- ANNEX C COM paper MUT/01/06 ;1,3 Dichloropropanol
- ANNEX D IARC Monograph on 2,3-Dibromopropan-1-ol (IARC 2000 Vol77 p439-454)

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ANNEX A

**COC paper CC/91/4:
1,3-Dichloropropan-2-ol**

ANNEX B

**Extract from COC minutes CC/MIN/91/1
(Item 5: 1,3-Dichloropropanol CC/91/4)**

ANNEX C

**COM paper MUT/01/06 ;
1,3 Dichloropropanol**

ANNEX D

**IARC Monograph on 2,3-Dibromopropan-1-ol (IARC
2000, Vol 77 p439-454)**