IARC MONOGRAPHS

SOME CHEMICALS PRESENT IN INDUSTRIAL AND CONSUMER PRODUCTS, FOOD AND DRINKING-WATER

VOLUME 101

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, which met in Lyon, 15-22 February 2011

LYON, FRANCE - 2013

IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer

World Health Organization

3-MONOCHLORO-1,2-PROPANEDIOL

There appears to be no general consensus on a common trivial name for this agent: α-chlorohydrin and 3-monochloro-1,2-propanediol are equally used; however, a preference for 3-monochloro-1,2-propanediol, and especially the abbreviation 3-MCPD, was noted in the more recent literature.

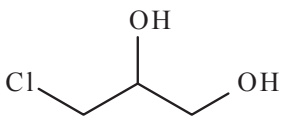
1. Exposure Data

1.1 Chemical and physical data

1.1.1 Nomenclature

From Merck Index (2010) and SciFinder (2010)
Chem. Abstr. Serv. Reg. No.: 96-24-2
Chem. Abstr. Name:
3-Chloro-1,2-propanediol
IUPAC Systematic Name:
3-Chloropropane-1,2-diol
Synonyms: Chlorodeoxyglycerol; 1-chloro-2,3-dihydroxypropane; 3-chloro-1,2-dihydroxypropane; α-chlorohydrin; chloropropanediol; 1-chloropropane-2,3-diol; 3-chloropropanediol; 3-chloro-propylene glycol; 3-chloro-1,2-propylene glycol; 1,2-dihydroxy-3-chloropropane; 2,3-dihydroxypropyl chloride; glyceryl chloride; glycerol chlorohydrin; glycerol 3-chlorohydrin; glyceryl α-chlorohydrin; 3-MCPD; 3-monochloropropane-1,2-diol
EPA Chemical Code: 117101
EINECS No.: 202-492-4

1.1.2 Structural and molecular formulae and relative molecular mass



$C_3H_7ClO_2$
Relative molecular mass: 110.54

1.1.3 Chemical and physical properties of the pure substance

From Liu *et al.* (2005), Beilstein (2010), Merck Index (2010), and SciFinder (2010)
Description: Liquid with a pleasant odour, and a tendency to turn to a straw colour
Boiling-point: 114–120 °C
Melting-point: Decomposes at 213 °C
Density: d_4 = 1.3218 at 20 °C
Refractive index: n_D = 1.4831 at 20 °C
Solubility: Soluble in water, alcohol, diethyl ether and acetone
Vapour pressure: 0.195–5.445 mmHg at 50–100 °C

1.1.4 Technical products and impurities

The purity of 3-monochloro-1,2-propanediol (3-MCPD) has been discussed (Jones & Cooper, 1999). The commercial product, which is racemic (*R*,*S*)-3-MCPD was shown to contain various impurities such as hydrochloric acid, glycerol, chlorinated acetic acids and chlorinated dioxolanes, indicating that many studies in the past may have been confounded by the impurities.

1.1.5 Analysis

Most methods for the analysis of 3-MCPD focus on the trace analysis at microgram per kilogram levels in various food matrices, which is relatively complicated (Wenzl *et al.*, 2007). The three main physical characteristics that contribute to these complications have been attributed to the absence of a suitable chromophore, a high boiling-point and a low molecular weight (Hamlet *et al.*, 2002a). Initial methods that were developed for the determination of chloropropanols without derivatization showed low sensitivity (Table 1.1). Because of the absence of a chromophore, approaches based on high-performance liquid chromatography with ultraviolet or fluorescence detection cannot be applied, and only one such method with refractive index detection that has been used to study the kinetics of 3-MCPD formation in model systems appears to be unsuitable to determine trace quantities of the compound in food matrices (Hamlet & Sadd, 2002).

Direct analysis by gas chromatography (GC) without derivatization is also restricted. The low volatility and high polarity of 3-MCPD give rise to unfavourable interactions with components of the GC system that result in poor peak shape and low sensitivity. For example, during GC, 3-MCPD can react with other components of the sample to form hydrochloric acid in the presence of water, and with active sites in the column and non-volatile residues in the column inlet (Kissa, 1992). Interferences may also arise from the reaction of 3-MCPD with ketones contained in the matrix to form ketals (Kissa, 1992). Peak broadening and ghost peaks were observed with GC-based methods for the analysis of underivatized 3-MCPD (Rodman & Ross, 1986).

The low molecular weight of 3-MCPD aggravates detection by mass spectrometry (MS) because diagnostic ions cannot be distinguished reliably from background chemical noise. Due to these apparent limitations, the methods based on direct GC (e.g. Wittmann, 1991; Spyres, 1993) are more or less obsolete, and, because of their high limits of detection, are unsuitable to control maximum levels of 3-MCPD (see Section 1.4).

Xing & Cao (2007) developed a simple and rapid method applied capillary electrophoresis with electrochemical detection. However, its sensitivity appears to be insufficient to determine contents in the lower microgram per kilogram range found in foods.

None of the methods that use underivatized analytes is of sufficient sensitivity or selectivity to determine low microgram per kilogram levels in foodstuffs, nor is derivatization using sylilation with bis(trimethylsilyl)trifluoroacetamide (Kissa, 1992; Bodén *et al.*, 1997), the detection limits of which were above 0.02 mg/kg using MS.

In combination with GC-MS, the three most common derivatives that give adequate sensitivity and selectivity are: (1) cyclic derivatives from the reaction with *n*-butylboronic acid or phenylboronic acid (PBA) (Rodman & Ross, 1986; Pesselman & Feit, 1988); (2) heptafluorobutyrate derivatives from heptafluorobutyrylimidazole (HFBI) or heptafluorobutyric anhydride (van Bergen *et al.*, 1992; Hamlet, 1998; Chung *et al.*, 2002); and (3) cyclic ketal derivatives from ketones (Meierhans *et al.*, 1998; Dayrit & Niñonuevo, 2004; Rétho & Blanchard, 2005). These methods are summarized in Table 1.1. For further details on the derivatization of 3-MCPD, see Wenzl *et al.* (2007).

Table 1.1 Selected methods for the analysis of 3-monochloro-1,2-propanediol (MCPD) in various matrices

Matrix	Analytes	Pre-treatment	Clean up	Derivatization	Detection	LOD for 3-MCPD (µg/kg)	Reference
Seasonings	2-MCPD, 3-MCPD, 1,3-DCP, 2,3-DCP	Water, pH adjustment	Extrelut	None	GC-MS SIM	100	Wittmann (1991)
HVP	3-MCPD	20% NaCl solution	Extrelut	None	GC-ECD	250	Spyres (1993)
Cereal products	MCPD esters	Ethyl acetate extraction	Preparative TLC	None	GC-MS Scan	-	Hamlet & Sadd (2004)
Model systems	3-MCPD	-	-	None	HPLC-RI	-	Hamlet & Sadd (2002)
Solvents	3-MCPD	-	-	BSTFA	GC-FID	5000	Kissa (1992)
Paper	3-MCPD, 1,3-DCP	Acetonitrile extraction	-	BSTFA	GC-MS SIM	40	Bodén *et al.* (1997)
Soya sauce	3-MCPD	Dilution with buffer	-	None	CE-ECD	130	Xing & Cao (2007)
Standards	3-MCPD	-	-	PBA	GC-MI-FTIR	-	Rodman & Ross (1986)
Aqueous solutions	3-MCPD	-	-	BBA	GC-ECD	100	Pesselman & Feit (1988)
HVP	3-MCPD	20% NaCl solution	-	PBA	GC-FID	500–1000	Plantinga *et al.* (1991), Anon (1995)
Various foods	3-MCPD	20% NaCl solution	-	PBA	GC-MS SIM	3–10	Breitling-Utzmann *et al.* (2003)
Various foods	3-MCPD	20% NaCl solution	-	PBA	GC-MS/MS MRM (triple quadruple)	5	Kuballa & Ruge (2003)
Various foods	Free and bound 3-MCPD	Fat extraction, interesterification	-	PBA	GC-MS SIM	3	Divinová *et al.* (2004)
HVP, soya sauce	3-MCPD	Dilution 1:10	HS-SPME	PBA	GC-MS SIM	3.87	Huang *et al.* (2005)
HVP	2-MCPD, 3-MCPD, 1,3-DCP, 2,3-DCP	5M NaCl solution	Extrelut, two-stage extraction	HFBI	GC-ECD, GC-MS	50–100	van Bergen *et al.* (1992)
HVP, seasonings	3-MCPD, 2-MCPD	5M NaCl solution	Extrelut	HFBI	GC-MS/MS MRM (ion trap)	5	Hamlet & Sutton (1997)

Table 1.1 (continued)

Matrix	Analytes	Pre-treatment	Clean up	Derivatization	Detection	LOD for 3-MCPD (µg/kg)	Reference
Various foods	3-MCPD, 2-MCPD	5M NaCl solution	Extrelut	HFBI	GC-MS SIM or GC-MS/MS MRM (ion trap)	5–10	Hamlet (1998), Brereton *et al.* (2001)
Water	3-MCPD, 1,3-DCP (& bromo-propanediols)	Ethyl acetate extraction	-	HFBA	GC-ECD	0.7	Matthew & Anastasio (2000)
Soya sauce	1,3-DCP, 3-MCPD	5M NaCl solution	Silica gel (60 mesh)	HFBA	GC-MS SIM	5	Chung *et al.* (2002)
Cereal products	Free and bound 3-MCPD	Enzyme hydrolysis (lipase)	Extrelut	HFBI	GC-MS	-	Hamlet & Sadd (2004)
Model systems	3-MCPD, 2-MCPD	Hexane extraction	ASE	HFBI	GC-MS	5	Bel-Rhlid *et al.* (2004), Robert *et al.* (2004)
Soy sauce, flavouring	2-MCPD, 3-MCPD, 1,3-DCP, 2,3-DCP	5M NaCl solution	Extrelut	HFBA-Et_3N	GC-MS EI SIM or NCI SIM	3 (EI), 0.6 (NCI)	Xu *et al.* (2006)
Various foods	1,3-DCP, 3-MCPD	Saturated NaCl solution	Aluminium oxide	HFBA	GC-MS SIM	1	Abu-El-Haj *et al.* (2007)
Various foods	3-MCPD, 2-MCPD	Saturated NaCl solution	Extrelut	Acetone	GC-MS SIM	10	Meierhans *et al.* (1998)
Soya sauce	3-MCPD	Saturated NaCl solution	Extrelut	4-Heptanone	GC-MS Scan	1.2	Dayrit & Niñonuevo (2004)
Various foods	3-MCPD	Pure water extraction	Extrelut	Acetone, filtration over aluminium oxide	GC-MS SIM	2–5	Rétho & Blanchard (2005)
Blood, urine	3-MCPD	Dilution, acidification, (enzymatic pretreatment)	Silica gel (60 mesh)	HFBA	GC-MS NCI SIM	2	Berger-Preiss *et al.* (2010)
Various foods	3-MCPD and 3-MCPD esters	20% NaCl solution	LLE with MTBE	PBA	GC-MS SIM	1–6	Küsters *et al.* (2010)

Table 1.1 (continued)

Matrix	Analytes	Pre-treatment	Clean up	Derivatization	Detection	LOD for 3-MCPD (µg/kg)	Reference
Seasoning	3-MCPD, 1,3-DCP, 2,3-DCP	No data	No data	TSIM	GC-MS SIM	0.14	Cao *et al.* (2009)
Oils	3-MCPD after cleavage of MCPD esters	Cleavage with sodium methoxide	Different LLE steps	PBA	GC-MS SIM	50–150	Weißhaar (2008)
Soya sauce	1,3-DCP, 3-MCPD	NaCl addition	HS-SPME	MSTFA	GC-MS SIM	4.62	Lee *et al.* (2007)
Oils	Bound 3-MCPD	Alkaline release	LLE	PBA	GC-MS SIM	50	Kuhlmann (2010)

BBA, *n*-butylboronic acid; BSTFA, bis(trimethylsilyl)trifluoroacetamide; CE-ECD, capillary electrophoresis with electrochemical detection; DCP, dichloropropanol; EI, electron-impact ionization; Et_3N, triethylamine; GC-ECD, gas chromatography with electron capture detection; GC-FID, gas chromatography with flame ionization detection; GC-MI-FTIR, gas chromatography-matrix isolation-Fourier transform infrared spectroscopy; GC-MS, gas chromatography-mass spectrometry; GC-MS/MS, gas chromatography-tandem mass spectrometry; HFBA, heptafluorobutyric anhydride; HFBI, heptafluorobutyrylimidazole; HPLC-RI, high-performance liquid chromatography with refractive index detection; HS-SPME, headspace solid-phase microextraction; HVP, acid-hydrolysed vegetable protein; LLE, liquid liquid extraction; LOD, limit of detection; MCPD, monochloro-1,2-propanediol; MRM, multiple reaction monitoring; MS, mass spectrometry; MSTFA, *N*-methyl-*N*-(trimethylsilyl)-trifluoroacetamide; MTBE, methyl *tert*-butyl ether; NaCl, sodium chloride; NCI, negative chemical ionization; PBA, phenylboronic acid; SIM, selected ion monitoring; TLC, thin-layer chromatography; TSIM, 1-trimethylsilylimidazole
Updated from Wenzl *et al.* (2007)

Of the different procedures, the PBA derivatization method is the most common. For example, it is used as a German reference method for food (Anon., 1995). An advantage of PBA derivatization is that no sample clean-up is required because PBA reacts specifically with diols to form non-polar cyclic derivatives that are extractable into *n*-hexane. The disadvantage of PBA is that other chloropropanols, such as 1,3-dichloro-2-propanol (1,3-DCP) cannot be determined simultaneously using this method. Sensitivity can be further improved by the application of triple quadruple MS/MS (Kuballa & Ruge, 2003). Sample preparation may possibly be improved by headspace solid-phase microextraction (Huang *et al.*, 2005).

HFBI/heptafluorobutyric anhydride derivatization is also very commonly applied, although it is less selective than that with boronic acids. The procedure has been validated by a collaborative trial (Brereton *et al.*, 2001). Repeatability ranged from 0.005 to 0.013 mg/kg and reproducibility from 0.010 to 0.027 mg/kg. The validation of the method was judged to be satisfactory and the method was adopted by the Association of Official Analytical Chemists International as an official method (Brereton *et al.*, 2001). The method was also adopted as European norm EN 14573 (European Standard, 2005). The HFBI method was found to be more labour-intensive than the PBA method but has the advantage of analysing both 1,3-DCP and 3-MCPD simultaneously during the same GC-MS run. The procedure can also be used with little modification to analyse blood and urine samples of rats in the context of toxicological studies (Berger-Preiss *et al.*, 2010).

Currently, only a few methods exist to analyse so-called 'bound' 3-MCPD, which is a 3-MCPD ester bound with fatty acids. Unhydrolysed MCPD esters can be analysed directly by extraction into an organic solvent, clean-up by a preparative thin-layer chromatography (Davídek *et al.*, 1980) and analysis using GC-MS (Hamlet & Sadd, 2004). More commonly, bound 3-MCPD is released from the esters and analysed in free form, through enzyme hydrolysis with a commercial lipase from *Aspergillus* (Hamlet & Sadd, 2004), interesterification of the sample with sulfuric acid (Divinová *et al.*, 2004), or cleavage with sodium methoxide (Weißhaar, 2008) or methanolic sodium hydroxide (Kuhlmann, 2010).

1.2 Production and use

1.2.1 Production

Chlorohydrins are readily prepared by the reaction of an alkene with chlorine and water (Richey, 2000). The reaction of allyl alcohol with chlorine and water at 50–60 °C gives a yield of 88% monochlorohydrins and 9% dichlorohydrins (Liu *et al.*, 2005). A 85–88% yield was reported by the reaction of glycerol with aqueous hydrochloric acid in the presence of a catalytic quantity of acetic acid (Richey, 2000). An anhydrous procedure that involves the reaction of glycerol and hydrogen chloride gas in the presence of acetic acid has also been described (Richey, 2000).

3-MCPD is listed in the CHEMCATS database (SciFinder, 2010) as being available at 96 suppliers worldwide in amounts up to bulk quantities. The commercial market for chlorohydrins has been described as small (Richey, 2000). 3-MCPD was available from at least three manufacturers in the USA in steel drums (227.3–240 kg net) (Richey, 2000).

1.2.2 Use

According to the Merck Index (2010), 3-MCPD has been used to lower the freezing-point of dynamite and in the manufacture of dye intermediates. 3-MCPD is one of the few chemosterilants that has been commercialized for rodent control (Ericsson, 1982; Buckle, 2005; EPA, 2006). It has been used at a dose of 90–100 mg/kg body

weight (bw) to sterilize male Norway rats, and is available as a 1% ready-to-use bait and as a 20% concentrate (trade names: Epibloc, Gametrics). It has been reported that chemosterilants are not widely used in pest control because their effects are often transient and the presence of rodents — sterile or otherwise — is considered to be undesirable (Buckle, 2005).

3-MCPD may be used as a raw material for the synthesis of guaifenesin, a secretomotoric drug (Yale *et al.*, 1950; Bub & Friedrich, 2005), and for the synthesis of an intermediate in the production of the statin drug, atorvastatin (Kleemann, 2008). It was also used in the final step of the synthesis of iohexol, a contrast medium for angiography and urography (Lin, 2000).

1.3 Occurrence

1.3.1 Natural occurrence

3-MCPD is not known to occur as a natural product.

1.3.2 Occupational exposure

Individuals who are potentially exposed to 3-MCPD include production workers and users of chemosterilants for rodent control. The EPA (2006) considered that the risk of occupational exposure from its use as a rodenticide was unlikely, because the end-use product is packaged in poly-paper sachets, which are placed intact into tamper-resistant (closed loading) systems.

1.3.3 Occurrence in food

Chloropropanols are foodborne contaminants that can be formed during the processing of various foodstuffs (Wenzl *et al.*, 2007). This class of food contaminant was first recognized at the Institute of Chemical Technology in Prague (Velíšek *et al.*, 1978) in acid-hydrolysed vegetable protein (HVP), a seasoning ingredient that is widely used in a variety of processed and prepared foods such as soups, sauces, bouillon cubes and soya sauce (Calta *et al.*, 2004). 3-MCPD is the most abundant chloropropanol found in foodstuff, while 1,3-DCP generally occurs at lower levels (see the *IARC Monograph* on 1,3-dichloro-2-propanol in this volume). Their isomers — 2-MCPD and 2,3-DCP — are usually found at much lower concentrations (Wenzl *et al.*, 2007).

During the last decade, renewed interest in chloropropanols and the development of analytical methods of their presence in food matrices other than acid-HVP was triggered by the detection of 3-MCPD in a wide range of foods and food ingredients, notably in thermally processed foods such as malts, cereal products and meat (Brereton *et al.*, 2001; Hamlet *et al.*, 2002a, b; Breitling-Utzmann *et al.*, 2003). In addition, domestic processing (e.g. grilling and toasting) can produce substantial increases in the 3-MCPD content of bread or cheese (Crews *et al.*, 2001; Breitling-Utzmann *et al.*, 2003).

Several studies on the mechanism of 3-MCPD formation have been performed (Hamlet & Sadd, 2002; Hamlet *et al.*, 2003; Velíšek *et al.*, 2003; Calta *et al.*, 2004; Doležal *et al.*, 2004; Hamlet *et al.*, 2004a, b; Robert *et al.*, 2004; Breitling-Utzmann *et al.*, 2005; Hamlet & Sadd, 2005; Muller *et al.*, 2005), and showed that it is formed from glycerol or acylglycerols and chloride ions in heat-processed foodstuffs that contain fat with low water activity. Although the overall levels of 3-MCPD in bakery products are relatively low, the high level of consumption of bread, and its additional formation from toasting, indicate that this staple food alone can be a significant dietary source of 3-MCPD (Breitling-Utzmann *et al.*, 2003). In malt products, 3-MCPD was only found in coloured malts and at highest levels in the most intensely coloured samples. Additional heat treatments, including kilning or roasting, were judged to be a significant factor in the formation of 3-MCPD in these ingredients (Hamlet *et al.*, 2002b; Muller *et al.*, 2005). The occurrence

of 3-MCPD in beer, which is generally less than 10 µg/L, was reviewed recently (IARC, 2010).

Concentrations of 3-MCPD above 0.02 mg/kg were recently found in smoked fermented sausages and smoked ham (Kuntzer & Weißhaar, 2006; Jira, 2010), and the smoking process was identified as a major source. In contrast to the formation of 3-MCPD in acid-HVP, soya sauce and bakery products, lipids are not precursors of 3-MCPD in smoked foods. A hypothetical mechanism, in which 3-hydroxyacetone is the precursor, was suggested for the formation of 3-MCPD in wood smoke (Kuntzer & Weißhaar, 2006). Further details on the mechanisms of formation are available in several recent reviews (Hamlet, 2009; Hamlet & Sadd, 2009; Velíšek, 2009).

Data from a large international survey with over 5000 analytical results on the occurrence of 3-MCPD in food have been published (JECFA, 2007), and are summarized in Table 1.2. The average concentration of 3-MCPD in soya sauce and soya sauce-related products was much higher (average, 8 mg/kg) than that in any other food or food ingredient (average, < 0.3 mg/kg). Data from Japan show that soya sauce produced by traditional fermentation contains insignificant average amounts of 3-MCPD (0.003 mg/kg) compared with soya sauce made with acid-HVP (1.8 mg/kg) (JECFA, 2007). Estimated average dietary exposures of the general population from a wide range of foods, including soya sauce and soya sauce-related products, ranged from 0.02 to 0.7 µg/kg bw per day, and those for consumers at the high percentile (95th), including young children, ranged from 0.06 to 2.3 µg/kg bw per day. The exposures were calculated by linking data on individual consumption and body weight from national food consumption surveys with data on mean occurrence obtained from food contamination surveys (JECFA, 2007).

Other exposure estimates have been published since that time. For secondary school students in China, Hong Kong Special Administrative Region, the average exposure was estimated to be 0.063–0.150 µg/kg bw per day, while that for high consumers was 0.152–0.300 µg/kg bw per day (Yau *et al.*, 2008).

In the Republic of Korea, the mean intake level of 3-MCPD was estimated to range from 0.0009 to 0.0026 µg/kg bw per day and that at the 95th percentile of consumption was 0.005 µg/kg bw per day (Hwang *et al.*, 2009). [The Working Group noted that the exposure estimate of Hwang *et al.* (2009) only included soya sauce and did not consider total food consumption.]

Since the implementation of limits on permissible concentrations (see Section 1.4), actions by industry have reduced the level of contamination by chloropropanols of acid-HVP prepared in Europe (Crews *et al.*, 2002). A recent survey confirmed that the limit was still exceeded in only single samples of soya sauce on the European market (Schlee *et al.*, 2011).

In foodstuffs, 3-MCPD occurs, not only in its free form, but also as esters with higher fatty acids (so-called bound 3-MCPD) (Table 1.3). 3-MCPD esters were found in goats' milk and human milk (Zelinková *et al.*, 2008; Rahn & Yaylayan, 2010). During food processing (especially during oil refining), the formation of process-induced 3-MCPD esters may occur and various mechanisms are currently under investigation that most probably involve a nucleophilic attack by chloride ions (Rahn & Yaylayan, 2010). Evidence has been found that the content of bound 3-MCPD exceeded that of free 3-MCPD by at least five- and up to 396-fold (Svejkovská *et al.*, 2004). Hamlet & Sadd (2004) found MCPD esters in baked cereal products and showed that they might be generated as stable intermediates or by-products of the formation reaction from mono- and diacylglycerol precursors. The esters were also found in food groups that did not contain free 3-MCPD (e.g. coffee creamers, cream aerosols, bouillon cubes; Karšulínová *et al.*, 2007). In refined fats and oils, the highest concentrations were detected in palm oil and palm oil-based fats (Weißhaar & Perz, 2010). This is consistent with findings

Table 1.2 Summary of the distribution-weighted concentration of 3-monochloro-1,2-propanediol in soya sauce and soya sauce-based products, in other foods and in food ingredients from various countries, 2001–06[a]

Product	LOQ (mg/kg)	No.	*n* < LOQ	Mean[b] (mg/kg)	Maximum (mg/kg)
Soya sauce and soya sauce-based products	0.006–5.000	2629	1433	8.39	1779
Dairy products (cheeses)	0.005–0.010	149	138	0.007	0.095
Fat, oils and fat emulsions	0.005–0.010	38	24	0.081	1.5
Nuts, seeds and processed vegetables	0.01	37	14	0.061	0.69
Cereals and cereal products (flours, starch, pasta, noodles and bakery products)	0.005–0.020	577	348	0.023	0.945
Meat and meat products	0.005–0.010	251	170	0.027	0.41
Fish products	0.005–0.010	89	68	0.012	0.191
Salts, spices, soup sauces, salads and protein products	0.01–2.5	454	248	0.286	50.7
Foodstuffs intended for particular nutritional uses	0.005–0.080	137	128	0.007	0.02
Ready-to-eat savouries	0.006–0.020	23	15	0.01	0.041
Composite food	0.01	24	19	0.013	0.113
Coffee, roasted	0.005–0.010	23	23	0.005	0.005
Cocoa paste and chocolate products	0.005–0.080	15	13	0.007	0.005
Beer and malt beverages	0.005–0.080	138	128	0.008	0.03
Confectionery, sugar-based (chewing gum, candy and nougats)	0.01	27	24	0.007	0.023
Food ingredients (including acid-hydrolysed vegetable proteins, meat extracts, malts, modified starches and seasonings)	0.01–1.15	489	262	0.099	2.5

[a] Includes data of surveys before intervention to reduce occurrence had been undertaken by government or industry

[b] Data below the limit of detection or LOQ have been assumed to be half of those limits and the mean was weighted according to the number of samples per country

LOQ, limit of quantification

Data summarized from JECFA (2007)

Table 1.3 Summary of the concentrations of 3-monochloro-1,2-propanediol esters in foodstuffs quantified as 3-monochloro-1,2-propanediol [a]

Product	No.	Mean (mg/kg)	Maximum (mg/kg)	Reference
Bread (toast)	7	0.086	0.16	Hamlet & Sadd (2004)
Coffee	15	0.14	0.39	Doležal *et al.* (2005)
Oils				
Virgin seed oils	9	0.063	< 0.3	Zelinková *et al.* (2006)
Virgin olive oils	4	0.075	< 0.3	Zelinková *et al.* (2006)
Virgin germ oils	2	0.1	< 0.3	Zelinková *et al.* (2006)
Refined seed oils	5	0.524	1.234	Zelinková *et al.* (2006)
Refined olive oils	5	1.426	2.462	Zelinková *et al.* (2006)
Vegetable oil–fat mixes	11	1.534	2.435	Seefelder *et al.* (2008)
Refined palm oil and palm oil-based fats	12	3.24	5.8	Weißhaar & Perz (2010)
Other refined vegetable oils	57	0.4–1.7[b]	(no data)	Weißhaar & Perz (2010)
Infant and baby foods	14	0.289	0.588	Zelinková *et al.* (2009b)
Human breast milk	12	0.036	0.076	Zelinková *et al.* (2008)
Infant formula and follow-up formula	10	2.568	4.169	BfR (2007)

[a] Includes data of surveys before intervention to reduce occurrence had been undertaken by government or industry
[b] Range
Data updated from Hamlet & Sadd (2009)

that frying oil is the major source of 3-MCPD fatty acid esters in potato products (French fries and chips) (Hamlet, 2009; Hamlet & Sadd, 2009; Zelinková *et al.*, 2009a).

These esters should also be treated as food contaminants because 3-MCPD may be released *in vivo* by a lipase-catalysed hydrolysis reaction (Wenzl *et al.*, 2007). It was assumed that 3-MCPD esters behave similarly to triacylglycerols and undergo similar metabolism and digestion, which could either lead to the release of free 3-MCPD or to its incorporation into lipoprotein particles, depending on the positioning of the 3-MCPD fatty acid ester group on the glycerol backbone (Schilter *et al.*, 2010). Recent in-vitro studies confirmed that 3-MCPD fatty acid esters are probably hydrolysed in the human intestine followed by rapid resorption of free 3-MCPD (Buhrke *et al.*, 2010). After 4 hours of incubation with small intestine juice containing pancreatic lipase, the release of free 3-MCPD ranged between 25 and 50% from palm oil, and ≈82% was released from toasted bread (Schilter *et al.*, 2010). These results indicated that 3-MCPD fatty acid esters substantially increase the amount of 3-MCPD ingested from food (Buhrke *et al.*, 2010).

[The Working Group noted that, in light of the recent evidence that 3-MCPD occurs in a bound form as 3-MCPD esters, it can be assumed that all of the exposure values mentioned above are probably underestimates.]

1.3.4 Environmental occurrence

3-MCPD can occur as a contaminant in drinking-water from water purification plants that use epichlorohydrin-linked cationic polymer resins or in wastewaters (Nienow *et al.*, 2009).

1.4 Regulations and guidelines

Regulations and guidelines on permissible concentrations of 3-MCPD in foodstuffs are summarized in Table 1.4. The Scientific Committee on Food of the European

Table 1.4 International maximum concentration limits/specifications for 3-monochloro-1,2-propanediol in foodstuffs

Country/Region	3-MCPD (mg/kg)	Scope
Australia/New Zealand	0.2	Soya/oyster sauces
Canada	1	Soya/oyster sauces
the People's Republic of China	1	Acid-HVP
European Union	0.02	HVP and soya sauces (40% solids)
Republic of Korea	0.3	Soya sauce containing acid-HVP
	1	HVP
Malaysia	0.02	Liquid foods with acid-HVP
	1	Acid-HVP, industrial product
Switzerland	0.2	Savoury sauces
Thailand	1	Hydrolysed soya bean protein
USA	1	Acid-HVP

HVP, hydrolysed vegetable protein; 3-MCPD, 3-monochloro-1,2-propanediol
Adapted from Hamlet & Sadd (2009)

Commission considered that a threshold-based approach for deriving a tolerable daily intake would be appropriate, and determined a value of 2 µg/kg bw (SCF, 2001). This value was confirmed as a provisional maximum tolerable daily intake (JECFA, 2007). The European Commission has set a regulatory limit of 0.02 mg/kg for 3-MCPD in HVP and soya sauce (European Commission, 2001).

2. Cancer in Humans

No data were available to the Working Group.

3. Studies in Experimental Animals

3.1 Oral administration

3.1.1 Mouse

See Table 3.1

Four groups of 50 male and 50 female B6C3F$_1$ mice received 0 (control), 30, 100 or 300 ppm 3-MCPD in the drinking-water up to day 100 and 0 or 200 ppm thereafter until 104 weeks (0, 4.2, 14.3 or 33.0 and 0, 3.7, 12.2 or 31.0 mg/kg bw in males and females, respectively). No neoplasms attributable to treatment with 3-MCPD were observed (Jeong *et al.*, 2010).

3.1.2 Rat

See Table 3.2

Groups of 26 male and 26 female Charles River Sprague-Dawley (CD) rats were administered 30 mg/kg bw or 60 mg/kg bw (maximum tolerated dose) 3-MCPD by gavage twice a week. Groups of 20 males and 20 females served as untreated controls. After 10 weeks, the doses were increased to 35 and 70 mg/kg bw, respectively, and treatment was continued until week 72. The study was terminated after 2 years. Three parathyroid adenomas were found in high-dose males, but this finding was not statistically significant compared with the control group. While females showed no signs of toxicity, male rats had a higher mortality rate than controls (Weisburger *et al.*, 1981).

Groups of 50 male and 50 female Sprague-Dawley rats received drinking-water containing 0, 25, 100 or 400 ppm 3-MCPD for 100 and 104 weeks, respectively. The incidence of renal tubule

Table 3.1 Carcinogenicity studies of 3-monochloro-1,2-propanediol in mice

Strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance
B6C3F$_1$ (M, F) 104 wk Jeong *et al.* (2010)	Drinking-water 0 (control), 30, 100 and 300 µg/mL until d 100 followed by 200 µg/mL until termination of the experiment 50/group	Liver (hepatocellular carcinoma): M–13/50, 7/49, 4/49, 13/49; F–0/48, 1/50, 3/50, 1/50 Lymphoma (all): M–8/50, 6/50, 6/50, 7/50; F–12/50, 10/50, 17/50, 8/50 Lung (bronchioalveolar adenoma): M–5/50, 5/50, 5/50, 2/50; F–1/48, 3/50, 3/50, 1/50 Lung (bronchioalveolar carcinoma): M–8/50, 2/50, 1/50, 4/50; F–1/48, 3/50, 2/50, 0/50 Kidney (renal tubule adenoma): M–1/50, 1/50, 0/48, 0/49; F–1/45, 0/46, 0/47, 0/47 Kidney (renal tubule adenocarcinoma): M–0/50, 1/50, 0/48, 0/49; F–0/45, 0/46, 0/47, 0/47	NS
ICR/Ha Swiss (F) 580 d Van Duuren *et al.* (1974)	Subcutaneous injection in the left flank of 0 (control) or 1.0 mg in 0.05 mL tricaprylin once/wk 50/group	Skin (sarcoma): 1/50, 1/50 Skin (squamous-cell carcinoma): 0/50, 0/50 Skin (adenocarcinoma): 0/50, 0/50	NS
ICR/Ha Swiss (F) 580 d Van Duuren *et al.* (1974)	Dermal application to the interscapular region of 0 (control) or 2.0 mg in 0.1 mL acetone 3 × /wk 50/group	Skin (papilloma): 0/50, 0/50 Skin (carcinoma): 0/50, 0/50	NS

d, day or days; F, female; M, male; NS, not significant; wk, week or weeks

Table 3.2 Carcinogenicity studies of 3-monochloro-1,2-propanediol in rats

Strain (sex) Duration Reference	Dosing regimen Animals/group at start	Tumour incidence	Significance	Comments
CD (M, F) 104 wk Weisburger *et al.* (1981)	Gavage, twice/wk Group 1: control; Group 2: 30 mg/kg bw for 10 wk, followed by 35 mg/kg bw for 62 wk; Group 3: 60 mg/kg bw for 10 wk, followed by 70 mg/kg bw for 62 wk 20–26/group	Parathyroid (adenoma): M–0/20, 0/26, 3/26; F–0/20, 0/26, 0/26	NS	
Sprague-Dawley (M, F) 100–104 wk Cho *et al.* (2008)	Drinking-water 0, 25, 100 or 400 ppm 50/group	Kidney (renal tubule adenoma): M–0/50, 0/50, 1/50, 4/50; F–0/50, 0/50, 1/50, 6/50* Kidney (renal tubule carcinoma): M–0/50, 0/50, 0/50, 5/50*; F–1/50, 0/50, 1/50, 3/50 Kidney (renal tubule adenoma or carcinoma): M–0/50, 0/50, 1/50, 7/50*; F–1/50, 0/50, 2/50, 9/50* Testis (Leydig-cell adenoma): M–1/50, 1/50, 4/50, 14/50* Pituitary gland (adenoma): M–25/50, 26/50, 24/50, 13/50*	 NS *$P < 0.05$ (poly-3 test) *$P < 0.05$ (poly-3 test) NS *$P < 0.05$ (poly-3 test) *$P < 0.05$ (poly-3 test) *$P < 0.05$ (decrease, poly-3 test)	Survival: M–28, 34, 18, and 26%; F–30, 44, 22, and 32%

bw, body weight; F, female; M, male; NS, not significant; wk, week or weeks

carcinoma, renal tubule adenoma or carcinoma (combined) and Leydig-cell adenoma showed dose-related positive trends in male rats, and the incidence of renal tubule carcinoma and Leydig-cell adenoma was significantly increased in high-dose males. The incidence of renal tubule adenoma or carcinoma (combined) showed a positive trend in female rats, and the increase was also significant in the high-dose group (Cho *et al.*, 2008).

[Kidney tumours are spontaneous neoplasms in experimental animals.]

3.2 Subcutaneous administration

3.2.1 Mouse

See Table 3.1

Groups of 50 female ICR/Ha Swiss mice received weekly subcutaneous injections of 0 (control) or 1.0 mg 3-MCPD in 0.05 mL tricaprylin for 580 days. Median survival time was 487 days. At termination of the study, one 3-MCPD-treated and one vehicle-treated mouse had a sarcoma at the site of injection. No other neoplasms were observed (Van Duuren *et al.*, 1974).

3.3 Dermal application

3.3.1 Mouse

Two groups of 50 female ICR/Ha Swiss mice received topical applications of 0 (control) or 2.0 mg 3-MCPD in 0.1 mL acetone three times a week for up to 580 days. Throughout the duration of the study, no skin tumours were observed (Van Duuren *et al.*, 1974).

4. Other Relevant Data

4.1 Absorption, distribution, metabolism and excretion

4.1.1 Humans

No data were available to the Working Group

4.1.2 Experimental systems

(a) Absorption, distribution and excretion

Most studies appear to have been conducted with racemic 3-MCPD, and only limited information is available on the various toxicological properties of the (*R*)- and (*S*)-isomers of 3-MCPD (e.g. see Jones & Cooper, 1999).

Available data on the absorption, distribution and excretion of 3-MCPD in experimental systems have been reviewed previously (JECFA, 2002).

3-MCPD crosses the blood–testis barrier and the blood–brain barrier and is widely distributed in the body fluids (Edwards *et al.*, 1975). [^{14}C]3-MCPD has been found to accumulate in the cauda epididymis of rats and, to a lesser extent, in that of mice, as observed by autoradiography (Crabo & Appelgren, 1972). In contrast, no tissue-specific retention of radiolabel was observed in rats given an intraperitoneal injection of 100 mg/kg bw [^{36}Cl]3-MCPD. The 3-MCPD metabolite β-chlorolactate did not accumulate in the tissues either (Jones *et al.*, 1978).

Male Wistar rats given a single intraperitoneal injection of 100 mg/kg bw [^{14}C]3-MCPD exhaled 30% of the dose as [^{14}C]carbon dioxide and excreted 8.5% unchanged in the urine after 24 hours (Jones, 1975). After a single intraperitoneal injection of 100 mg/kg bw [^{36}Cl]3-MCPD into rats, 23% of the radiolabel was recovered in the urine as β-chlorolactate (Jones *et al.*, 1978).

(b) Metabolism

Available data on the metabolism of 3-MCPD in experimental systems have been reviewed previously (JECFA, 2002).

In rats, 3-MCPD may be detoxified by conjugation with glutathione, yielding *S*-(2,3-dihydroxypropyl)cysteine and the corresponding mercapturic acid, *N*-acetyl-S-(2,3-dihydroxypropyl)cysteine (Jones, 1975). The compound also undergoes oxidation to β-chlorolactic acid and then to oxalic acid (Jones & Murcott, 1976). An intermediate metabolite, β-chlorolactaldehyde, may also be formed, because traces have been found in the urine of rats (Jones *et al.*, 1978). [The Working Group noted that the intermediate formation of an epoxide has been postulated but not proven (Jones, 1975).]

There is evidence that microbial enzymes — halohydrin dehalogenases — can dehalogenate haloalcohols to produce glycidol (van den Wijngaard *et al.*, 1989), which is a direct-acting alkylating agent that is mutagenic in a wide range of in-vivo and in-vitro test system and was evaluated by IARC as *probably carcinogenic to humans (Group 2A,* IARC, 2000). [The Working Group noted that insufficient information was available to determine which bacteria were used in these studies.]

In a review of the metabolism of 3-MCPD, it was concluded that the main metabolic route in mammals is the formation of β-chlorolactate and oxalic acid, while many bacteria metabolize 3-MCPD primarily via glycidol (Lynch *et al.*, 1998).

[The Working Group noted the absence of experimental evidence to propose a definite metabolic pathway of 3-MCPD in mammals, and that the formation of glycidol has yet to be established. The Working Group further noted the absence of specific information on the enzymes involved in its metabolism in mammals.]

Proposed metabolic pathways for 3-MCPD are summarized in Fig. 4.1.

4.2 Genetic and related effects

4.2.1 Humans

No data were available to the Working Group

4.2.2 Experimental systems

Genotoxicity studies of 3-MCPD *in vitro* and *in vivo* have recently been reviewed (JECFA, 2002), and the data are summarized in Table 4.1.

In vitro, 3-MCPD induced reverse mutation in various strains of *Salmonella typhimurium*, and DNA strand breaks in the Comet assay with Chinese hamster ovary cells.

No effects of 3-MCPD were observed in studies *in vivo* on micronucleus formation in male Han Wistar rat bone-marrow cells and unscheduled DNA synthesis in male Han Wistar rat hepatocytes (Robjohns *et al.*, 2003).

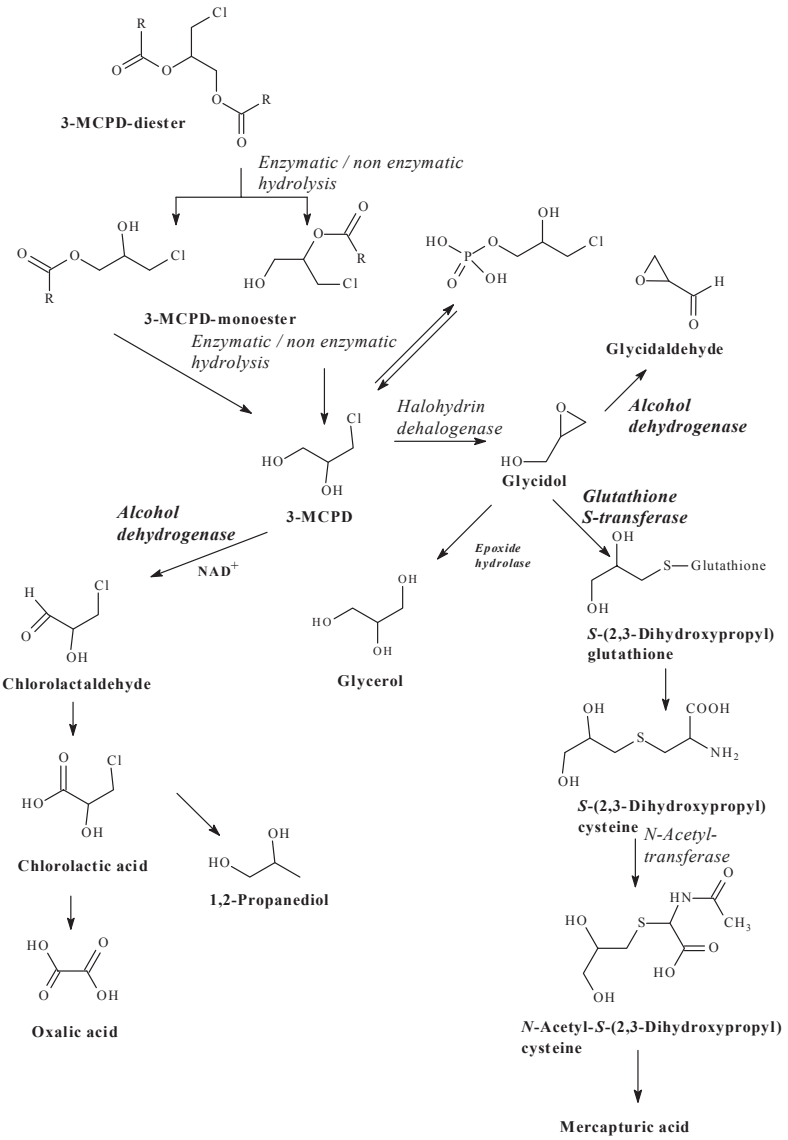
4.3 Mechanistic considerations

4.3.1 Effects on cell physiology and function

Available data on the effects of 3-MCPD on cell function have been reviewed previously (JECFA, 2002, 2007). The major effects on testicular tissue and kidney are discussed in detail below. Other effects on cell function include immunotoxicity (Lee *et al.*, 2004, 2005; Byun *et al.*, 2006) and neurotoxicity, which may be mediated, at least in part, through disturbances in the nitric oxide signalling pathway (Kim, 2008).

In a study in male Crl:HanWistBR rats, a clear reduction in the ratio of polychromatic to normochromatic erythrocytes was observed with the highest dose (60 mg/kg bw per day for 2 days), indicating bone-marrow cytotoxicity and that the substance and/or its metabolites had reached the bone marrow (Robjohns *et al.*, 2003). This finding is consistent with a study in primates,

Fig. 4.1 Hypothesized metabolic pathways for 3-monochloro-1,2-propanediol based on data from bacterial and putative mammalian pathways



Adapted from Lynch *et al.* (1998), based on data from Jones *et al.* (1978)
3-MCPD; 3-monochloro-1,2-propanediol

Table 4.1 Genetic and related effects of 3-monochloro-1,2-propanediol

Test system	Results		Dose (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Salmonella typhimurium TA100, TA1535, reverse mutation	+	+	40 mg/plate	Stolzenberg & Hine (1979, 1980)
Salmonella typhimurium TA100, reverse mutation	NT	-	NR	Majeska & Matheson (1983)
Salmonella typhimurium TA100, TA1535, reverse mutation	+	+	1.0–3.33 mg/plate	Zeiger *et al.* (1988)
Salmonella typhimurium TA100, reverse mutation	+	+	0.62 mg/plate	Ohkubo *et al.* (1995)
Salmonella typhimurium TA1535, reverse mutation	+	+	1 mg/plate	Silhánková *et al.* (1982)
Salmonella typhimurium TA1537, TA1538, TA98, reverse mutation	-	-	22 mg/plate	Silhánková *et al.* (1982)
Salmonella typhimurium TA97, reverse mutation	NT	-	10 mg/plate	Zeiger *et al.* (1988)
Salmonella typhimurium TA98, reverse mutation	(+)	-	110 mg/plate	Stolzenberg & Hine (1979)
Salmonella typhimurium TA98, reverse mutation	+	-	10 mg/plate	Zeiger *et al.* (1988)
Salmonella typhimurium TA98, reverse mutation	+	-	1.25 mg/plate	Ohkubo *et al.* (1995)
Salmonella typhimurium TM677, forward mutation	+	-	0.05 mg/plate	Ohkubo *et al.* (1995)
Escherichia coli WP2, TM930, TM1080, reverse mutation	-	-	22 mg/plate	Silhánková *et al.* (1982)
Schizosaccharomyces pombe, forward mutation	+	-	11 mg/mL	Rossi *et al.* (1983)
Mutation, DNA synthesis inhibition, HeLa cells *in vitro*	-	-	NR	Painter & Howard (1982)
Transformation assay, mouse fibroblasts, M2 clone *in vitro*	+	NT	0.25 mg/mL	Piasecki *et al.* (1990)
DNA strand breaks (Comet assay), Chinese hamster ovary cells *in vitro*	+	NT	2.5 mg/mL	El Ramy *et al.* (2007)
Drosophila melanogaster, somatic mutation, wing-spot test	-		1.1 mg/mL	Frei & Würgler (1997)
ICR/Ha Swiss male mice, dominant lethal mutation	-		125 mg/kg bw, ip × 1 or 20 mg/kg bw, po × 5	Epstein *et al.* (1972)
Male rats, dominant lethal mutation	-		10 mg/kg bw, po × 5	Jones *et al.*(1969)
Male Wistar rats, dominant lethal mutation	-		20 mg/kg bw, po × 5	Jones & Jackson (1976)

Table 4.1 (continued)

Test system	Results		Dose (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Micronucleus formation, male Han Wistar rat bone-marrow cells *in vivo*	-		60 mg/kg bw, po × 2	Robjohns *et al.* (2003)
Unscheduled DNA synthesis, male Han Wistar rat hepatocytes *in vivo*	-		100 mg/kg bw, po x 1	Robjohns *et al.* (2003)
DNA strand breaks (Comet assay), male Sprague-Dawley rat leukocytes, liver, kidney, testis and bone marrow	-		60 mg/kg bw, po x 2	El Ramy *et al.* (2007)
DNA strand breaks (Comet assay), male F344 rats leukocytes and testis	-		60 mg/kg bw, po x 2	El Ramy *et al.* (2007)

+, positive; (+), weakly positive; –, negative; bw, body weight; HID, highest ineffective dose; ip, intraperitoneal; LED, lowest effective dose; NT, not tested; NR, not reported; po, oral

in which three of six male macaque monkeys (*Macaca mulatta*) given 30 mg/kg bw 3-MCPD orally per day for 6 weeks showed haematological abnormalities, including anaemia, leukopenia and severe thrombocytopenia. Two of the affected monkeys died during the study due to bone-marrow depression (Kirton *et al.*, 1970).

(a) Testicular toxicity

Incubation of ram sperm with 3-MCPD *in vitro* inhibited the glycolysis of spermatozoa (Brown-Woodman *et al.*, 1975).

The activity of all glycolytic enzymes in the epididymal and testicular tissue of rats was reduced following daily subcutaneous injections of 6.5 mg/kg bw 3-MCPD for 9 days (Kaur & Guraya, 1981a). It has been suggested that the mechanism involved is the inhibition of glyceraldehyde-3-phosphate dehydrogenase and triosephosphate isomerase by the 3-MCPD metabolite, β-chlorolactaldehyde (Jones & Porter, 1995; Lynch *et al.*, 1998).

The inhibition of spermatozoan glycolysis by 3-MCPD (and/or its metabolites) resulted in reduced sperm motility. The inhibition was reversible and has been attributed to the *S*-enantiomer of the substance (Porter & Jones, 1982; Stevenson & Jones, 1984; Jones & Porter, 1995). In addition, 3-MCPD decreased testosterone secretion in cultured Leydig cells from rats (Paz *et al.*, 1985). No effect on concentrations of testosterone or luteinizing hormone was detected in the blood of male rats during a 28-day study of reproductive toxicity with doses of up to 5 mg/kg bw per day (Kwack *et al.*, 2004).

Rats that received 6.5 mg/kg bw 3-MCPD per day for 9 days had significantly decreased ($P < 0.05$) levels of RNA and protein in the testis and epididymis, and these changes were paralleled by increases in the concentrations of proteinase and ribonuclease. The DNA content was unchanged (Kaur & Guraya, 1981b).

The spermatotoxic effect is mediated by reduced H^+-adenosine triphosphatase expression in the cauda epididymis (Kwack *et al.*, 2004).

(b) Renal toxicity

Increased blood urea nitrogen and serum creatinine concentrations, chronic progressive nephropathy and renal tubule-cell lesions — all indicative of overt nephrotoxicity — were generally seen at doses somewhat higher than those that caused testicular and epididymal effects (JECFA, 2002). The nephrotoxicity was associated with the *R*-enantiomer of 3-MCPD (Porter & Jones, 1982; Dobbie *et al.*, 1988).

Oxalic acid, a metabolite of 3-MCPD, appeared to play an important role in the development of renal damage (Jones *et al.*, 1979). Birefringent crystals characteristic of calcium oxalate that were seen in tubules at the corticomedullary junction of rats 1 day after a single subcutaneous injection of 75 mg/kg bw 3-MCPD were considered to be early morphological changes. On day 75, focal tubule necrosis, regeneration and tubule dilatation were observed in the kidneys (Kluwe *et al.*, 1983).

4.4 Mechanisms of carcinogenesis

A genotoxic mechanism of carcinogenicity was originally assumed for 3-MCPD, based on positive results in several in-vitro assays (SCF, 2001). Following the publication of negative results in in-vivo assays for micronucleus formation in rat bone marrow and unscheduled DNA synthesis (Robjohns *et al.*, 2003), this assessment was questioned. [The Working Group noted that there is no evidence to suggest that 3-MCPD is not genotoxic. Further research appears to be necessary to assess the formation of glycidol as a putative metabolite.]

The kidney tumours observed in Sprague-Dawley rats (Cho *et al.*, 2008) may have been caused by the cytotoxic, metabolically formed

oxalate (Hwang *et al.*, 2009). A genotoxic mechanism of action may also be involved.

5. Summary of Data Reported

5.1 Exposure data

3-Monochloro-1,2-propanediol is used as intermediate in the synthesis of several drugs and as a chemosterilant for rodent control. The major source of human exposure is its formation as a heat-induced contaminant during food processing. The highest levels of 3-monochloro-1,2-propanediol in free form in food were generally detected in soya sauce and soya sauce-based products (average, 8 mg/kg; maximum levels, up to > 1000 mg/kg), as well as in foods and food ingredients that contain acid-hydrolysed vegetable protein. Staple foods, such as bread (especially when toasted), may contribute to the daily intake of 3-monochloro-1,2-propanediol exposure. Free 3-monochloro-1,2-propanediol is regulated in many jurisdictions and its level of contamination has decreased in recent years. Considerable additional exposure may occur through ingestion of the bound form of esters of 3-monochloro-1,2-propanediol with higher fatty acids in refined vegetable oils, as well as infant formulae. However, no data on exposure to bound 3-monochloro-1,2-propanediol in the form of esters were available.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

In three studies in mice, administration of 3-monochloro-1,2-propanediol in the drinking-water, by subcutaneous injection or by dermal application did not increase the incidence of tumours. Administration of 3-monochloro-1,2-propanediol in the drinking-water to rats increased the incidence of renal tubule carcinoma, renal tubule adenoma or carcinoma (combined) and Leydig cell adenoma in males, and that of renal tubule adenoma or carcinoma (combined) in females in one study. In another study, administration by gavage to rats did not increase tumour incidence.

Kidney tumours are rare spontaneous neoplasms in experimental animals.

5.4 Other relevant data

3-Monochloro-1,2-propanediol can be metabolized in rodents by alcohol dehydrogenase to chlorolactic acid, which was identified as a major metabolite in the urine. Chlorolactaldehyde is formed as an intermediate, and the chlorolactic acid may be oxidized further to oxalic acid. In bacteria, 3-monochloro-1,2-propanediol can be metabolized by halohydrin dehalogenase, to generate glycidol, which is classified by IARC as *probably carcinogenic to humans (Group 2A)*. A pathway that involves the glycidol intermediate may also be active in mammals, because glycidol can be detoxified further by glutathione *S*-transferase to form mercapturic acid metabolites — putative products of the reaction — which have been identified *in vivo*.

3-Monochloro-1,2-propanediol is mutagenic *in vitro*, but the limited available data *in vivo* showed negative results. Most of the target tissues of cancer in experimental animals were not tested for genetic effects *in vivo*.

3-Monochloro-1,2-propanediol exhibits nephrotoxicity, immunotoxicity, neurotoxicity, and testicular toxicity in rodents. Inhibition of glycolysis in the cells of the testes has been postulated as the mechanism for the adverse testicular effects. Chronic nephropathy has been proposed as a mechanism for the adverse effects on the kidney. Overall, the mechanistic data for cancer

are weak, but a genotoxic mechanism may be involved.

6. Evaluation

6.1 Cancer in humans

No data were available to the Working Group.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of 3-monochloro-1,2-propanediol.

6.3 Overall evaluation

3-Monochloro-1,2-propanediol is *possibly carcinogenic to humans (Group 2B).*

References

Abu-El-Haj S, Bogusz MJ, Ibrahim Z *et al.* (2007). Rapid and simple determination of chloropropanols (3-MCPD and 1,3-DCP) in food products using isotope dilution GC-MS. *Food Contr*, 18: 81–90. doi:10.1016/j.foodcont.2005.08.014

Anon (1995). [*Bestimmung von 3-Chlor-1,2-Propandiol (3-MCPD) in Speisewürzen (Eiweißhydrolysate). Amtliche Sammlung von Untersuchungsverfahren nach § 35 LMBG. L 52.02–1.*] Berlin, Germany: Beuth Verlag.

Beilstein (2010). *CrossFire Beilstein Database*. Frankfurt am Main, Germany: Elsevier Information Systems GmbH

Bel-Rhlid R, Talmon JP, Fay LB, Juillerat MA (2004). Biodegradation of 3-chloro-1,2-propanediol with Saccharomyces cerevisiae. *J Agric Food Chem*, 52: 6165–6169. doi:10.1021/jf048980k PMID:15453682

Berger-Preiss E, Gerling S, Apel E *et al.* (2010). Development and validation of an analytical method for determination of 3-chloropropane-1,2-diol in rat blood and urine by gas chromatography-mass spectrometry in negative chemical ionization mode. *Anal Bioanal Chem*, 398: 313–318. doi:10.1007/s00216-010-3928-9 PMID:20640896

BfR (2007). *Infant formula and follow-up formula may contain harmful 3-MCPD fatty acid esters.* Berlin, Germany: Bundesinstitut für Risikobewertung.

Bodén L, Lundgren M, Stensiö KE, Gorzynski M (1997). Determination of 1,3-dichloro-2-propanol and 3-chloro-1,2-propanediol in papers treated with polyamidoamine-epichlorohydrin wet-strength resins by gas chromatography-mass spectrometry using selective ion monitoring. *J Chromatogr A*, 788: 195–203. doi:10.1016/S0021-9673(97)00711-5

Breitling-Utzmann CM, Hrenn H, Haase NU, Unbehend GM (2005). Influence of dough ingredients on 3-chloropropane-1,2-diol (3-MCPD) formation in toast. *Food Addit Contam*, 22: 97–103. doi:10.1080/02652030500037936 PMID:15823998

Breitling-Utzmann CM, Kobler H, Herbolzheimer D *et al.* (2003). 3-MCPD - Occurrence in bread crust and various food groups as well as formation in toast.] *Deut Lebensm Rundsch*, 99: 280–285.

Brereton P, Kelly J, Crews C *et al.* (2001). Determination of 3-chloro-1,2-propanediol in foods and food ingredients by gas chromatography with mass spectrometric detection: collaborative study. *J AOAC Int*, 84: 455–465. PMID:11324611

Brown-Woodman PDC, White IG, Salamon S (1975). Proceedings: effect of α-chlorohydrin on the fertility of rams and on the metabolism of spermatozoa in vitro. *J Reprod Fertil*, 43: 381 doi:10.1530/jrf.0.0430381 PMID:1127664

Bub O, Friedrich L (2005). *Cough remedies*. In: *Ullmann's Encyclopedia of Industrial Chemistry*. Weinheim, Germany: Wiley-VCH Verlag GmbH & Co. KGaA.

Buckle A (2005). *Rodenticides*. In: *Ullmann's Encyclopedia of Industrial Chemistry*, Weinheim. Germany: Wiley-VCH Verlag GmbH & Co. KGaA.

Buhrke T, Weißhaar R, Lampen A (2010). Bioavailability of 3-monochloro-1,2-propanediol (3-MCPD) and 3-MCPD fatty acid esters.] *Naunyn Schmiedebergs Arch Pharmacol*, 381: 85

Byun JA, Ryu MH, Lee JK (2006). The immunomodulatory effects of 3-monochloro-1,2-propanediol on murine splenocyte and peritoneal macrophage function in vitro. *Toxicol In Vitro*, 20: 272–278. doi:10.1016/j.tiv.2005.06.042 PMID:16122900

Calta P, Velíšek J, Doležal M *et al.* (2004). Formation of 3-chloropropane-1,2-diol in systems simulating processed foods. *Eur Food Res Technol*, 218: 501–506. doi:10.1007/s00217-003-0865-2

Cao XJ, Song GX, Gao YH *et al.* (2009). A Novel Derivatization Method Coupled with GC-MS for the Simultaneous Determination of Chloropropanols. *Chromatographia*, 70: 661–664. doi:10.1365/s10337-009-1203-z

Cho WS, Han BS, Nam KT *et al.* (2008). Carcinogenicity study of 3-monochloropropane-1,2-diol in Sprague-

Dawley rats. *Food Chem Toxicol*, 46(9): 3172–7. doi:10.1016/j.fct.2008.07.003 PMID:18680782

Chung WC, Hui KY, Cheng SC (2002). Sensitive method for the determination of 1,3-dichloropropan-2-ol and 3-chloropropane-1,2-diol in soy sauce by capillary gas chromatography with mass spectrometric detection. *J Chromatogr A*, 952: 185–192. doi:10.1016/S0021-9673(02)00062-6 PMID:12064530

Crabo B & Appelgren LE (1972). Distribution of (14 C) -chlorohydrin in mice and rats. *J Reprod Fertil*, 30: 161–163. doi:10.1530/jrf.0.0300161 PMID:5035336

Crews C, Brereton P, Davies A (2001). The effects of domestic cooking on the levels of 3-monochloropropanediol in foods. *Food Addit Contam*, 18: 271–280. doi:10.1080/02652030120064 PMID:11339260

Crews C, LeBrun G, Brereton PA (2002). Determination of 1,3-dichloropropanol in soy sauces by automated headspace gas chromatography-mass spectrometry. *Food Addit Contam*, 19: 343–349. doi:10.1080/02652030110098580 PMID:11962691

Davídek J, Velíšek J, Kubelka V *et al.* (1980). Glycerol Chlorohydrins and Their Esters As Products of the Hydrolysis of Tripalmitin, Tristearin and Triolein with Hydrochloric-Acid.] *Z Lebensm Unters Forsch*, 171: 14–17. doi:10.1007/BF01044410

Dayrit FM & Niñonuevo MR (2004). Development of an analytical method for 3-monochloropropane-1,2-diol in soy sauce using 4-heptanone as derivatizing agent. *Food Addit Contam*, 21: 204–209. doi:10.1080/02652030310001656352 PMID:15195467

Divinová V, Svejkovská B, Doležal M *et al.* (2004). Determination of free and bound 3-chloropropane-1,2-diol by gas chromatography with mass spectrometric detection using deuterated 3-chloropropane-1,2-diol as internal standard. *Czech J Food Sci*, 22: 182–189.

Dobbie MS, Porter KE, Jones AR (1988). Is the nephrotoxicity of (R)-3-chlorolactate in the rat caused by 3-chloropyruvate? *Xenobiotica*, 18: 1389–1399. doi:10.3109/00498258809042262 PMID:3245232

Doležal M, Calta P, Velíšek J (2004). Formation and decomposition of 3-chloropropane-1,2-diol in model systems. *Czech J Food Sci*, 22: 263–266.

Doležal M, Chaloupská M, Divinová V *et al.* (2005). Occurrence of 3-chloropropane-1,2-diol and its esters in coffee. *Eur Food Res Technol*, 221: 221–225. doi:10.1007/s00217-004-1118-8

Edwards EM, Jones AR, Waites GM (1975). The entry of α-chlorohydrin into body fluids of male rats and its effect upon the incorporation of glycerol into lipids. *J Reprod Fertil*, 43: 225–232. doi:10.1530/jrf.0.0430225 PMID:1127646

El Ramy R, Ould Elhkim M, Lezmi S, Poul JM (2007). Evaluation of the genotoxic potential of 3-monochloropropane-1,2-diol (3-MCPD) and its metabolites, glycidol and beta-chlorolactic acid, using the single cell gel/comet assay. *Food Chem Toxicol*, 45: 41–48. doi:10.1016/j.fct.2006.07.014 PMID:16971032

EPA (2006). *Pesticide fact sheet*. In: *Alpha-Chlorohydrin*. Washington, DC: United States Environmental Protection Agency.

Epstein SS, Arnold E, Andrea J *et al.* (1972). Detection of chemical mutagens by the dominant lethal assay in the mouse. *Toxicol Appl Pharmacol*, 23: 288–325. doi:10.1016/0041-008X(72)90192-5 PMID:5074577

Ericsson RJ (1982). *Alpha-chlorohydrin (Epibloc): A toxicant-sterilant as an alternative in rodent control*. Marsh RE, editor. Davis, CA: University of California, pp. 6–9.

European Commission (2001). Commission Regulation (EC) No 466/2001 of 8 March 2001 setting maximum levels for certain contaminants in foodstuffs *Off J Europ Comm*, L77: 1–13.

European Standard (2005). *EN 14573:2004 Foodstuffs - Determination of 3-monochloropropane-1,2-diol by GC/MS*. Berlin, Germany: Beuth Verlag.

Frei H & Würgler FE (1997). The vicinal chloroalcohols 1,3-dichloro-2-propanol (DC2P), 3-chloro-1,2-propanediol (3CPD) and 2-chloro-1,3-propanediol (2CPD) are not genotoxic in vivo in the wing spot test of Drosophila melanogaster. *Mutat Res*, 394: 59–68. PMID:9434844

Hamlet CG (1998). Analytical methods for the determination of 3-chloro-1,2-propandiol and 2-chloro-1,3-propandiol in hydrolysed vegetable protein, seasonings and food products using gas chromatography/ion trap tandem mass spectrometry. *Food Addit Contam*, 15: 451–465. doi:10.1080/02652039809374666 PMID:9764216

Hamlet CG (2009). *Chloropropanols and their Fatty Acid Esters*. In: *Bioactive compounds in foods*. Gilbert J & Senyuva HZ, editors. Oxford, UK: Blackwell Publishing Ltd., pp. 323–357.

Hamlet CG, Jayaratne SM, Matthews W (2002b). 3-Monochloropropane-1,2-diol (3-MCPD) in food ingredients from UK food producers and ingredient suppliers. *Food Addit Contam*, 19: 15–21. doi:10.1080/02652030110072344 PMID:11817372

Hamlet CG & Sadd PA (2002). Kinetics of 3-chloropropane-1,2-diol (3-MCPD) degradation in high temperature model systems. *Eur Food Res Technol*, 215: 46–50. doi:10.1007/s00217-002-0523-0

Hamlet CG & Sadd PA (2004). Chloropropanols and their esters in cereal products. *Czech J Food Sci*, 22: 259–262.

Hamlet CG & Sadd PA (2005). Effects of yeast stress and pH on 3-monochloropropanediol (3-MCPD)-producing reactions in model dough systems. *Food Addit Contam*, 22: 616–623. doi:10.1080/02652030500150093 PMID:16019837

Hamlet CG, Sadd PA (2009). *Chloropropanols and chloroesters*. In: *Process-induced food toxicants: occurrence, formation, mitigation and health risks*. Stadler RH & Lineback DR, editors. Hoboken, NJ: Wiley, pp. 175–214.

Hamlet CG, Sadd PA, Crews C *et al.* (2002a). Occurrence of 3-chloro-propane-1,2-diol (3-MCPD) and related compounds in foods: a review. *Food Addit Contam*, 19: 619–631. doi:10.1080/02652030210132391 PMID:12113657

Hamlet CG, Sadd PA, Gray DA (2003). Influence of composition, moisture, pH and temperature on the formation and decay kinetics of monochloropropanediols in wheat flour dough. *Eur Food Res Technol*, 216: 122–128.

Hamlet CG, Sadd PA, Gray DA (2004a). Generation of monochloropropanediols (MCPDs) in model dough systems. 1. Leavened doughs. *J Agric Food Chem*, 52: 2059–2066. doi:10.1021/jf035077w PMID:15053552

Hamlet CG, Sadd PA, Gray DA (2004b). Generation of monochloropropanediols (MCPDs) in model dough systems. 2. Unleavened doughs. *J Agric Food Chem*, 52: 2067–2072. doi:10.1021/jf035078o PMID:15053553

Hamlet CG & Sutton PG (1997). Determination of the chloropropanols, 3-chloro-1,2-propandiol and 2-chloro-1,3-propandiol, in hydrolysed vegetable proteins and seasonings by gas chromatography ion trap tandem mass spectrometry. *Rapid Commun Mass Spectrom*, 11: 1417–1424. doi:10.1002/(SICI)1097-0231(19970830)11:13<1417::AID-RCM986>3.0.CO;2-S

Huang MJ, Jiang GB, He B *et al.* (2005). Determination of 3-chloropropane-1,2-diol in liquid hydrolyzed vegetable proteins and soy sauce by solid-phase microextraction and gas chromatography/mass spectrometry. *Anal Sci*, 21: 1343–1347. doi:10.2116/analsci.21.1343 PMID:16317903

Hwang M, Yoon E, Kim J *et al.* (2009). Toxicity value for 3-monochloropropane-1,2-diol using a benchmark dose methodology. *Regul Toxicol Pharmacol*, 53: 102–106. doi:10.1016/j.yrtph.2008.12.005 PMID:19133308

IARC (2000). Some industrial chemicals. *IARC Monogr Eval Carcinog Risks Hum*, 77: 1–529. PMID:11236796

IARC (2010). Alcohol consumption and ethyl carbamate. *IARC Monogr Eval Carcinog Risks Hum*, 96: 1–1428.

JECFA (2002). 3-Chloro-1,2-propanediol. Safety evaluation of certain food additives and contaminants. Prepared by the fifty-seventh meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), Geneva*WHO Food Addit Ser*, 48:

JECFA (2007). 3-Chloro-1,2-propanediol (addendum). Safety evaluation of certain food additives and contaminants. Prepared by the sixty-seventh meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), Geneva*WHO Food Addit Ser*, 58: 239–267.

Jeong J, Han BS, Cho WS *et al.* (2010). Carcinogenicity study of 3-monochloropropane-1, 2-diol (3-MCPD) administered by drinking water to B6C3F$_1$ mice showed no carcinogenic potential. *Arch Toxicol*, 84: 719–729. doi:10.1007/s00204-010-0552-6 PMID:20461361

Jira W (2010). 3-Monochloropropane-1,2-diol (3-MCPD) in smoked meat products.] *Fleischwirtsch*, 90: 115–118.

Jones AR (1975). The metabolism of 3-chloro,- 3-bromo- and 3-iodoprpan-1,2-diol in rats and mice. *Xenobiotica*, 5: 155–165. doi:10.3109/00498257509056101 PMID:1166663

Jones AR & Cooper TG (1999). A re-appraisal of the post-testicular action and toxicity of chlorinated antifertility compounds. *Int J Androl*, 22: 130–138. doi:10.1046/j.1365-2605.1999.00163.x PMID:10367232

Jones AR, Davies P, Edwards K, Jackson H (1969). Antifertility effects and metabolism of alpha and epi-chlorhydrins in the rat. *Nature*, 224: 83 doi:10.1038/224083a0 PMID:5822916

Jones AR, Gadiel P, Murcott C (1979). The renal toxicity of the rodenticide α-chlorohydrin in the rat. *Naturwissenschaften*, 66: 425 doi:10.1007/BF00368082 PMID:503241

Jones AR, Milton DH, Murcott C (1978). The oxidative metabolism of α-chlorohydrin in the male rat and the formation of spermatocoeles. *Xenobiotica*, 8: 573–582. doi:10.3109/00498257809061257 PMID:695700

Jones AR & Murcott C (1976). The oxidative metabolism of α-chlorohydrin and the chemical induction of spermatocoeles. *Experientia*, 32: 1135–1136. doi:10.1007/BF01927587 PMID:971742

Jones AR & Porter LM (1995). Inhibition of glycolysis in boar spermatozoa by α-chlorohydrin phosphate appears to be mediated by phosphatase activity. *Reprod Fertil Dev*, 7: 1089–1094. doi:10.1071/RD9951089 PMID:8848575

Jones P & Jackson H (1976). Antifertility and dominant lethal mutation studies in male rats with dl-alpha-chlorohydrin and an amino-analogue. *Contraception*, 13: 639–646. doi:10.1016/0010-7824(76)90019-6 PMID:1261265

Karšulínová L, Folprechtová B, Doležal M *et al.* (2007). Analysis of the lipid fractions of coffee creamers, cream aerosols, and bouillon cubes for their health risk associated constituents. *Czech J Food Sci*, 25: 257–264.

Kaur S & Guraya SS (1981a). Effect of low doses of alpha chlorohydrin on the enzymes of glycolytic and phosphogluconate pathways in the rat testis and epididymis. *Int J Androl*, 4: 196–207. doi:10.1111/j.1365-2605.1981.tb00703.x PMID:6265379

Kaur S & Guraya SS (1981b). Biochemical observations on the protein and nucleic acid metabolism of the rat testis and epididymis after treatment with low doses of alpha-chlorohydrin. *Int J Fertil*, 26: 8–13. PMID:6165692

Kim K (2008). Differential expression of neuronal and inducible nitric oxide synthase in rat brain after subchronic administration of 3-monochloro-1,2-propanediol. *Food Chem Toxicol*, 46: 955–960. doi:10.1016/j.fct.2007.10.025 PMID:18063462

Kirton KT, Ericsson RJ, Ray JA, Forbes AD (1970). Male antifertility compounds: efficacy of U-5897 in primates (Macacamulatta). *J Reprod Fertil*, 21: 275–278. doi:10.1530/jrf.0.0210275 PMID:4986219

Kissa E (1992). Determination of 3-Chloropropanediol and Related Dioxolanes by Gas-Chromatography. *J Chromatogr A*, 605: 134–138. doi:10.1016/0021-9673(92)85038-U

Kleemann A (2008). *Cardiovascular drugs*. In: *Ullmann's Encyclopedia of Industrial Chemistry*. Weinheim, Germany: Wiley-VCH Verlag GmbH & Co. KGaA.

Kluwe WM, Gupta BN, Lamb JC 4th (1983). The comparative effects of 1,2-dibromo-3-chloropropane (DBCP) and its metabolites, 3-chloro-1,2-propane-oxide (epichlorohydrin), 3-chloro-1,2-propanediol (alphachlorohydrin), and oxalic acid, on the urogenital system of male rats. *Toxicol Appl Pharmacol*, 70: 67–86. doi:10.1016/0041-008X(83)90180-1 PMID:6612740

Kuballa T & Ruge W (2003). [Nachweis und Bestimmung von 3-Monochlorpropan-1,2-diol (3-MCPD) mit GC-MS/MS] *Lebensmittelchem*, 57: 57–58.

Kuhlmann J (2010). Determination of bound 2,3-epoxy-1-propanol (glycidol) and bound monochloropropane-diol (MCPD) in refined oils *Eur J Lipid Sci Technol*, n/a.

Kuntzer J & Weißhaar R (2006). The smoking process - A potent source of 3-chloropropane-1,2-diol (3-MCPD) in meat products.] *Deut Lebensm Rundsch*, 102: 397–400.

Küsters M, Bimber U, Ossenbrüggen A *et al.* (2010). Rapid and simple micromethod for the simultaneous determination of 3-MCPD and 3-MCPD esters in different foodstuffs. *J Agric Food Chem*, 58: 6570–6577. doi:10.1021/jf100416w PMID:20450199

Kwack SJ, Kim SS, Choi YW *et al.* (2004). Mechanism of antifertility in male rats treated with 3-monochloro-1,2-propanediol (3-MCPD). *J Toxicol Environ Health A*, 67: 2001–2011. doi:10.1080/15287390490514651 PMID:15513898

Lee JK, Byun JA, Park SH *et al.* (2004). Evaluation of the potential immunotoxicity of 3-monochloro-1,2-propanediol in Balb/c mice. I. Effect on antibody forming cell, mitogen-stimulated lymphocyte proliferation, splenic subset, and natural killer cell activity. *Toxicology*, 204: 1–11. doi:10.1016/j.tox.2004.04.005 PMID:15369844

Lee JK, Byun JA, Park SH *et al.* (2005). Evaluation of the potential immunotoxicity of 3-monochloro-1,2-propanediol in Balb/c mice II. Effect on thymic subset, delayed-type hypersensitivity, mixed-lymphocyte reaction, and peritoneal macrophage activity. *Toxicology*, 211: 187–196. doi:10.1016/j.tox.2005.03.005 PMID:15925022

Lee MR, Chiu TC, Dou JP (2007). Determination of 1,3-dichloro-2-propanol and 3-chloro-1,2-propandiol in soy sauce by headspace derivatization solid-phase microextraction combined with gas chromatography-mass spectrometry. *Anal Chim Acta*, 591: 167–172. doi:10.1016/j.aca.2007.03.057 PMID:17481404

Lin Y (2000). *Radiopaques*. In: *Kirk-Othmer Encyclopedia of Chemical Technology*. Hoboken, NJ: John Wiley & Sons.

Liu GYT, Richey WF, Betso JE (2005). *Chlorohydrins*. In: *Ullmann's Encyclopedia of Industrial Chemistry*. Weinheim, Germany: Wiley-VCH Verlag GmbH & Co. KGaA.

Lynch BS, Bryant DW, Hook GJ *et al.* (1998). Carcinogenicity of monochloro-1,2-propanediol (α-chlorohydrin, 3-MCPD). *Int J Toxicol*, 17: 47–76. doi:10.1080/109158198226756

Majeska JB & Matheson DW (1983). Quantitative estimate of mutagenicity of tris-[1,3-dichloro-2-propyl]-phosphate (TCPP) and its possible metabolites in Salmonella. *Environ Mutagen*, 5: 478

Matthew BM & Anastasio C (2000). Determination of halogenated mono-alcohols and diols in water by gas chromatography with electron-capture detection. *J Chromatogr A*, 866: 65–77. doi:10.1016/S0021-9673(99)01081-X PMID:10681010

Meierhans DC, Bruehlmann S, Meili J, Taeschler C (1998). Sensitive method for the determination of 3-chloro-propane-1,2-diol and 2-chloropropane-1,3-diol by capillary gas chromatography with mass spectrometric detection. *J Chromatogr A*, 802: 325–333. doi:10.1016/S0021-9673(97)01188-6

Merck Index (2010). *The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals (14th Edition - Version 14.6)*. Whitehouse Station, NJ: Merck & Co., Inc.

Muller RE, Booer CD, Slaiding IR *et al.* (2005). *Modeling the formation of heat generated toxins during the processing of malt*. *Proc Congr Eur Brew Conv*, 30th: 167–1–167/12.

Nienow AM, Poyer IC, Hua I, Jafvert CT (2009). Hydrolysis and H2O2-assisted UV photolysis of 3-chloro-1,2-propanediol. *Chemosphere*, 75: 1015–1020. doi:10.1016/j.chemosphere.2009.01.053 PMID:19282021

Ohkubo T, Hayashi T, Watanabe E *et al.* (1995). Mutagenicity of chlorohydrins. [in Japanese] *Nippon Suisan Gakkai Shi*, 61: 596–601. doi:10.2331/suisan.61.596

Painter RB & Howard R (1982). The Hela DNA-synthesis inhibition test as a rapid screen for mutagenic carcinogens. *Mutat Res*, 92: 427–437. doi:10.1016/0027-5107(82)90241-X PMID:7088012

Paz G, Carmon A, Homonnai ZT (1985). Effect of α-chlorohydrin on metabolism and testosterone secretion by rat testicular interstitial cells. *Int J Androl*, 8: 139–146. doi:10.1111/j.1365-2605.1985.tb00827.x PMID:3860478

Pesselman RL & Feit MJ (1988). Determination of residual epichlorohydrin and 3-chloropropanediol in water by gas chromatography with electron-capture detection. *J Chromatogr A*, 439: 448–452. doi:10.1016/S0021-9673(01)83859-0 PMID:3403653

Piasecki A, Ruge A, Marquardt H (1990). Malignant transformation of mouse M2-fibroblasts by glycerol chlorohydrines contained in protein hydrolysates

and commercial food. *Arzneimittelforschung*, 40: 1054–1055. PMID:2080943

Plantinga WJ, van Toorn WG, van der Stegen GHD (1991). Determination of 3-Chloropropane-1,2-Diol in Liquid Hydrolyzed Vegetable Proteins by Capillary Gas-Chromatography with Flame Ionization Detection. *J Chromatogr A*, 555: 311–314. doi:10.1016/S0021-9673(01)87196-X

Porter KE & Jones AR (1982). The effect of the isomers of α-cholorohydrin and racemic β-chlorolactate on the rat kidney. *Chem Biol Interact*, 41: 95–104. doi:10.1016/0009-2797(82)90020-5 PMID:6807557

Rahn AKK & Yaylayan VA (2010). What do we know about the molecular mechanism of 3-MCPD ester formation? *Eur J Lipid Sci Technol*, n/a.

Rétho C & Blanchard F (2005). Determination of 3-chloropropane-1,2-diol as its 1,3-dioxolane derivative at the microg kg-1 level: application to a wide range of foods. *Food Addit Contam*, 22: 1189–1197. doi:10.1080/02652030500197680 PMID:16356881

Richey WF (2000). *Chlorohydrins*. In: *Kirk-Othmer Encyclopedia of Chemical Technology*. Hoboken, NJ: John Wiley & Sons.

Robert MC, Oberson JM, Stadler RH (2004). Model studies on the formation of monochloropropanediols in the presence of lipase. *J Agric Food Chem*, 52: 5102–5108. doi:10.1021/jf049837u PMID:15291482

Robjohns S, Marshall R, Fellows M, Kowalczyk G (2003). In vivo genotoxicity studies with 3-monochloropropan-1,2-diol. *Mutagenesis*, 18: 401–404. doi:10.1093/mutage/geg017 PMID:12960406

Rodman LE & Ross RD (1986). Gas-liquid chromatography of 3-chloropropanediol. *J Chromatogr A*, 369: 97–103. doi:10.1016/S0021-9673(00)90101-8 PMID:3793835

Rossi AM, Migliore L, Lascialfari D *et al.* (1983). Genotoxicity, metabolism and blood kinetics of epichlorohydrin in mice. *Mutat Res*, 118: 213–226. doi:10.1016/0165-1218(83)90144-1 PMID:6877269

SCF (2001). *Opinion of the scientific committee on food on 3-monochloro-propane-1,2-diol (3-MCPD)*. Brussels, Belgium: European Commission.

Schilter B, Scholz G, Seefelder W (2010). Fatty acid esters of chloropropanols and related compounds in food: toxicological aspects *Eur J Lipid Sci Technol*, n/a.

Schlee C, Ruge W, Kuballa T *et al.* (2011). [3-Monochlor-1,2-propandiol in Lebensmitteln. Aktueller Wissensstand und Untersuchungsergebnisse.]*Deut Lebensm Rundsch*, In press

SciFinder (2010). *SciFinder Databases: Registry, Chemcats*. American Chemical Society.

Seefelder W, Varga N, Studer A *et al.* (2008). Esters of 3-chloro-1,2-propanediol (3-MCPD) in vegetable oils: significance in the formation of 3-MCPD. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess*, 25: 391–400. PMID:18348037

Silhánková L, Smíd F, Cerná M *et al.* (1982). Mutagenicity of glycerol chlorohydrines and of their esters with higher fatty acids present in protein hydrolysates. *Mutat Res*, 103: 77–81. doi:10.1016/0165-7992(82)90090-2 PMID:7035914

Spyres G (1993). Determination of 3-Chloropropane-1,2-Diol in Hydrolyzed Vegetable Proteins by Capillary Gas-Chromatography with Electrolytic Conductivity Detection. *J Chromatogr A*, 638: 71–74. doi:10.1016/0021-9673(93)85009-V

Stevenson D & Jones AR (1984). The action of (R)- and (S)-α-chlorohydrin and their metabolites on the metabolism of boar sperm. *Int J Androl*, 7: 79–86. doi:10.1111/j.1365-2605.1984.tb00762.x PMID:6715067

Stolzenberg SJ & Hine CH (1979). Mutagenicity of halogenated and oxygenated three-carbon compounds. *J Toxicol Environ Health*, 5: 1149–1158. doi:10.1080/15287397909529820 PMID:393836

Stolzenberg SJ & Hine CH (1980). Mutagenicity of 2- and 3-carbon halogenated compounds in the Salmonella/mammalian-microsome test. *Environ Mutagen*, 2: 59–66. doi:10.1002/em.2860020109 PMID:7035158

Svejkovská B, Novotný O, Divinová V *et al.* (2004). Esters of 3-chloropropane-1,2-diol in foodstuffs. *Czech J Food Sci*, 22: 190–196.

van Bergen CA, Collier PD, Cromie DDO *et al.* (1992). Determination of Chloropropanols in Protein Hydrolysates. *J Chromatogr A*, 589: 109–119. doi:10.1016/0021-9673(92)80011-I

van den Wijngaard AJ, Janssen DB, Witholt B (1989). Degradation of epichlorohydrin and halohydrins by bacterial cultures isolated from freshwater sediment. *J Gen Microbiol*, 135: 2199–2208.

Van Duuren BL, Goldschmidt BM, Katz C *et al.* (1974). Carcinogenic activity of alkylating agents. *J Natl Cancer Inst*, 53: 695–700. PMID:4412318

Velíšek J (2009). *Chloropropanols*. In: *Process-induced food toxicants: occurrence, formation, mitigation and health risks*. Stadler RH & Lineback DR, editors. Hoboken, NJ: Wiley, pp. 539–562.

Velíšek J, Calta P, Crews C *et al.* (2003). 3-Chloropropane-1,2-diol in models simulating processed foods: precursors and agents causing its decomposition. *Czech J Food Sci*, 21: 153–161.

Velíšek J, Davídek J, Hajslová J *et al.* (1978). Chlorohydrins in protein hydrolysates. *Z Lebensm Unters Forsch*, 167: 241–244. doi:10.1007/BF01135595 PMID:716635

Weisburger EK, Ulland BM, Nam J *et al.* (1981). Carcinogenicity tests of certain environmental and industrial chemicals. *J Natl Cancer Inst*, 67: 75–88. PMID:6942197

Weißhaar R (2008). Determination of total 3-chloropropane-1,2-diol (3-MCPD) in edible oils by cleavage of MCPD esters with sodium methoxide. *Eur J Lipid Sci Technol*, 110: 183–186. doi:10.1002/ejlt.200700197

Weißhaar R & Perz R (2010). Fatty acid esters of glycidol in refined fats and oils. *Eur J Lipid Sci Technol*, 112: 158–165. doi:10.1002/ejlt.200900137

Wenzl T, Lachenmeier DW, Gökmen V (2007). Analysis of heat-induced contaminants (acrylamide, chloropropanols and furan) in carbohydrate-rich food. *Anal Bioanal Chem*, 389: 119–137. doi:10.1007/s00216-007-1459-9 PMID:17673989

Wittmann R (1991). Bestimmung von Dichlorpropanolen und Monochlorpropandiolen in Würzen und würzehaltigen Lebensmitteln *Z Lebensm Unters Forsch*, 193: 224–229. doi:10.1007/BF01199970

Xing X & Cao Y (2007). Determination of 3-chloro-1,2-propanediol in soy sauces by capillary electrophoresis with electrochemical detection. *Food Contr*, 18: 167–172. doi:10.1016/j.foodcont.2005.09.006

Xu X, Ren Y, Wu P *et al.* (2006). The simultaneous separation and determination of chloropropanols in soy sauce and other flavoring with gas chromatography-mass spectrometry in negative chemical and electron impact ionization modes. *Food Addit Contam*, 23: 110–119. doi:10.1080/02652030500391929 PMID:16449052

Yale HL, Pribyl EJ, Braker W *et al.* (1950). Muscle-relaxing compounds similar to 3-(*o*-toloxy)-1,2-propanediol. I. Aromatic ethers of polyhydroxy alcohols and related compounds. *J Am Chem Soc*, 72: 3710–3716. doi:10.1021/ja01164a107

Yau JCW, Kwong KP, Chung SWC *et al.* (2008). Dietary exposure to chloropropanols of secondary school students in Hong Kong. *Food Addit Contam Part B Surveill*, 1: 93–99. doi:10.1080/02652030802488142

Zeiger E, Anderson B, Haworth S *et al.* (1988). Salmonella mutagenicity tests: IV. Results from the testing of 300 chemicals. *Environ Mol Mutagen*, 11: Suppl 121–157. doi:10.1002/em.2850110602 PMID:3277844

Zelinková Z, Doležal M, Velíšek J (2009a). 3-Chloropropane-1,2-diol Fatty Acid Esters in Potato Products. *Czech J Food Sci*, 27: S421–S424.

Zelinková Z, Doležal M, Velíšek J (2009b). Occurrence of 3-chloropropane-1,2-diol fatty acid esters in infant and baby foods. *Eur Food Res Technol*, 228: 571–578. doi:10.1007/s00217-008-0965-0

Zelinková Z, Novotný O, Schůrek J *et al.* (2008). Occurrence of 3-MCPD fatty acid esters in human breast milk. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess*, 25: 669–676. PMID:18484295

Zelinková Z, Svejkovská B, Velísek J, Dolezal M (2006). Fatty acid esters of 3-chloropropane-1,2-diol in edible oils. *Food Addit Contam*, 23: 1290–1298. doi:10.1080/02652030600887628 PMID:17118872