

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:

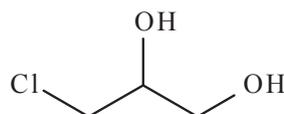
3-Chloro-1,2-propanediol

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



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 silylation 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-Rhliid 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 ₃ N	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; Et₃N, 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.	<i>n</i> < 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 B6C3F₁ 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 <i>et al.</i> (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 <i>et al.</i> (1974)	Subcutaneous injection in the left flank of 0 (control) or 1.0 mg in 0.05 mL tricapylin 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 <i>et al.</i> (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 * <i>P</i> < 0.05 (poly-3 test) * <i>P</i> < 0.05 (poly-3 test) NS * <i>P</i> < 0.05 (poly-3 test) * <i>P</i> < 0.05 (poly-3 test) * <i>P</i> < 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 tricapylin 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](#)). [¹⁴C]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 [³⁶Cl]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 [¹⁴C]3-MCPD exhaled 30% of the dose as [¹⁴C]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 [³⁶Cl]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 ([IECFA, 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 ([IECFA, 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](#)).

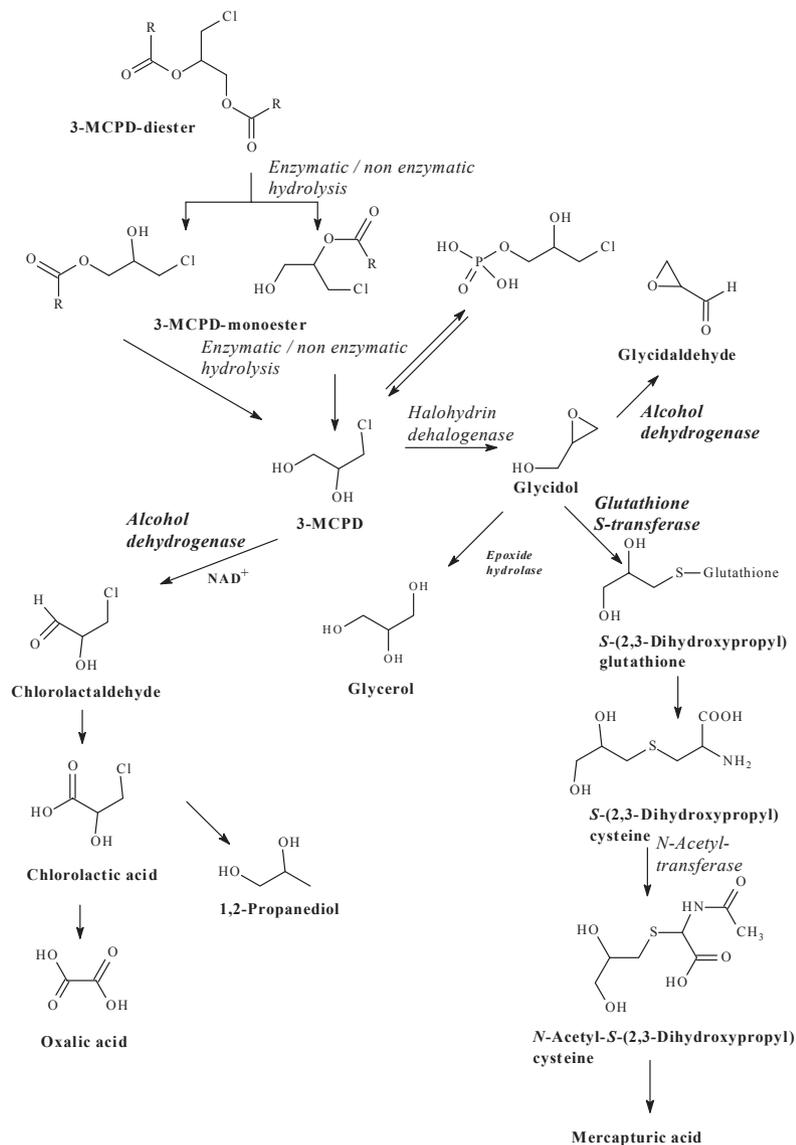
4.3 Mechanistic considerations

4.3.1 Effects on cell physiology and function

Available data on the effects of 3-MCPD on cell function have been reviewed previously ([IECFA, 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		
<i>Salmonella typhimurium</i> TA100, TA1535, reverse mutation	+	+	40 mg/plate	Stolzenberg & Hine (1979, 1980)
<i>Salmonella typhimurium</i> TA100, reverse mutation	NT	-	NR	Majeska & Matheson (1983)
<i>Salmonella typhimurium</i> TA100, TA1535, reverse mutation	+	+	1.0–3.33 mg/plate	Zeiger et al. (1988)
<i>Salmonella typhimurium</i> TA100, reverse mutation	+	+	0.62 mg/plate	Ohkubo et al. (1995)
<i>Salmonella typhimurium</i> TA1535, reverse mutation	+	+	1 mg/plate	Silhánková et al. (1982)
<i>Salmonella typhimurium</i> TA1537, TA1538, TA98, reverse mutation	-	-	22 mg/plate	Silhánková et al. (1982)
<i>Salmonella typhimurium</i> TA97, reverse mutation	NT	-	10 mg/plate	Zeiger et al. (1988)
<i>Salmonella typhimurium</i> TA98, reverse mutation	(+)	-	110 mg/plate	Stolzenberg & Hine (1979)
<i>Salmonella typhimurium</i> TA98, reverse mutation	+	-	10 mg/plate	Zeiger et al. (1988)
<i>Salmonella typhimurium</i> TA98, reverse mutation	+	-	1.25 mg/plate	Ohkubo et al. (1995)
<i>Salmonella typhimurium</i> TM677, forward mutation	+	-	0.05 mg/plate	Ohkubo et al. (1995)
<i>Escherichia coli</i> WP2, TM930, TM1080, reverse mutation	-	-	22 mg/plate	Silhánková et al. (1982)
<i>Schizosaccharomyces pombe</i> , forward mutation	+	-	11 mg/mL	Rossi et al. (1983)
Mutation, DNA synthesis inhibition, HeLa cells <i>in vitro</i>	-	-	NR	Painter & Howard (1982)
Transformation assay, mouse fibroblasts, M2 clone <i>in vitro</i>	+	NT	0.25 mg/mL	Piasecki et al. (1990)
DNA strand breaks (Comet assay), Chinese hamster ovary cells <i>in vitro</i>	+	NT	2.5 mg/mL	El Ramy et al. (2007)
<i>Drosophila melanogaster</i> , 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 <i>in vivo</i>	-		60 mg/kg bw, po × 2	Robjohns <i>et al.</i> (2003)
Unscheduled DNA synthesis, male Han Wistar rat hepatocytes <i>in vivo</i>	-		100 mg/kg bw, po x 1	Robjohns <i>et al.</i> (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 <i>et al.</i> (2007)
DNA strand breaks (Comet assay), male F344 rats leukocytes and testis	-		60 mg/kg bw, po x 2	El Ramy <i>et al.</i> (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, leucopenia 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 triose-phosphate 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)*.

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