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Date: 5/5/2009 3:22 PM
Subject: IHPC Comments on the Prioritization of 3-MCPD for Proposition65 Review
Attachments: IHPC Comments to OEHHA on 3-MCPD.PDF

Ms. Oshita:

On behalf of Martin Hahn, Executive Director of the International Hydrolyzed Protein Council (IHPC), an international, non-governmental organization that represents manufacturers, users, and sellers of hydrolyzed proteins throughout the world (including acid hydrolyzed vegetable proteins (acid-HVPs), autolyzed yeasts and yeast extracts), please accept the attached comments on the prioritization of 3-monochloropropane-1,2-diol (3-MCPD) by the Carcinogen Identification Committee (CIC) under Proposition 65. As described in the attached comments, 3-MCPD should be ranked as a “no priority” chemical by the CIC and OEHHA for purposes of further Proposition 65 assessment because 3-MCPD is not a carcinogen as defined by the Proposition 65 regulations, and even if it were considered to be a carcinogen by the CIC and OEHHA, total dietary intake of 3-MCPD falls below conservative “safe harbor” levels, resulting in no Proposition 65 warnings needed for any food product.

Please contact us if you have any questions regarding IHPC's comments or if we can provide any more information to assist your assessment of 3-MCPD.

<<IHPC Comments to OEHHA on 3-MCPD.PDF¤>>

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INTERNATIONAL HYDROLYZED PROTEIN COUNCIL

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May 5, 2009

Ms. Cynthia Oshita
Office of Environmental Health Hazard Assessment
Proposition 65 Implementation
1001 I Street, 19th Floor
Sacramento, CA 95812-4010

Re: Comments and Data Supporting the Ranking of 3-Monochloropropane-1,2-Diol (3-MCPD) as a "No Priority" Chemical by the Proposition 65 Carcinogen Identification Committee (CIC)

Ms. Oshita:

The International Hydrolyzed Protein Council (IHPC) is submitting comments on 3-monochloropropane-1,2-diol (3-MCPD), a chemical that is found in relatively low levels in certain foods and food ingredients processed at high temperatures in the presence of chlorine. On March 6, 2009, 3-MCPD was proposed by the California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA) for review by the Carcinogen Identification Committee (CIC) under Proposition 65. As described in more detail below, 3-MCPD should be ranked as a "no priority" chemical by the CIC and OEHHA for purposes of further Proposition 65 assessment because 3-MCPD is not a carcinogen as defined by the Proposition 65 regulations, and even if it were considered to be a carcinogen by the CIC and OEHHA, total dietary intake of 3-MCPD falls below conservative "safe harbor" levels, resulting in no Proposition 65 warnings needed for any food product.

IHPC is an international non-governmental organization with headquarters in Washington, D.C. and represents manufacturers, users, or sellers of hydrolyzed proteins throughout the world. Hydrolyzed proteins include acid-hydrolyzed vegetable proteins (acid-HVPs), autolyzed yeasts and yeast extracts. 3-MCPD has been found in acid-HVPs and foods containing acid-HVPs, such as some soy sauces and related products, and also has been found in a variety of foods not connected to acid-HVPs.

Through its representation of the hydrolyzed protein industry, IHPC has gained intimate knowledge of 3-MCPD, both in terms of its occurrence in foods and its safety profile, as established through an array of studies published in the scientific literature since the mid-1970s. IHPC submitted comments and industry data to support the safety analysis of 3-MCPD performed by the Joint FAO/WHO Expert Committee on Food Additives (JEFCA) in 2002 and its re-analysis in 2006 (published in 2007). IHPC also participated extensively in the development by Codex Alimentarius in 2008 of a Code of Practice for the reduction of 3-MCPD in the manufacture of acid-HVPs and products that contain acid-HVPs and a draft Maximum Level (ML) for 3-MCPD in liquid condiments containing acid-HVPs.

At the recent request of IHPC, CanTox, one of the world's leading health science consulting firms, reviewed the publicly available toxicology data on 3-MCPD, evaluated its carcinogenic potential, developed appropriate safe harbor levels based on the criteria in the Proposition 65 regulations, and compared these safe harbor levels to estimates of total dietary exposure. CanTox evaluated all relevant safety data and made the following observations on 3-MCPD:

- 3-MCPD does not meet the definition of "causing cancer" in the Proposition 65 regulations at 27 CCR §25306(e) because no epidemiology data demonstrating an association between 3-MCPD and cancer were identified, and sufficient evidence of carcinogenicity was not found in animals in multiple species or strains, in multiple experiments, or, to an unusual degree, in a single experiment.

- If 3-MCPD is considered to be a carcinogen by OEHHA, it should be considered a threshold carcinogen for which linearized, multistage modeling and the calculation of a safe harbor level via the application of a 1 in 100,000 excess risk of cancer based on lifetime exposure do not apply. Instead, the use of benchmark dose methodology, which reflects the leading edge of risk assessment, should be used. The safe harbor based on the benchmark dose is 609 µg/day.

- A more conservative approach would involve the evaluation of 3-MCPD as a non-threshold carcinogen, which would entail the utilization of a linearized, multistage model and the application of a 1 in 100,000 excess risk of cancer. This approach results in a safe harbor of 117 µg/day. Once again, CanTox believes the benchmark dose of 609 µg/day is more appropriate for 3-MCPD.

CanTox then calculated anticipated dietary exposure levels from 3-MCPD. In its assessment, CanTox relied on the extensive data and information that had been submitted to JECFA by various member companies in the 2002 and 2007 reviews of 3-MCPD. JECFA estimated total mean dietary exposures to 3-MCPD on the basis of data submitted by its member countries. The data included the levels of 3-MCPD found in a wide variety of foods such as baked goods, meats, beer, and numerous other products. A review of the intake data revealed that certain soy sauces (specifically those made from an acid hydrolysis process in which the manufacturer did not control for 3-MCPD) contributed the highest dietary exposure levels to 3-MCPD. In its evaluation of the JECFA reports, CanTox estimated a lifetime dietary exposure to 3-MCPD of approximately 33 µg/day and 112 µg/day of 3-MCPD for the mean and 95th percentile consumers, respectively. Both of these values are below the safe harbor levels calculated from the benchmark dose (609 µg/day) and the linearized, multistage models (117 µg/day).

CanTox provides an explanation for deviating from the 3-MCPD dietary exposure assessment found in the 2007 JECFA report. JECFA based its exposure assessment of 3-MCPD on the levels consumed by the sub-population of young children in the United Kingdom. It is inappropriate to use these values when calculating an estimate of lifetime exposure, as would be calculated under the Proposition 65 regulations. CanTox calculated an amortized lifetime exposure that reflected the reported levels of exposure to young children and adults.

Finally, it is important to note the JECFA exposure estimates will result in an overestimation of dietary exposure to 3-MCPD in the U.S. diet. While it is not possible to parse out the contribution of each food in the 2007 JECFA exposure assessment, soy sauce remained the primary contributor to 3-MCPD intake. Since the JECFA reviews, Codex has established a Code of Practice and an ML that limits 3-MCPD in soy sauce to 0.4 µg/g (*i.e.,* 0.4 part per million), a level that is well below the 18 µg/g used in the 2002 JECFA review. Moreover, the U.S. Food and Drug Administration has adopted a 1 µg/g limit for 3-MCPD in acid-HVPs and Asian style sauces and considers any product in excess of these levels adulterated and subject to domestic seizure or import detention. 1/ The controls implemented by FDA and Codex will further ensure soy sauces will not contribute

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1/ *See* FDA, Compliance Policy Guide: Sec. 500.500 Guidance Levels for 3-MCPD (3-chloro-1,2-propanediol) in Acid-Hydrolyzed Protein and Asian-Style Sauces (March 11, 2008), available at http://www.fda.gov/ora/compliance_ref/cpg/cpgfod/cpg500-500.html.

dietary 3-MCPD levels that would exceed the safe harbor, regardless of whether it is based on the benchmark dose or the linearized, multistage model.

In conclusion, we encourage the CIC and OEHHA to rank 3-MCPD as a "no priority" chemical for purposes of further Proposition 65 assessment. It is unclear whether 3-MCPD falls within the OEHHA definition of carcinogen, and even if it does, it currently is present in the diet below the safe harbor levels calculated from the benchmark dose and the linearized, multistage models. Because total dietary exposure to 3-MCPD does not exceed even the most conservative safe harbor level calculated, and due to the FDA limit on 3-MCPD in acid-HVPs and Asian style sauces, which represent the biggest single contributors of 3-MCPD in the diet, Proposition 65 warnings definitely would not triggered for any single food.

If IHPC can provide any additional information that would be useful to CIC and OEHHA for the review of 3-MCPD, please contact us.

Sincerely,

Martin J. Hahn

Attachment: CanTox Health Sciences International, "Response to OEHHA Regarding Selection of 3-Monochloroproane-1,2-Diol for Review by the Carcinogen Identification Committee" (May 5, 2009) 25 pp.

CANTOX
HEALTH SCIENCES INTERNATIONAL

Response to OEHHA Regarding Selection of 3-Monochloropropane-1,2-Diol for Review by the Carcinogen Identification Committee

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RESPONSE TO OEHHA REGARDING SELECTION OF 3-MONOCHLOROPROPANE-1,2-DIOL FOR REVIEW BY THE CARCINOGEN IDENTIFICATION COMMITTEE

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RESPONSE TO OEHHA REGARDING SELECTION OF 3-MONOCHLOROPROPANE-1,2-DIOL FOR REVIEW BY THE CARCINOGEN IDENTIFICATION COMMITTEE

1.0 INTRODUCTION

3-Monochloropropane-1,2-Diol (3-MCPD) is a trace contaminant that may form in various foods during food processing, cooking and storage as a result of chloride ions reacting with lipids. The Office of Environmental Health Hazard Assessment (OEHHA) of the California Environmental Protection Agency (CalEPA), through its Proposition 65 prioritization process, has selected 3-MCPD for review by the Carcinogen Identification Committee to determine the need for the development of a hazard characterization profile, and subsequently, to determine if this substance should be included on the listing of "Chemicals Known to the State to Cause Cancer or Reproductive Toxicity", also referred to as the Proposition 65 list.

Cantox Health Sciences International (Cantox) was requested by Hogan & Hartson, LLP to review the information pertinent to the carcinogenicity of 3-Monochloropropane-1,2-Diol (3-MCPD) and to derive a Safe Harbor Level for 3-MCPD for comparison to potential exposures. In addition, the studies identified in the OEHHA preliminary toxicology summary, as well as other recent toxicology data, were reviewed to determine if 3-MCPD meets the criteria "as causing cancer" as defined in Title 27, Division 4, Chapter 1, California Code of Regulations.

1.1 Overview of Pr oposition 65 Listing

The Safe Drinking Water and Toxic Enforcement Act of 1986, more commonly referred to as Proposition 65, requires businesses to inform citizens if the products they purchase contain chemicals that are considered by the State of California to cause cancer or birth defects or other reproductive harm. As required under Proposition 65, OEHHA on behalf of the Governor of California, revises and republishes the Proposition 65 list at least once per year. The most recent version was published in December 2008 (CalEPA, 2008).

OEHHA has two Science Advisory Boards, the Carcinogen Identification Committee (CIC) and the Developmental and Reproductive Toxicant Identification Committee (DART IC) that assist with the chemical selection Proposition 65 process. A new chemical may be added to the Proposition 65 list if CIC finds that a chemical has been clearly shown to cause cancer, or if DART finds that the chemical has been clearly shown to cause cancer or birth defects or other reproductive harm. The decision to list a chemical is based on the most current scientific information. The committees also consider responses from the public before a chemical is listed.

A chemical also may be added to the Proposition 65 list if a designated "Authoritative Body" [e.g., International Agency for Research on Cancer; National Institute of Occupational Safety and Health; National Toxicology Program, U.S. Environmental Protection Agency, and U.S. Food and Drug Administration (FDA)], has concluded that the chemical causes cancer or birth defects or other reproductive harm. Also, a chemical may be listed if a state or federal government agency required that it be labeled as causing cancer or birth defects or other reproductive harm. These are often prescription drugs dictated by the FDA to contain warning labels for these adverse effects. Finally, chemicals identified in the California Labor Code as causing cancer or birth defects or other reproductive harm are listed.

The OEHHA Science Advisory Boards are assisted by OEHHA staff in prioritizing chemicals for consideration of listing. The chemical 3-MCPD is one of 38 chemicals that have been proposed by OEHHA for review by the CIC. The Proposition 65 legislation includes provisions for public comment. Hence, the release of the 38 chemicals proposed for CIC consideration on March 6, 2009 also initiated the 60 day public comment period which closes on May 5, 2009.

2.0 RELEVANT 3-MCPD STUDIES IDENTIFIED BY OEHHA

During the preliminary toxicological evaluation, OEHHA identified the following data for 3-MCPD:

- 19-Month subcutaneous Injection study in female CHR/Ha Swiss mice (Van Duuren et al., 1974).
- 19-Month dermal application study in female CHR/Ha Swiss mice (Van Duuren et al., 1974).
- Two-year drinking water bioassays in Sprague-Dawley rats (Cho et al., 2008).
- Two-year drinking water bioassays in Fischer 344 rats (Sunahara et al., 1993).
- Two-year (72 week) oral gavage bioassay in CD rats (Weisburger et al., 1981).
- Numerous in vitro and in vivo genotoxicity assays.

No cancer epidemiology studies were identified.

Details of the studies were not provided. In this brief report, summaries are provided for the studies evaluated by OEHHA. Many of these have been summarized in detail in the Joint FAO/WHO Expert Committee on Food Additives (JECFA) monograph compiled for 3-MCPD (JECFA, 2002), and therefore, only the main findings are reported here in brief. A carcinogenicity study by Cho et al. (2008) and in vitro and in vivo genotoxicity tests conducted

by El Ramy et al. (2007), however, are summarized in detail as these studies were published subsequent to the JECFA monograph on 3-MCPD. In addition, one in vivo genotoxicity study by Robjohns et al. (2003) was identified that was not evaluated by OEHHA, and therefore, is summarized below.

2.1 Carcinogenicity

The animal carcinogenicity data evaluated by OEHHA consisted of the following five studies; the first four of which were extensively summarized in the JECFA monograph compiled for 3-MCPD (JECFA, 2002).

Mice

The 19-month study by Van Duuren et al. (1974) involved administration of 3-MCPD to 50 female ICR/Ha Swiss mice via weekly subcutaneous injection at a dose of 1.0 mg in 0.05 mL tricaprylin. Treatments were continued for a 580-day period. At study termination, one 3-MCPD-treated and one vehicle control-treated mouse were found to have a local, site-of-injection sarcoma. No other significant treatment-related lesions were found at autopsy.

Van Duuren et al. (1974) also conducted a 19-month study in female CHR/Ha Swiss mice involving topical administration of 3-MCPD to 50 mice at a dose of 2 mg in 0.1 mL acetone three times weekly for a period of up to 580 days (Van Duuren et al., 1974). Throughout the course of the study, no skin tumors were observed to develop. Also, no treatment-related proliferative lesions were found at necropsy. The lack of activity of 3-MCPD in the Swiss mouse skin painting assay is significant in that numerous genotoxic compounds, but relatively few non-genotoxic compounds, are active in this assay (Grasso et al., 1991).

Based on the available data, 3-MCPD does not appear to be carcinogenic to mice at the dose levels administered in the above studies. It is reiterated that the administrations were via non-oral routes of exposure.

Rats

3-MCPD has been evaluated for carcinogenicity in rats following oral gavage administration. Groups of 26 male and 26 female Sprague-Dawley rats were administered either 30 mg (low-dose) or 60 mg (high-dose) of 3-MCPD by gavage twice weekly in the study by Weisburger et al. (1981). A group of 20 vehicle controls of each sex were administered a saline solution. After 10 weeks the doses were increased to 35 and 70 mg, respectively, and continued until Week 72, following which a 32-week observation period ensued. Signs of toxicity included a significantly increased mortality rate in males compared to controls and significantly reduced body weights in high-dose males compared to controls (Weisburger et al., 1981). Histopathology revealed severe testicular degeneration and atrophy in all 3-MCPD-treated male rats, which were frequently accompanied by testicular polyarteritis. Three benign parathyroid

adenomas were found in high-dose males, the incidence of which was not significantly different compared to that of matched vehicle controls. Therefore, oral administration of 3-MCPD did not result in carcinogenic effects at doses of up to 60 mg/animal provided twice weekly and under the conditions of this study.

3-MCPD also has been evaluated for carcinogenicity in rats following oral administration via drinking water in a study by Sunahara et al. (1993). Groups of 50 male and 50 female Fischer F344 rats received 0, 20, 50, or 100 ppm 3-MCPD in their drinking water (tap water) for a period of 104 weeks. The doses administered were equivalent to intakes of 0, 1.1, 5.2, or 28 mg/kg body weight/day, respectively, for males and 0, 1.4, 7.0, or 35 mg/kg body weight, respectively, for females. The drinking water alone also contained 3-MCPD at a mean concentration of 2.7 ppm, equivalent to intakes of 0.15 mg/kg body weight/day for males and 0.19 mg/kg body weight/day for females. A significant reduction in body weight gain was reported for males and females at the mid- and high-dose levels (50 and 100 ppm, respectively) compared to the control, which may have been resultant of the decreased food and water consumption observed in these animals. The incidence of mortality was unaffected by 3-MCPD at any dose level and no effect of 3-MCPD on clinical signs was reported. The results of the hematological evaluations and blood chemistry tests were variable, but did not show any consistent dose-related effects, except for significantly increased blood urea nitrogen (BUN) and creatinine in mid- and high-dose animals.

Notable histological findings in the Sunahara et al. (1993) study are summarized in the following table (Table 2.1-1):

Table 2.1-1 Summary of Histopathological Findings in the Sunahara *et al.* (1993) 2-Year Drinking Water Rat Carcinogenicity Study

Organ and Lesion	Dose Group, ppm			
	0	**20**	**100**	**500**
Males (mg/kg body weight/day)	**0**	**1.1**	**5.2**	**28**
TESTES				
Number Examined	50	50	50	50
Leydig-cell Hyperplasia	39	27*	4***	0***
Leydig-cell Adenoma	38	43*	50***	47*
Leydig-cell Carcinoma	0	0	0	3
MAMMARY GLAND				
Number Examined	45	48	47	49
Glandular Hyperplasia	4	13	24***	43***
Fibroadenoma	0	0	2	10**
Adenoma	0	0	1	1
Adenocarcinoma	0	0	1	1
KIDNEYS				
Number Examined	50	50	50	50
Nephropathy	36	40	45*	49***
Tubular Hyperplasia	3	6	15**	34**
Tubular Adenoma	0	0	1	5

Table 2.1-1 Summary of Histopathological Findings in the Sunahara ***et al.*** (1993) 2-Year Drinking Water Rat Carcinogenicity Study

Organ and Lesion	Dose Group, ppm			
	0	20	100	500
Females (mg/kg body weight/day)	0	1.4	7.0	35
KIDNEYS				
Number Examined	50	50	50	50
Nephropathy	24	23	42***	48***
Tubular Hyperplasia	2	4	20***	31***
Tubular Adenoma	0	1	0	9**

* Statistically significant at P<0.05 (pair-wise Fisher's test between treated and controls).
** Statistically significant at P<0.01.
*** Statistically significant at P<0.001.

At necropsy, and following histopathological examination, the following significant treatment-related effects were observed:

- The incidence of renal tubular adenomas was increased in high-dose animals of both sexes, but only significantly in the female high-dose group. These benign tumors were not associated with early death and no malignant kidney tumors were observed in any group. All of the adenomas were microscopic and most were classified as early adenoma; borderline between hyperplasia and adenoma.

- Also in kidneys of mid- and high-dose groups (both sexes), a significant, dose-dependent increase in atypical renal tubular hyperplasia and a significantly increased incidence and severity of chronic progressive nephropathy were observed. There were clear correlations between the severity of the nephropathy and the incidence/degree of renal tubular hyperplasia and presence of renal tubular adenomas.

- The incidence of testicular Leydig cell adenomas was significantly increased in all 3-MCPD dose groups. These benign tumors were not associated with early death. Further progression to adenocarcinoma occurred in 3/50 male rats of the high-dose group. The incidence of Leydig cell hyperplasia declined in a dose-related manner in treated groups as morphologic progression from hyperplasia to adenoma occurred in the higher dose levels.

- A dose-dependent increase in epithelial single-cell degeneration in the epididymides and atrophy of the seminal vesicles was observed and was significant in the mid- and high-dose groups.

- The incidence of fibroadenoma of the mammary gland was significantly increased in male rats of the high-dose group. In addition, an increase in the incidence and severity of generalized mammary hyperplasia in mid- and high-dose males was observed.

- In addition, there was a statistically significant reduction in the incidences of pancreatic islet-cell hyperplasia, and adenomas at the two highest doses and in islet-cell carcinomas at all three doses compared to controls.

Based on the findings of this study, oral administration of 3-MCPD resulted in a dose-dependent increase in the incidence of renal tubular adenomas, which were considered to be secondary to the increased incidence of chronic progressive nephropathy (CPN). Oral administration of 3-MCPD also resulted in a dose-dependent increase in the incidences of testicular Leydig cell adenomas and mammary gland fibroadenomas in males, which were both suggested to be hormone-mediated. Leydig cell adenomas, which are the most common tumor type in rats, are likely of little significant to humans (Prentice and Miekle, 1995; Cook et al., 1999) and as such are not a relevant tumor type for deriving a tolerable daily intake.

Another carcinogenicity study involving oral administration of 3-MCPD via drinking water was conducted by Cho et al. (2008). This was a two-year carcinogenicity study on 3-MCPD that was conducted in Sprague-Dawley rats in accordance with the OECD guideline for Test No. 451: Carcinogenicity Studies. Groups of 50 male and female rats were administered 3-MCPD at doses of 0 (control), 25 (low-dose), 100 (mid-dose), or 400 (high-dose) ppm in drinking water provided ad libitum. Doses selected were based on the results of a prior 13-week oral toxicity study conducted in Sprague-Dawley rats, in which adverse effects were observed at doses above 40 mg/kg body weight/day (Shin et al., 2002). Body weights and water and food consumption were recorded weekly, and animals were observed at least once daily for general appearance, behavior, signs of toxicity, morbidity, and mortality. Male and female rats were necropsied at 100 and 104 weeks, respectively. A complete macroscopic examination was performed on all animals, and all organs/tissues were subsequently examined microscopically. Although outlined as a requirement in the OECD guideline for Test No. 451, differential blood counts were not determined.

At study end, survival rates within all groups were low (<50%), but were similar amongst all treated and control groups. The high mortality rates were largely attributed to moribund sacrifices caused by spontaneous pituitary gland tumors that occurred in all groups. Food consumption also was similar among all groups, and body weights and water consumption were similar among the control, low-, and mid-dose groups. Body weights and water consumption of males and females of the high-dose group, however, were significantly reduced compared to animals of the control group throughout the duration of the study. Based on weekly water consumption data, the average daily intakes of 3-MCPD were approximately 1.97, 8.27, and 29.50 mg/kg body weight/day for males and 2.68, 10.34, and 37.03 for females in the low-, mid-, and high-dose groups, respectively.

Notable histological findings in the Cho et al. (2008) study are summarized in the Table 2.1-2:

Table 2.1-2 Summary of Histopathological Findings in the Cho ***et al.*** (2008) 2-Year Drinking Water Rat Carcinogenicity Study

Organ and Lesion	Dose Group, ppm			
	0	25	100	400
Males (mg/kg body weight/day)	0	1.97	8.27	29.5
TESTES				
Number Examined	50	50	50	50
Atrophy	6	16*	13*	34*
Arteritis/periarterious	3	15*	9*	11*
Leydig-cell Adenoma	1	1	4	14*
KIDNEYS				
Number Examined	50	50	50	50
Nephropathy	15	27*	39*	41*
Tubular Hyperplasia	1	11*	21*	36*
Tubular Adenoma	0	0	1	4
Tubular Carcinoma	0	0	0	5*
Tubular Adenoma or Carcinoma	0	0	1	7*
Females (mg/kg body weight/day)	0	2.68	10.34	37.03
KIDNEYS				
Number Examined	50	50	50	50
Nephropathy	6	8	23*	42*
Tubular Hyperplasia	1	0	1	10*
Tubular Adenoma	0	0	1	6*
Tubular Carcinoma	1	0	1	3
Tubular Adenoma or Carcinoma	1	0	2	9*

* Statistically significant at P<0.05 (poly-3 test).

Increased incidences of the following neoplastic lesions were observed in the high-dose groups compared to the control group:

- Incidences of renal tubule adenoma were significantly increased (at 12%) in high-dose females compared to the control females (0%) and incidences of renal tubule carcinoma were significantly increased (at 10%) in high-dose males compared to the control males (0%).

- Neoplastic lesions of the kidney were accompanied by dose-dependent increases in non-neoplastic lesions characterized as renal tubule hyperplasia and chronic progressive nephropathy in males and females exposed to 3-MCPD. In males, the increases were significantly different in all dose-groups compared to the control group for both lesion types. In females, a significant increase was observed in the high-dose group for renal tubule hyperplasia and in the mid- and high-dose groups for chronic progressive nephropathy.

- High-dose males presented with a significantly increased incidence of Leydig cell tumors (28%) compared to control males (2%). These observed changes were confirmed to be outside the range of historical data reported for Sprague-Dawley rats.

- Although Leydig cell tumors in male rats were associated with a significantly increased incidence in seminiferous tubular atrophy and arteritis/periarteritis in all dose groups compared to the control group, no evidence of increased incidence of hyperplasia was noted.

- No significant increases in neoplastic lesions were observed between the low- or mid-dose groups compared to the control group.

When viewed together, the studies by Sunahara et al. (1993) and Cho et al. (2008) demonstrate that oral administration of 3-MCPD results in a dose-dependent increase in the incidence of testicular Leydig cell adenomas and of renal tubular adenomas (in both sexes) associated with renal tubule hyperplasia and chronic progressive nephropathy. Leydig-cell adenomas, which is the most common tumor type observed in male rats, were significantly increased at the lowest-dose tested of 20 ppm (1.4 mg/kg body weight/day) in males. This tumor type is of little relevance to humans (Prentice and Miekle, 1995). Renal effects were observed to be significant at doses of 25 ppm (1.97 mg/kg body weight/day) and greater, with tubule adenomas significantly increased at doses of 100 ppm (28 mg/kg body weight/day) and greater. As with the Leydig cell tumors, the renal adenomas are likely of little relevance to humans (Hard and Khan, 2004) since they occur as a result of the exacerbation of rodent-specific CPN. Renal tubule carcinoma was induced by very high doses of 3-MCPD in male and female rats (400 ppm or approximately 29.5 mg/kg body weight/day for males and 37 mg/kg body weight/day for females). Unlike in the Sunahara et al., (1993) study, there were no statistically significant differences in mammary tumors or associated findings in treated rats compared to control animals.

2.2 Genotoxicity

A summary of all identified genotoxicity studies is presented in Table 2.2-1 below; most of which were evaluated by JECFA in the monograph for 3-MCPD (JECFA, 2002). An additional study considered by OEHHA is summarized below, along with a study not cited by OEHHA in their preliminary toxicological evaluation of 3-MCPD.

OEHHA cited an in vitro genotoxicity study by El Ramy et al. (2007), which employed the comet assay in Chinese Hamster Ovary (CHO) cells. Cells were treated with 3-MCPD at concentrations of 0 (vehicle alone), 0.5, 1, 2.5, or 5 mg/mL for 3 hours. Cells also were treated with β-chlorolactic acid, the principle metabolite of 3-MCPD, at concentrations of 0.1, 0.25, 0.5, or 1 mg/mL. 3-MCPD significantly induced DNA damage, expressed as olive Tail Moment and percentage of DNA in the comet tail, at the two highest concentrations tested (2.5 and 5 mg/mL) at which minimal cytotoxicity was observed. In contrast, β-chlorolactic acid did not induce DNA damage at any of the concentrations tested. The comet assay also was employed in two in vivo genotoxicity experiments (El Ramy et al., 2007). In the first experiment, male Sprague-Dawley rats were orally administered 0 (vehicle alone), 25, or 60 mg/kg body weight of 3-MCPD, at 24

and 3 hours prior to sacrifice. Blood, liver, kidneys, testes, and bone marrow were collected for analysis in the comet assay. In the second experiment, male Fischer 344 rats were orally administered 0 (vehicle alone) or 60 mg/kg body weight/day of 3-MCPD 24 and 3 hours prior to sacrifice. Blood and testes were collected for analysis in the comet assay. In both experiments, 3-MCPD did not induce DNA damage in any organ compared to the control. In addition, the percentage of highly damaged cells remained low and was similar between control and treated groups. Histopathological examination of the testes and kidneys from 3-MCPD-treated Sprague-Dawley rats revealed no microscopic abnormalities. A significant increase in the incidence of hepatocellular mitotic figures was observed in the livers of rats treated with 3-MCPD compared to controls.

An additional genotoxicity study was identified in the publicly available literature that was not included in the OEHHA evaluation. In this study, 3-MCPD was examined for genotoxicity in an in vivo rat bone marrow micronucleus test conducted in accordance with the OECD guideline for Test No. 474: Mammalian Erythrocyte Micronucleus Test (Robjohns et al., 2003). Groups of 6 Han Wistar rats were orally administered 3-MCPD at 0 (vehicle alone), 15, 30, or 60 mg/kg body weight/day by gavage for two consecutive days. Bone marrow was sampled 24 hours later and smears were scored for micronucleated polychromatic erythrocytes. Although, increased cytotoxicity was observed with increasing dose, the frequency of micronucleated polychromatic erythrocytes were similar and not significantly different between all treated and control groups. In addition, the values obtained fell within the laboratory historical negative control range.

3-MCPD also was examined for genotoxicity in an in vivo unscheduled DNA synthesis (UDS) test conducted with rat liver cells in accordance with the OECD guideline for Test No. 486: Unscheduled DNA Synthesis (UDS) Test with Mammalian Liver Cells in vivo (Robjohns et al., 2003). Groups of 4 Han Wistar rats were orally administered 3-MCPD at 0 (vehicle alone), 40, or 100 mg/kg body weight/day by gavage for 2 to 4 hours or 12 to 14 hours, following which hepatocytes were isolated for UDS determination. Net nuclear grains (NNG) counts were well below the threshold value of 0 (required for a positive response) for all 3-MCPD dose groups. In addition, no more than 0.3% of cells from any 3-MCPD dose group were observed to be in repair. In both experiments, positive controls were confirmed to be genotoxic.

Table 2.2-1 Results of Genotoxicity Tests on 3-Chloro-1,2-propanediol

Test system	Test object	Doses	Results (+S9/-S9)	Reference
In vitro				
Bacterial reverse mutation assay	Salmonella typhimurium TA1535	2-200 µmole/plate	+/+	Silhánková et al., 1982
Bacterial reverse mutation assay	S. typhimurium TA1537, TA1538, TA98	2-200 µmole/plate	-/-	Silhánková et al., 1982

Table 2.2-1 Results of Genotoxicity Tests on 3-Chloro-1,2-propanediol

Test system	Test object	Doses	Results (+S9/-S9)	Reference
Bacterial reverse mutation assay	*S. typhimurium* TA1535, TA100	100-1,000 µmole/plate	+/+	Stolzenberg and Hine, 1979
Bacterial reverse mutation assay	*S. typhimurium* TA98	100-1,000 µmole/plate	-/NR	Stolzenberg and Hine, 1979
Bacterial reverse mutation assay	*S. typhimurium* TA100	10-1,000 µmole/plate	+/+	Stolzenberg and Hine, 1980
Bacterial reverse mutation assay	*S. typhimurium* TA100, TA1535	100-10,000 µg/plate	+/+	Zeiger *et al.*, 1988
Bacterial reverse mutation assay	*S. typhimurium* TA98	100-10,000 µg/plate	-/+	Zeiger *et al.*, 1988
Bacterial reverse mutation assay	*S. typhimurium* TA97	100-10,000 µg/plate	-/NT	Zeiger *et al.*, 1988
Bacterial reverse mutation assay	*S. typhimurium* TA100	not reported	-/NT	Majeska and Matheson, 1983
Bacterial reverse mutation assay	*S. typhimurium* TA100	10-1,250 µg/plate	+/+	Ohkubo *et al.*, 1995
Bacterial reverse mutation assay	*S. typhimurium* TA677, TA98	10-1,250 µg/plate	-/+	Ohkubo *et al.*, 1995
Bacterial reverse mutation assay	*Escherichia coli* WP2, TM930, TM1080	2-200 µmole/plate	-/-	Ohkubo *et al.*, 1995
Forward mutation assay	yeast (S. pombe)	100-300mM	-/+	Rossi *et al.*, 1983
Mammalian mutation assay	Mouse lymphoma TK locus	2-9 mg/mL	+/-	Henderson *et al.*, 1987
Mammalian mutation assay	Chinese hamster V79 cells HPRT	0.3-70 mM	equivocal	Görlitz, 1991
SCE assay	Chinese hamster V79 cells	700-2,800 µg/mL	+/+	May, 1991
Transformation assay	Mouse M2 fibroblasts	100-2,000 µg/mL	+	Piasecki *et al.*, 1990
DNA synthesis inhibition	HeLa cells	not reported	-/-	Painter and Howard, 1982
Comet assay	Chinese hamster ovary cells	500 to 5,000 µg/mL	NT/+	El Ramy *et al.*, 2007
In vivo				
Somatic mutation (wing spot test)	Drosophila melanogaster	0.05-10 mM	-	Frei and Würgler, 1997
Dominant lethal assay	mice (male)	5 and 10 mg/kg bw/d orally for 5 days	-	Jones *et al.*, 1969
Dominant lethal assay	ICR/Ha Swiss mice (male)	125 mg/kg bw i.p. or 20 mg/kg bw/d orally for 5 days	-	Epstein *et al.*, 1972
Dominant lethal assay	Wistar rats (male)	5,10, and 20 mg/kg bw/d orally for 5 days	-	Jones and Jackson, 1976

Table 2.2-1 Results of Genotoxicity Tests on 3-Chloro-1,2-propanediol

Test system	Test object	Doses	Results (+S9/-S9)	Reference
Bone marrow micronucleus test	OF_1 mice	40 to 120 mg/kg bw	-	Jaccaud and Aeschbacher, 1989 Cited In: JECFA, 2002
Bone marrow micronucleus test	Han Wistar rats (male)	15, 30, and 60 mg/kg bw for 2 days	-	Marshall, 2000 Cited In: JECFA, 2002
UDS assay	Han Wistar rats (male)	40 and 100 mg/kg bw	-	Fellows, 2000 Cited In: JECFA, 2002
Bone marrow micronucleus test	Han Wistar rats (male)	15, 30, or 60 mg/kg bw/d orally for 2 days	-	Robjohns *et al.*, 2003
UDS assay	Han Wistar rats (male)	40 or 100 mg/kg bw/d orally for 2 days	-	Robjohns *et al.*, 2003
Comet assay	Sprague-Dawley rats (male); blood, liver, kidneys, testes, and bone marrow	25 and 60 mg/kg bw orally twice in 24 hours	-	El Ramy *et al.*, 2007
Comet assay	Fischer 344 (males); blood and testes	60 mg/kg bw orally twice in 24 hours	-	El Ramy *et al.*, 2007

Abbreviations: - = negative; + = positive; bw = body weight; d = day; NR = not reported; NT = not tested; SCE = sister chromatid exchange; UDS = unscheduled DNA synthesis

Collectively, although the data show that 3-MCPD is genotoxic *in vitro*, the *in vivo* genotoxicity data clearly demonstrate that 3-MCPD is not a genotoxic compound in mammalian species, notably in the kidney, at doses between 5 to 125 mg/kg body weight. Furthermore, differences in the metabolism of 3-MCPD between mammals and bacteria may explain the positive results in the *in vitro* assays in bacteria (Lynch *et al*., 1998). *In vitro*, 3-MCPD is likely metabolized to genotoxic intermediates, particularly glycidol; however, the primary urinary metabolite in rats was β-chlorolactic acid which is formed by a pathway not producing glycidol or other genotoxic intermediates. However, oxalic acid is a degradation product of β-chlorolactic acid and has been found to induce the observed nephrotoxic effects.

2.3 Evaluation of Toxicity Data

The available evidence for 3-MCPD does not meet the OEHHA criteria of “as cancer causing” in humans.

The definition of “as cancer causing” as specified in 27 CCR §25306(e), follows:

“(e) For purposes of this section, “as causing cancer” means that either of the following criteria has been satisfied:

(1) Sufficient evidence of carcinogenicity exists from studies in humans. For purposes of this paragraph, “sufficient evidence” means studies in humans indicate that there is a causal relationship between the chemical and cancer.

(2) Sufficient evidence of carcinogenicity exists from studies in experimental animals. For purposes of this paragraph, “sufficient evidence” means studies in experimental animals indicate that there is an increased incidence of malignant tumors or combined malignant and benign tumors in multiple species or strains, in multiple experiments (e.g., with different routes of administration or using different dose levels), or, to an unusual degree, in a single experiment with regard to high incidence, site or type of tumor, or age at onset.”

Item 1 does not apply as no epidemiology data demonstrating an association between 3-MCPD and cancer were identified.

Regarding item 2, carcinogenicity studies in mice and rats were identified. The studies in mice, which included a skin painting study and subcutaneous injection study, did not demonstrate a tumorigenic response (Van Duuren et al., 1974). Likewise no treatment-related increases in malignant tumors were observed in an oral gavage study in Sprague-Dawley rats (Weisburger et al., 1981). The drinking water study in Fischer 344 rats demonstrated statistically significant dose dependent increases in the incidences of adenomas and chronic progressive nephropathy; however, an increased incidence of carcinomas (i.e., malignant tumors) was not observed (although the incidence of islet-cell carcinomas was significantly decreased in 3-MCPD treated rats) (Sunahara et al., 1993). Only in the most recent drinking water study in Sprague-Dawley rats was an statistically significant increase in renal tubular carcinomas observed and only at the highest dose (Cho et al., 2008), but not to an unusual degree nor particularly with a high incidence (10% in males and 12% in females at the high dose versus 0% in low dose). This response was attributed to a progression of chronic progressive nephropathy. Finally, the lack of a genotoxic-mechanism for 3-MCPD supports that low dose human exposures would be unlikely to result in malignancies.

3.0 DEVELOPMENT OF SAFE HARBOR LEVELS

Products are exempt from the requirement of a Proposition 65 warning if exposure to a listed chemical is below the Safe Harbor Level established by OEHHA. If a chemical does not have a Safe Harbor Level established by OEHHA, labeling is still not required if a business can show that the exposure to the listed chemicals is below the daily intake level that is associated with one excess case of cancer (above background) in an exposed population of 100,000, assuming a lifetime exposure, for a carcinogen, or is at least 1,000 times lower than the no observable adverse effect level for reproductive effects, for a reproductive toxicant. The Safe Harbor Level is referred to as a No Significant Risk Level (NSRL) for a carcinogen and as a Maximum Allowable Dose Level (MADL) for a reproductive toxicant.

The default principles and assumptions for quantitative risk assessment applicable to the derivation of a NSRL are specified in 27 CCR §25703. One of the defaults is to assume the absence of a carcinogenic threshold dose and to utilize a linearized multistage model. However, the actual language of the legislation is that "in the absence of principles or assumptions scientifically more appropriate, based upon the available data," the default principles and assumptions shall apply.

As the scientific data available for 3-MCPD, including negative in vivo genotoxicity data and evidence that renal tumors in rats are clearly associated with chronic progressive nephropathy, strongly support a threshold for tumorigenicity, it can be argued that a Safe Harbor Level based on a threshold is scientifically more appropriate.

The increased incidence of renal tubular adenomas was considered to be secondary to the increased incidence of chronic progressive nephropathy (CPN). CPN is regarded as an age-related, spontaneously-occurring, rodent-specific disease. As a result, renal tubule tumors that arise due to exacerbation of this condition are not relevant to humans (Hard and Khan, 2004; Lock and Hard, 2004; Hard et al., 2007).

JECFA and the EU Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment have also concluded that 3-MCPD acts as non-genotoxic carcinogen (CMC, 2000; JECFA, 2002). While JECFA is not specifically identified in 27 CCR §25306(m) as an authoritative body for the identification of chemicals as causing cancer, it is a WHO authoritative agency, with reputable scientist staff, as is the WHO International Agency for Research on Cancer (IARC), which is listed in 27 CCR §25306(m).

Thus, for the purpose of this assessment, Safe Harbor Levels were calculated assuming both a threshold (non-genotoxic) dose response, and linear dose response mechanism.

3.1 Safe Harbor Level Based on Assumption of a Threshold (Non-Genotoxic) Mechanism for Carcinogenic Response

At their 57th meeting (JECFA, 2002) established a provisional maximum tolerable daily intake (PMTDI) of 2 µg/kg body weight/day for 3-MCPD based on the Sunahara et al., (1993) drinking water carcinogenicity study in Fischer 344 rats. This limit was based on the lowest-observed-effect level (LOEL) of 1.1 mg/kg body weight/day associated with renal hyperplasia in male rats, to which a safety factor of 500 was applied, 10 fold each to account for inter- and intra-species differences and 5 fold to account for extrapolation from a LOEL. The LOEL from this study was concluded by JECFA to be close to the no-observed-effect level (NOEL) as no renal or mammary tumors were observed at this dose and the finding of increased tubular hyperplasia was not statistically significant, but, rather was considered reflective of a treatment-related, dose-dependent increase. The PMTDI was retained following re-evaluation of 3-MCPD by JECFA in 2006 (JECFA, 2007).

In the more recent 2 year drinking water study in Sprague-Dawley rats, male rats were administered slightly higher doses of 3-MCPD than in the Sunahara et al. (1993) study. The LOEL was 1.97 mg/kg body weight at which renal hyperplasia and chronic progressive nephropathy was observed. Similar findings were observed in females but at higher doses. Using benchmark dose methodology, Hwang et al. (2009) derived a lower-bound Bench Mark Dose associated with a 10% incidence at the lower 95% confidence interval ($BMDL_{10}$) of 0.87 mg/kg body weight/day based on renal tubular hyperplasia in male rats (Cho et al., 2008). The $BMDL_{10}$ for female rats was 19.47 mg/kg body weight/day. The dose of 0.87 mg/kg body weight/day was proposed by the authors as the "point of departure", which is used as an alternative to a no-observed-adverse-effect level (NOAEL), for deriving a human tolerable daily intake level of 3-MCPD. With the application of a 100-fold safety factor to the $BMDL_{10}$ to account for inter-and intra-species difference, a human exposure limit of 8.7 µg/kg body weight/day is obtained. It was noted by the authors that the $BMDL_{10}$ dose based on renal tubular hyperplasia was lower than the $BMDL_{01}$ value (lower bound BMD associated with a 1% incidence) for renal adenomas and carcinomas, and was thus a more conservative value as the basis for the point of departure.

The BMD approach is the leading edge of risk assessment, and compensates for the criticisms of the NOEL approach which include that (i) the NOEL by definition must be one of the experimental doses tests and (ii) once the NOEL is defined, the rest of the dose-response curve is ignored. The BMD approach is being used more often in risk assessment, particularly for application to pivotal studies for which a dose response is seen, but for which the lowest dose in the studies is a LOEL rather than a NOEL. The National Toxicology Program, U.S. Environmental Protection Agency, and World Health Organization are often utilizing Bench Mark Dose methodology to evaluate new chemicals and to update previous evaluations.

Rats from different strains will have different sensitivities to chemicals and different historical tumor patterns and predispositions to tumor types. However, it is noteworthy that the dose-response for renal tubular hyperplasia for both Sprague Dawley and Fischer 344 Rats in the 2-year drinking water studies, as indicated in Table 3-1 and Figure 3-1, showed a comparable sensitivity and were in line when plotted.

Table 3-1 Comparison of Renal Tubular Hyperplasia in Sprague-Dawley (SD) (Cho ***et al.***, 2008) and Fischer 344 (Sunahara ***et al***., 1993) Male Rats

Strain	Dose (mg/kg Body Weight/Day)	Response (%)
Fischer 344	0	3/50 (6)
Sprague Dawley	0	1/50 (2)
Sprague Dawley $BMDL_{10}$	0.87	10% response on lower confidence interval
Fischer 344	1.1	6/50 (12)
Sprague Dawley	1.97	11/50* (22)
Fischer 344	5.2	15/50* (30)
Sprague Dawley	8.27	21/50* (42)
Fischer 344	28	34/50* (68)
Sprague Dawley	29.5	36/50* (72)

* Difference from controls is statistically significant

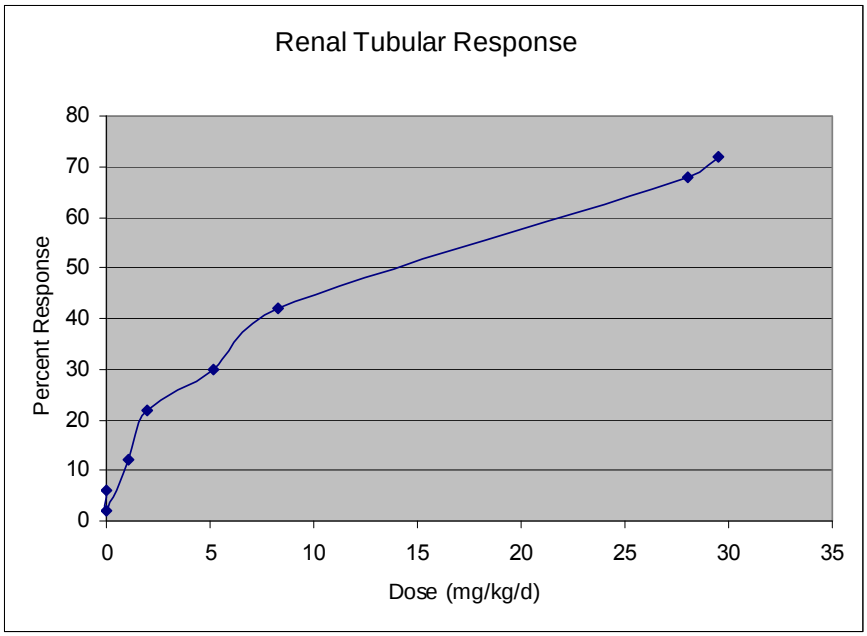

Figure 3-1 Renal Tubular Hyperplasia Dose Response for Sprague-Dawley and Fischer 344 Male Rats.

As discussed previously, the response at the low dose in the Fischer 344 rat study was not statistically significant, however, this dose was considered a LOEL by JECFA instead of a NOEL given the trend increase and dose-response relationship. Given the comparable sensitivity of Sprague-Dawley rats and Fischer 344 rats, the $BMDL_{10}$ based on the Sprague-Dawley study, which is lower than the LOEL from the Fischer 344 rat study, is likely close to the true NOEL for both species. As such, the $BMDL_{10}$ is a suitable and conservative point of

departure for deriving the tolerable human daily intake, with the application of a 100-fold safety factor.

Thus, on the basis of the Hwang et al., (2009) $BMDL_{10}$ calculation, a Safe Harbor Level for 3-MCPD of 609 µg/day[1] is obtained for 3-MCPD, assuming a body weight of 70 kg.

3.2 Safe Harbor Level Based on Assumption of a Linear Dose Response Mechanism for Carcinogenic Response

The default principles and assumption for quantitative risk assessment applicable to the derivation of a NSRL are specified in 27 CCR §25703. The default for a carcinogen is to assume no threshold and to utilize a linearized multistage model to determine the oral slope factor (also referred to as a unit cancer risk). The NSRL is calculated from the oral slope factor to correspond to the dose associated with a risk level of 1 excess cancer in a 100,000 exposed individuals, and converted to a µg/day dose by assuming a 70 kg body weight.

A unit cancer risk for 3-MCPD of 0.0021 $(mg/kg\ body\ weight/day)^{-1}$ was reported in the JECFA (2002) report. This value was attributed to the Quantitative Risk Assessment Committee of the U.S. Food and Drug Administration (2000). This unit cancer risk estimate was based on the incidence of Leydig cell carcinomas (3/50) in the high dose male Fischer 344 rats (compared to 0/50 in controls) in the Sunahara et al., (1993) study. The Leydig cell carcinomas were the only type of carcinoma observed that were considered treatment related. At a risk level of 1 in 100,000 and assuming a body weight of 70 kg, the Safe Harbor Level would be 350 µg/day. However, this value is not as appropriate for use since the incidence of Leydig carcinomas was not statistically significantly increased and since this tumor type is of highly questionable relevance to humans.

Hwang et al. (2009) also reported a linear multistage cancer slope factor for 3-MCPD, in addition to the bench mark dose modeling, based on the recent Cho et al. (2008) rat study (note: reported as a footnote to Table 3 in study publication). The slope factor of 0.006 $(mg/kg\ body\ weight/day)^{-1}$ was based on the increased incidence of male renal adenomas and carcinomas. At a risk level of 1 in 100,000 and assuming a body weight of 70 kg, the Safe Harbor Level based on this slope factor is 117 µg/day. While the tumor type is still of questionable relevance to human health, this value is representative of a worst-case Safe Harbor Level for 3-MCPD.

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[1] $BMDL_{10}$ of 0.87 mg/kg body weight/day/(UF of 100) x 1000 µg/mg x body weight of 70 kg = 609 µg/day

4.0 EXPOSURE ASSESSMENT

3-Chloro-1,2-propanol and its precursor, 3-MCPD are examples of food-borne or food-processing contaminants. The presence of 3-MCPD was detected in 1981 (Davidek *et al.,* 1982) in acid-hydrolyzed vegetable protein (acid-HVP), where the contaminants were formed as a byproduct of a reaction between hydrochloric acid and triglycerides in foods under a variety of conditions, such as food processing, cooking and storage. Thus, by treating protein-rich extracts from vegetable sources with concentrated hydrochloric acid at high temperatures, trace amounts of fats and oils react with the hot acid to form 3-MCPD. More recently, it was shown that 3-MCPD formed by the action of acid in the production of acid-HVP is a racemic mixture of its enantiomers, *(R)*- and *(S)*-3-MCPD. It was also revealed that the rates of decomposition of the two isomers treated with alkali are equal (Velisek *et al.,* 2002).

In raw acid-HVP, 3-MCPD occurs primarily in free form, and to a lesser extent, esterified with higher fatty acids (Velisek *et al.*, 1980). 3-MCPD was originally detected as a contaminant of the savory food ingredient acid-HVP; however, trace amounts of the compound was also detected in several foods and food ingredients, such as various cereal products in which the manufacturing process involves high temperatures, such as roasting or toasting. Recent findings have shown that 3-MCPD esters also occur in an array of both unprocessed and processed foods (Hamlet and Sadd, 2004a,b; Svejkovská *et al.,* 2004; 2006; Dolezal *et al.,* 2005; Zelinková *et al.,* 2006; Divinová *et al.,* 2007).

Esterified 3-MCPD can be easily released by a lipase-catalyzed hydrolysis reaction (Hamlet and Sadd, 2004a,b) and thus, due to food processing, high levels (in the range of 280 to 2,420 µg/kg) of bound 3-MCPD have been found in salty crackers, pickled herrings, doughnuts, crisp break, dark malt and French fries. Zelinková *et al*., 2006 reported that refined edible oils, such as olive oils, also contain relatively high levels of esterified 3-MCPD, with amounts ranging from <300 to 2462 µg/kg (Zelinková *et al.*, 2008). Furthermore, surveys conducted in the United States and Canada revealed that high amounts of 3-MCPD are present in soya sauce (>300 mg/kg) due the inclusion of hydrolyzed soya proteins and flavorings.

A survey submitted by the United Kingdom (UK) showed that in some savory foods, the mean residual concentration of 3-MCPD was 0.012 mg/kg. Therefore, based on the assumption that an average person consumes approximately 1,500 g/day of solid food, it was estimated that the intake of 3-MCPD from food other than soya sauce was approximately one-eighth of the diet, 180 g, from savory foods that might contain 3-MCPD. On this basis, the intake of 3-MCPD from foods other than soya sauce is approximately 2 µg/person/day. In contrast, following a survey of 90 samples of soya sauce, the mean concentration of 3-MCPD present was 18 mg/kg (ppm). In the U.S., the mean and 90th percentile consumption of soya sauce was estimated to be 8 and 16 g/person/day, respectively, with corresponding intakes of 3-MCPD of 140 µg/person/day for mean consumption and 290 µg/person/day at the 90th percentile (JECFA, 2002). Since these

data were generated, the U.S. FDA (2008) issued a compliance policy guide for 3-MCPD in acid-hydrolyzed protein (acid-HP) and Asian-style sauces. According to this policy, acid-HP is not Generally Recognized As Safe (GRAS) if it contains 3-MCPD at levels greater than 1 ppm. Thus, the concentration of 1 ppm is a more accurate value for determining current and future intakes of 3-MCPD than 18 ppm. In the U.S., using the same mean and 90th percentile consumption estimates of soya sauce of 8 and 16 g/person/day, the intakes of 3-MCPD based on 1 ppm would be 8 µg/person/day for mean consumption and 16 µg/person/day at the 90th percentile.

JECFA (2007) provided updated estimated national dietary intake data for 3-MCPD for 10 countries (Denmark, Finland, France, Germany, Ireland, the Netherlands, Norway, Sweden, UK and Thailand). Table 4-1 provides a summary of the estimated dietary intake of 3-MCPD from various food sources, including soy-based products, for the 10 countries surveyed.

Table 4-1. Estimated Dietary Intake of 3-Chloro- 1,2-Propanediol from Various Food Sources, Including Soya Sauce and Soy Sauce-Based Products [1]

Country	Population Group	Intake (µg/kg body weight/day)	
		Mean	P95[3]
Australia	All (≥ 2 years)	0.20	0.65
	2 to 12 years	0.17	0.18
	13 to 19 years	0.19	0.65
	≥ 20 years	0.21	0.75
Denmark	Adult	0.21	NR[4]
Finland	Adult	0.23	NR[4]
France	≥ 18 years	0.22	NR[4]
	3 to 14 years	0.30	NR[4]
Germany[2]	Adult	0.17	0.72
	4 years	0.48	1.70
	14 years	0.15	0.53
Ireland	Adult	0.36	0.68
Netherlands	Adult	0.30	1.38
	Children	0.34	1.69
Sweden	Adult	0.16	0.48
Thailand	Whole Population	0.02	0.06
United Kingdom[2]	≥ 18 years	0.40	1.30
	1.5 to 4.5 years	0.70	2.30

[1] Table reproduced from JECFA 2007
[2] Consumers only
[3] 95th Percentile: only 5% of consumers had exposure above this level.
[4] Not reported

Calculations of the national intakes were accomplished by correlating data on individual consumption of 3-MCPD-containing foods and food ingredients and body weight obtained from national food consumption surveys with mean occurrence data obtained from food contamination surveys. Following analysis of the national dietary intake data, the Committee concluded that an intake of 3-MCPD at a level of 0.7 µg/kg body weight/day from a variety of foods including soy sauce and soy sauce-containing food products could be taken to represent the average intake data for 3-MCPD for the general population. Additionally, an intake of 2.3 µg/kg body weight/day was recommended as being representative of consumers with a high intake of 3-MCPD (JECFA, 2007). However, it should be noted that these numbers were actually the maximum intakes by population group and specifically correspond to the mean and 95th percentile intakes from the U.K. survey for children aged 1.5 to 4.5 years of age.

To determine medium or average exposure over an average intake for 70 years, it would be more appropriate to use the combined data set for children and adults. To calculate the amortized average intake of 3-MCPD over a lifetime, children up to 17 years of age were assumed to have a 3-MCPD intake of 0.7 µg/kg body weight/day, while adults aged 18 to 70 were assumed to have an intake of 0.4 µg/kg body weight/day. The resultant amortized average intake over 70 years based on these data is 0.47 µg/kg body weight/day (~33 µg/person/day[2]) and the amortized 95th percentile intake of 3-MCPD based on 2.3 µg/kg body weight/day for children up to 17 years of age and 1.3 µg/kg body weight/day for adults corresponds to 1.6 µg/kg body weight/day or ~112 µg/person/day[3]. Notably, these amortized intake estimates are higher than the amortized intakes of 3-MCPD for all other jurisdictions presented in the EU survey (Table 4-1).

The level of exposure to 3-MCPD from foods other than soya sauce is relatively low, as it is found infrequently in foods. As the distribution of residual 3-MCPD present in soya sauce heavily skews the level of 3-MCPD exposure, exposures to 3-MCPD among populations that are not regular consumers of soy sauce would be expected to be considerably lower.

5.0 RISK CHARACTERIZATION

According to 27 CCR §25721(d)(4), “lifetime exposure shall be calculated using the average rate of intake or exposure for average users of the consumer product” (which would include foods). As per 27 CCR §25721(b) lifetime exposure is defined as “the reasonably anticipated rate of exposure for an individual to a given medium of exposure measured over a lifetime of seventy years.”

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[2] (0.7 µg/day x 17 years + 0.4 µg/day x 53 years)/70 years = 0.47 µg/day
[3] (2.3 µg/day x 17 years + 1.3 µg/day x 53 years)/70 years = 1.6 µg/day

Intakes of 3-MCPD are highest among consumers of soy sauce. As detailed in Section 4.0, an intake of 3-MCPD at a level of 0.47 µg/kg body weight/day from a variety of foods including soy sauce and soy sauce-containing food products represents the average intake data for 3-MCPD for the general population over a 70 year lifetime (1.6 µg/kg body weight/day is estimated for heavy consumers) in Europe (JECFA, 2007).

In the U.S., the mean consumption of soya sauce was 8 g/person/day; corresponding to intakes of 3-MCPD of approximately 8 µg/person/day (~0.11 µg/kg body weight/day) for mean consumption (16 µg/person, or ~0.23 µg/kg body weight/day, is estimated for heavy consumers). The U.S. data are based on the recent U.S. FDA (2008) guidance limit of 3-MCPD in acid-hydrolyzed protein of 1 ppm.

The calculated Safe Harbor Level of 609 µg/day (~8.7 µg/kg body weight/day) (discussed in Section 3.0) for 3-MCPD is well above the estimated intakes of 3-MCPD from the average consumption of a variety of foods including soy sauce and soy sauce-containing food products by Australian and European populations and from consumption of soy sauce by the U.S. population. It is also above the heavy consumption estimates for these populations.

The worst-case Safe Harbor Level of 117 µg/day (1.67 µg/kg body weight/day), if a linear dose response is assumed for 3-MCPD, also is above the average consumption estimates for 3-MCPD. It also is above the 90th percentile estimated intake of 3-MCPD for the U.S. population from soy sauce consumption and above the 95th percentile intake of 3-MCPD for European and Australian populations from consumption of a variety of foods including soy sauce and soy sauce-containing food products. Moreover, it bears noting that food manufacturing practices to limit the formation of 3-MCPD have been widely adopted since the collection of the data used here for the exposure calculations. Thus, intakes of 3-MCPD from the diet can be expected to be further reduced.

6.0 SUMMARY

The results of this assessment support the conclusion that potential exposures to 3-MCPD from its presence in foods would be below the Safe Harbor Level for 3-MCPD. In addition, the available evidence for 3-MCPD does not meet the OEHHA criteria of “as cancer causing” in humans for the following reasons: (i) no human epidemiology data were identified; (ii) no tumorigenic responses were observed in mice studies following skin painting or subcutaneous injection; (iii) no treatment-related increases in malignant tumors were observed in an oral gavage study in Sprague-Dawley rats; (iv) significant dose dependent increases in the incidences of adenomas and chronic progressive nephropathy was observed in a drinking water study in Fischer 344 rats, but an increased incidence of carcinomas (*i.e.,* malignant tumors) was not observed; (v) in the most recent drinking water study in Sprague-Dawley rats a statistically significant increase in renal tubular carcinomas was observed at the highest dose only, but not

to an unusual degree nor particularly with a high incidence (10% in males and 12% in females at the high dose versus 0% in low dose). Moreover, this response was attributed to a progression of chronic progressive nephropathy rather than a genotoxic mechanism. The lack of a genotoxic-mechanism for 3-MCPD further supports that low dose human exposures would be unlikely to result in malignancies.

In conclusion, the results of this assessment indicate that it is unnecessary to add 3-MCPD to the Proposition 65 list on the basis of potential exposures being below the calculated Safe Harbor Level. Also, the toxicology data support only a weak carcinogenic potential in rats, and only at high doses. Furthermore, the tumor types that are seen in these studies are considered of little relevance to humans.

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