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Date: 5/5/2009 3:23 PM
Subject: IHPC Comments on the Prioritization of 1,3-DCP for Proposition65 Review
Attachments: IHPC Comments to OEHHA on 1,3-DCP.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 1,3-dichloro-2-propanol (1,3-DCP) by the Carcinogen Identification Committee (CIC) under Proposition 65. As described in the attached comments, 1,3-DCP should be ranked as a “no priority” chemical by the CIC and OEHHA for purposes of further Proposition 65 assessment because total dietary intake of 1,3-DCP falls below the safe harbor level, 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 1,3-DCP.

<<IHPC Comments to OEHHA on 1,3-DCP.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 1,3-Dichloro-2-Propanol (1,3-DCP) 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 1,3-dichloro-2-propanol (1,3-DCP), a chemical that is found in very low levels in certain foods and food ingredients processed at high temperatures in the presence of chlorine. On March 6, 2009, 1,3-DCP 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, 1,3-DCP should be ranked as a "no priority" chemical by the CIC and OEHHA for purposes of further Proposition 65 assessment because <u>total</u> dietary intake of 1,3-DCP falls below the safe harbor level, resulting in no Proposition 65 warnings needed for any food product.

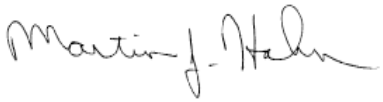
IHPC is an international non-governmental organization with headquarters in Washington, D.C. and represents manufacturers, users, or sellers of hydrolyzed proteins throughout the world. Hydrolyzed proteins include acid-hydrolyzed vegetable proteins (acid-HVPs), autolyzed yeasts and yeast extracts. 1,3-DCP has been found intermittently at very low levels in acid-HVPs and foods containing acid-HVPs, such as some soy sauces and related products, and also has been found, with very low occurrence, in various foods not connected to acid-HVPs. Through its representation of the hydrolyzed protein industry, IHPC has gained intimate knowledge of 1,3-DCP, 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 early 1990s. IHPC submitted comments and industry data to support the safety analysis of 1,3-DCP performed by the Joint FAO/WHO Expert Committee on Food Additives (JEFCA) in 2002 and its re-analysis in 2006.

At the recent request of IHPC, CanTox, one of the world's leading health science consulting firms, reviewed the publicly available toxicology data on 1,3-DCP, evaluated its carcinogenic potential, developed an appropriate safe harbor level based on the criteria in the Proposition 65 regulations, and compared this safe harbor level to estimates of total dietary exposure. As CanTox concluded in its attached report, total dietary intakes of 1,3-DCP, including intake estimates of heavy consumers of soy sauce, which is viewed by JECFA as contributing the highest dietary exposure levels to 1,3-DCP, are well below the safe harbor level. As a result, dietary exposure of 1,3-DCP from all possible food sources is within the safe harbor, and no Proposition 65 warning on any food would be required. For this reason, we encourage the CIC and OEHHA to rank 1,3-DCP as a "no priority" chemical for purposes of further Proposition 65 assessment.

If IHPC can provide any additional information that would be useful to CIC and OEHHA for the review of 1,3-DCP, please contact us.

Sincerely,



Martin J. Hahn

Attachment: CanTox Health Sciences International, "Response to OEHHA Regarding Selection of 1,3-Dichloro-2-Propanol for Review by the Carcinogen Identification Committee" (May 5, 2009) 18 pp.

CANTOX
HEALTH SCIENCES INTERNATIONAL

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

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

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

1.0 INTRODUCTION

1,3-Dichloro-2-propanol (DCP) 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 (Cal EPA), through its Proposition 65 prioritization process, has selected DCP 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 DCP and to derive a Safe Harbor Level for DCP for comparison to potential exposures.

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 of California 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 (Cal EPA, 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 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 DCP 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 DCP STUDIES IDENTIFIED BY OEHHA

During the preliminary toxicological evaluation, OEHHA identified the following data for DCP:

- 104-Week drinking water study in Wistar rats (Hercules, Inc., 1986)
- Review of toxicity data conducted by the National Toxicology Program (NTP, 2005)
- In vitro genotoxicity studies (Piasecki et al., 1990; Hahn et al., 1991).

No cancer epidemiology studies were identified.

Details of the studies were not provided. In this report, summaries are provided for the studies evaluated by OEHHA. All of these have been summarized in detail by the Joint FAO/WHO Expert Committee on Food Additives (JECFA, 2002, 2007), the NTP (2005), the Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC, 2001, 2004), and the Committee on Mutagenicity (COM, 2001, 2003); therefore, only the most relevant data are reported here in brief. No further human epidemiological or animal carcinogenicity studies that were not evaluated by OEHHA were identified.

2.1 Carcinogenicity

DCP was evaluated in a carcinogenicity study in which male and female Wistar rats (80/sex/group) were administered the compound in the drinking water at a concentration of 0, 27, 80, or 240 mg/L for a period of 104 weeks, designated as control, low-, mid-, and high-dose groups, respectively (Hercules, Inc., 1986). These doses were reported to provide exposures

equating to 0, 2.1, 6.2, or 19 mg/kg body weight/day in males, respectively, and 0, 3.4, 9.6, or 30 mg/kg body weight/day in females, respectively. Ten rats/sex/group were killed and evaluated after 26, 52, and 78 weeks of treatment; thus, 50 rats/sex/group were administered the compound for the entire duration of the study. There were no significant compound-related effects on food and water consumption and clinical signs of toxicity; however, mortality was significantly increased in both sexes in the high-dose group. Body weight gain was significantly decreased in males and females after 74 and 79 weeks, respectively, in the high-dose group. A number of compound-related non-neoplastic and neoplastic lesions were reported in a number of organs.

The tumor data observed in the Wistar rat study are summarized in the following table (Table 2.1-1):

Table 2.1-1 Summary of Histopathological Findings in the Hercules, Inc. (1986) 2-Year Drinking Water Rat Carcinogenicity Study

Organ and Lesion	Dose Group, ppm			
	0	27	80	240
Males (mg/kg body weight/day)	0	2.1	6.2	19
LIVER				
Number Examined[1]	80	80	80	80
Hepatocellular adenoma	1	0	1	1
Hepatocelluar carcinoma	0	0	2	11****
Hemangiosarcoma	0	0	0	1
KIDNEYS				
Number Examined[1]	80	80	80	80
Tubular Adenoma	0	0	3	10****
Tubule Carcinoma	0	0	0	1
TONGUE				
Number Examined[1]	80	80	79	80
Papilloma	0	1	0	6*****
Carcinoma	0	0	1	6*****
THYROID				
Number Examined[1]	80	80	80	78
Follicular Adenoma	0	0	3*	3*
Follicular Carcinoma	0	0	2	1
Females (mg/kg body weight/day)	0	3.4	9.6	30
LIVER				
Number Examined[1]	80	80	80	80
Hepatocellular adenoma	1	1	1	6***
Hepatocelluar carcinoma	0	0	1	44*****
Hemangiosarcoma	0	0	0	1
KIDNEYS				
Number Examined[1]	80	80	80	79
Tubular Adenoma	0	0	0	1
Tubule Carcinoma	0	0	0	0
TONGUE				
Number Examined[1]	80	80	80	79
Papilloma	0	0	0	7*****
Carcinoma	0	1	1	4**

Table 2.1-1 Summary of Histopathological Findings in the Hercules, Inc. (1986) 2-Year Drinking Water Rat Carcinogenicity Study

Organ and Lesion	Dose Group, ppm			
	0	27	80	240
THYROID				
Number Examined[1]	79	80	80	79
Follicular Adenoma	1	0	3	4
Follicular Carcinoma	0	0	0	2*

[1] includes 30 animals per group killed at interim sacrifice periods
* Statistically significant at P<0.05 (one-tailed analysis for positive trend).
** Statistically significant at P<0.01.
*** Statistically significant at P<0.005
**** Statistically significant at P<0.001
***** Statistically significant at P<0.0005

The observed histological lesions, as well as other relevant details, are discussed below for each affected organ.

Liver

- Clinical chemistry analysis revealed signs of hepatotoxicity in high-dose females, which included significantly increased cholesterol, serum aspartate aminotransferase (AST) (at 74 and 104 weeks), alanine aminotransferase (ALT) (at 78 and 104 weeks), alkaline phosphatase (ALP) (at 104 weeks), γ-glutamyl transferase (GGT) (at 104 weeks), increase glutathione (GSH), and decreased cytochrome P450 (CYP450) content. .

- Increased relative liver weight was reported in all treatment groups at Week 26, in mid- and high-dose groups at Week 52, and in high-dose rats at Weeks 78 and 104.

- Non-neoplastic hepatic lesions, considered to be compound-related, included increased incidence of fatty changes in the livers of males in the mid- and high-dose groups (identified at Week 52, with greater incidence by Week 78), a dose-dependent increase in incidence of sinusoidal peliosis in all treated groups (identified at Week 52, with greater incidence by Week 78), eosinophilic foci in both sexes in the mid- and high-dose groups, and glycogen-free foci in both sexes at the highest dose.

- Neoplastic lesions were identified in the liver and included increased incidence of hepatocelluar adenoma in high-dose females (after 26 weeks) and hepatocellular carcinoma in high-dose males and females (after 52 weeks). A significant positive trend was reported for both lesions.

Kidney

- Increased urinary protein and amylase levels were reported in high-dose females at Weeks 52, 78, and 104, suggestive of nephrotoxicity.

- Increased relative kidney weight was reported at all time points measured in high-dose females, in mid-dose males at Week 26, and in high-dose males at Weeks 26, 78, and 104.

- Neoplastic lesions were identified in the kidneys and included increased incidence of renal tubule adenoma in males in the high-dose group (after 78 weeks). A significant positive trend was reported for this lesion.

Thyroid

- Follicular hyperplasia was reported in high-dose males at the end of the study period.

- Neoplastic lesions were identified in the thyroid after 78 weeks and included increased incidence of thyroid follicular adenoma in males of the mid- and high-dose groups and increased incidence of thyroid follicular carcinoma in females in the high-dose group.

Tongue

- Neoplastic lesions were identified on the tongue after 52 weeks and included increased incidence of lingual papilloma and carcinoma in males and females of the high-dose group. A significant positive trend was reported for these lesions.

Other Organs/Tissues

- Stomach papilloma and carcinoma were reported one high-dose and 1 low-dose female, respectively.

- Carcinomas in the oral cavity were identified in one mid-dose female and 2 high-dose males.

2.2 Genotoxicity

The mutagenic and genotoxic potential of DCP has been evaluated in a variety of assays, the results of which are summarized in Table 2.2-1. In vitro testing in Salmonella typhimurium strains TA100, TA1535, TM677 has yielded positive results in a number of studies, both in the presence and absence of S9 metabolic activation (Nakamura et al., 1979; Stolzenberg and Hine, 1980; Lynn et al., 1981; Silhankovà et al., 1982; Majeska and Matheson, 1983; Zeiger et al., 1988; Hahn et al., 1991; Ohkubo et al., 1995). Other studies have suggested that metabolic activation is required for the mutagenicity of DCP in S. typhimurium strains TA97, TA98, and TA100 (Gold et al., 1978; Zeiger et al., 1988). In contrast, Silhankovà et al. (1982) reported negative results for mutagenicity in S. typhimurium strains TA98, TA1537, and TA1538, both with and without metabolic activation. Ohkubo et al. (1995) also reported negative results in S. typhimurium TA98; however, the test was conducted only in the absence of S9. Assays with

Escherichia coli TM930, PM21, and GC4798 have demonstrated positive results only in the presence of metabolic activation (Silhankovà et al., 1982; Hahn et al., 1991). Hahn et al. (1991) suggested that the mechanism by which DCP induces mutations in S. typhimurium TA100 and TA1535 may involve the formation of epichlorohydrin during the preincubation period. Their theory was supported by their results in E. coli PM21 and GC4798, which demonstrated that DCP induced mutations following a preincubation period with S9, but not in the absence of metabolic activation. Hahn et al. (1991) also noted that in the E. coli strains tested, induction factors for mutagenicity increased with increasing pH, again supporting this theory, as the formation of epichlorohydrin and hydrochloric acid from DCP is favored at high pH values. The authors confirmed the presence of epichlorohydrin by cochromatography and gas chromatography-mass spectrometry following incubation of DCP with S9.

Mammalian in vitro cell assays have all yielded positive results for DCP, including mutations at the TK locus in mouse lymphoma cells (with and without metabolic activation) (Henderson et al., 1987), sister chromatid exchange in Chinese hamster V79 cells (weak positive results with and without metabolic activation) (von der Hude et al., 1987), inhibition of DNA synthesis in HeLa cells (Painter and Howard, 1982), and transformation of mouse M2 fibroblasts (Piasecki et al., 1990).

In vivo, DCP tested negative in a wing spot somatic mutation test in Drosophila melanogaster at test concentrations ranging from 0.05 to 10 mM (Frei and Würgler, 1997). Howe (2002) conducted a bone marrow micronucleus test in which groups of 6 male Han Wistar rats were orally administered DCP at doses of 0, 25, 50, or 100 mg/kg body weight/day for 2 consecutive days. Piloerection, weight loss, and lethargy were reported at the highest dose (100 mg/kg body weight/day); however, there was no statistically significant increase in the frequency of micronuclei at any dose nor was there any toxicity to the bone marrow. Similarly, Beevers (2003) reported no significant increase in unscheduled DNA synthesis in the hepatocytes of Han Wistar rats (3/group) administered a single oral dose of 0, 40, or 100 mg/kg body weight of DCP. Information on liver toxicity in these assays was not provided.

Table 2.2-1 Results of Genotoxicity Tests on DCP

Test system	Test object	Doses	Results (+S9/-S9)	Reference
***In vitro* Assays**				
In vitro bacterial mutation assay	*Salmonella typhimurium* TA1535	2-200 µmol/plate	+/+	Silhankovà *et al*., 1982
In vitro bacterial mutation assay	*S. typhimurium* TA1537, TA1538, TA98	2-200 µmol/plate	-/-	Silhankovà *et al*., 1982
In vitro bacterial mutation assay	*S. typhimurium* TA100	0.078-0.775 µmol/plate	+/-	Gold *et al.*, 1978, cited in NTP, 2005
In vitro bacterial mutation assay	*S. typhimurium* TA100	0.775-7.753 µmol/plate	nt/-	Lynn *et al.*, 1981, cited in NTP, 2005
In vitro bacterial mutation assay	*S. typhimurium* TA100	10-1,000 µmol/plate	+/+	Stolzenberg and Hine, 1980
In vitro bacterial mutation assay	*S. typhimurium* TA100, TA1535	100-6,666 µg/plate	+/+	Zeiger *et al*., 1988
In vitro bacterial mutation assay	*S. typhimurium* TA97, TA98	100-6,666 µg/plate	+/-	Zeiger *et al*., 1988
In vitro bacterial mutation assay	*S. typhimurium* TA100, TA1535	3-300 µmol/plate	+/+	Nakamura *et al*., 1979
In vitro bacterial mutation assay	*S. typhimurium* TA100	responses reported at ≤ 500 µg/plate	+/nt	Majeska and Matheson, 1983
In vitro bacterial mutation assay	*S. typhimurium* TA100	1.0-62.8 µmol/plate	+/+	Hahn *et al*., 1991
In vitro bacterial mutation assay	*S. typhimurium* TA1535	1.0-78.6 µmol/plate	+/+	Hahn *et al*., 1991
In vitro bacterial mutation assay	*S. typhimurium* TA100, TA1535	up to 1,250 µg/plate	+/+	Ohkubo *et al*., 1995
In vitro bacterial mutation assay	*S. typhimurium* TA98	up to 1,250 µg/plate	nt/-	Ohkubo *et al*., 1995
In vitro bacterial mutation assay	*S. typhimurium* TM677	up to 100 µg/plate	+/+	Ohkubo *et al*., 1995
In vitro bacterial mutation assay	*Escherichia coli* TM930	2-200 µmol/plate	+/-	Silhankovà *et al*., 1982
In vitro SOS chromotest assay	*E. coli* PM21, GC4798	2.5-30 µmol/sample	+/-	Hahn *et al*., 1991
In vitro mammalian mutation assay	mouse lymphoma *Tk* locus	2-9 mg/mL	+/+	Henderson *et al*., 1987
In vitro mammalian SCE assay	Chinese hamster V79 cells	0.12-3.3 mM	weak +/+	von der Hude *et al*., 1987
DNA synthesis inhibition	HeLa cells	2.5 mM	+	Painter and Howard, 1982
In vitro transformation assay	mouse M2 fibroblasts	0.1-1 mg/mL	+	Piasecki *et al*., 1990

Table 2.2-1 Results of Genotoxicity Tests on DCP

Test system	Test object	Doses	Results (+S9/-S9)	Reference
***In vivo* Assays**				
In vivo somatic mutation (wing spot test)	*Drosophila melanogaster*	0.05-10 mM	-	Frei and Würgler, 1997
In vivo bone marrow micronucleus assay (oral exposure)	male Han Wistar rats (6/group)	25 to 100 mg/kg bw/d for 2 days	-	Howe, 2002, cited in JECFA, 2007
In vivo unscheduled DNA synthesis (oral exposure)	male Han Wistar rats (3/group)	40 to 100 mg/kg bw (single dose)	-	Beevers, 2003, cited in JECFA, 2007

nt = not tested

2.3 Evaluation of Toxicity Data

As previously stated, the toxicity data on DCP has been evaluated by a number of bodies, including JECFA, the NTP, the COC, and the COM. A brief summary of each of the reviews conducted by the various committees in an attempt to elucidate the mechanism by which DCP induces carcinogenicity is discussed below.

In a review of the carcinogenicity data provided by Hercules, Inc. (1986), JECFA (2002) noted that the increase in thyroid follicular cell neoplasms was “not reliable enough” to be included in a risk assessment or safety evaluation. It is assumed that JECFA meant that the response only just barely reached statistical significance, and thus could potentially have been due to chance rather than an actual treatment related effect. With respect to the increased incidence of renal tumors, JECFA (2002) noted that these tumors appeared concurrently with evidence of chronic progressive nephritis, which is common in aging rats; however, an increased incidence of renal tubule hyperplasia (not reported in the JECFA monograph) led JECFA to conclude that the renal neoplasms were compound-related and not the result of chronic progressive nephritis. With respect to the observed hepatic neoplasms, JECFA (2002) noted that sinusoidal peliosis was previously suggested to be a pre-neoplastic lesion of vascular hepatic neoplasia. Together with the increased incidence in fatty changes and hemosiderin-containing Kupffer cells, JECFA (2002) suggested that the hepatic lesions may be a result of metabolic disturbances in the liver.

In a subsequent evaluation of DCP, JECFA (2007) evaluated the results of this study and performed dose-response modeling on data for the groups of rats exposed for the entire study duration. Using several models, JECFA (2007) calculated benchmark doses for 10% extra risk of tumors (BMD_{10}) and 95% lower confidence limit for the benchmark dose ($BMDL_{10}$). The $BMDL_{10}$ values calculated by JECFA (2007) ranged from 7.2 to 19.1 mg/kg body weight/day for individual treatment-related tumors and 3.3 to 7.7 mg/kg body weight/day for tumor-bearing animals, as summarized in Table 2.3-1.

Table 2.3-1 Summary of Benchmark Doses and 95% Lower Confidence Limit for Benchmark Doses

Tumor Types	BMD_{10} Range (mg/kg bw/d)		$BMDL_{10}$ Range (mg/kg bw/d)	
	Males	Females	Males	Females
Tumor-bearing animals / all treatment-associated sites	5.4 to 7.5	8.5 to 10.3	3.3 to 6.1	6.6 to 7.7
Renal adenoma and carcinoma	11.1 to 12.2	N/A	7.2 to 7.7	N/A
Hepatocellular adenoma and carcinoma	14.4 to 16.0	11.2 to 14.6	10.3 to 12.3	9.1 to 10.1
Tongue papilloma and carcinoma	12.4 to 17.9	17.1 to 22.8	8.7 to 11.6	11.5 to 19.1

JECFA (2007)
BMD_{10} = benchmark dose for 10% extra risk of tumors; $BMDL_{10}$ = 95% lower confidence limit for the benchmark dose; N/A = not applicable

Following a review of the available carcinogenicity and genotoxicity data, JECFA (2002), the COC (2001, 2004), and the COM (2001) concluded that the positive results in *in vitro* assays, together with the evidence of carcinogenicity in rats, were sufficient to consider DCP as a genotoxic carcinogen. With the availability of the results of the more recent *in vivo* genotoxicity studies by Howe (2002) and Beevers (2003), JECFA (2007) re-evaluated DCP and concluded that despite the negative results in these *in vivo* assays, toxicity in the tissues assessed was not demonstrated, and thus it was unclear if the tissue were exposed to sufficient concentrations of DCP. The question of exposure in the *in vivo* study, together with the positive *in vitro* assays and the carcinogenic effects in rats, for which a mechanism has not been determined, led JECFA to conclude that a genotoxic mechanism of carcinogenicity for DCP could not be excluded.

In contrast, the COM (2003) was satisfied with the new *in vivo* data, stating that the "studies were adequately conducted and gave clear negative results" and concluded that DCP was not genotoxic *in vivo.* However, the COM (2003) noted that the role of metabolic activation in the *in vitro* studies is not clear. Following the COM (2003) evaluation, the COC (2004) released a statement noting that the increased incidence of renal and thyroid tumors in the 2-year drinking study in rats may have been secondary to sustained cell proliferation. With respect to the liver tumors, the COC (2004) noted evidence of hepatotoxicity at doses below those producing a neoplastic effect, and suggested that when taken together with the *in vivo* data in which unscheduled DNA synthesis was not observed in the livers of male rats (Beever, 2003), the evidence suggests that the hepatic neoplasms induced by DCP may be induced by a non-genotoxic mechanism. Upon consideration of the neoplasms observed on the tongue, the COC (2004) agreed that the effects were clearly compound-related and suggested that DCP may have produced an irritant effect; however, given that there are no data available to support this hypothesis, the COC noted that there was not sufficient evidence to suggested that the tongue neoplasms were not produced by a genotoxic mechanism.

DCP was nominated to the NTP by National Institute of Environmental Health Sciences (NIEHS) for toxicological characterization. In their review of toxicological data related to DCP, the NTP (2005) concluded that the in vivo genotoxicity studies were indicative of a lack of genotoxicity in vivo and suggested that if reactive genotoxic metabolites were formed, they were likely either too transient to be able to exert genotoxic effects in vivo or that the target tissues or endpoints evaluated in the in vivo studies were not relevant to the genotoxicity of DCP. The NTP noted that the role of the metabolism of DCP in vitro is unclear. The basis of the nomination was that further studies are needed to characterize the carcinogenic hazard of DCP exposure.

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 1000 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 (MADLs) 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 to determine an oral slope factor. 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, and converted to a µg/day dose by assuming a 70 kg body weight. 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.

The current scientific data available concerning the carcinogenic mechanism of DCP is unclear. While certain tumors such as the liver could be due to result of metabolic disturbances in the liver leading to a non-genotoxic mechanism, the relationship between DCP exposures and tumors of the tongue, which are not a common tumor type, has not been defined. Therefore, for the purpose of this assessment, a Safe Harbor Level was derived according to the conservative default assumptions of the Proposition 65 regulations.

An oral slope factor or unit risk for DCP of 0.01 (mg/kg body weight/day)$^{-1}$ was reported in the JECFA (2002) report. The tumor incidence data used to calculate the slope factor was the tubular adenoma data in male rats at the mid-dose. It should be noted that while 80 animals were examined, the slope factor was based only on the incidence data for the 50 animals/group

exposed for the full duration of the study. Thus, the slope of this simple data point was calculated as (3/50 – 0/50)/6.2 mg/kg body weight/day = 0.0096774 (mg/kg body weight/day)$^{-1}$. It was concluded that the response was essentially linear with dose in the observable region of the curve and thus is representative of cancer risk. The 95th upper bound confidence interval was not determined.

Based on the oral slope factor of 0.0096774 (mg/kg body weight/day)$^{-1}$, the risk specific dose (RsD) that would be associated with a risk level of 1 in 100,000, and assuming a body weight of 70 kg, is 70 µg/day.

To determine a slope factor based on the 95th upper bound confidence interval, the full incidence data set for tubular adenomas and carcinomas in male rats was analyzed using R(2.9.0) software for linear regression. The data was fit to the model, with the resultant slope factor determined to be 0.0121 (mg/kg body weight/day)$^{-1}$, which is slightly more conservative than that reported by JECFA (2002). Using the model, the lower and upper 95th confidence intervals were calculated for each point. The oral slope factor for the 95th upper bound confidence interval was determined to be 0.0132 (mg/kg body weight/day)$^{-1}$. Based on this slope factor, the RsD that would be associated with a risk level of 1 in 100,000, assuming a body weight of 70 kg, was calculated to be 53 µg/day. This RsD was adopted as the Safe Harbor Level for the purpose of this assessment.

In comparison, if future research, or the decisions of authoritative bodies, should support a non-linear relationship for the DCP associated tumors, the most conservative $BMDL_{10}$ of 3.3 mg/kg body weight/day calculated by JECFA, which is based on incidence of tumor-bearing animals for all treatment-associated sites, would correspond to a Safe Harbor Level of 2,310 µg/day[1]. This dose is obtained by using the $BMDL_{10}$ as the point of departure, applying an uncertainty factor (UF) of 100 to account for inter- and intraspecies and assuming a body weight of 70 kg.

4.0 EXPOSURE ASSESSMENT

DCP belongs to a group of chemical contaminants formed under certain processing, storage, and cooking conditions. During the production of acid-hydrolyzed vegetable protein (acid-HVP), such as soya beans, the reaction of hydrochloric acid and residual vegetable fat from the raw materials used generates DCP as a byproduct (Davidek *et al.,* 1982; Crews *et al.,* 2003; Nyman *et al.,* 2003; Fu *et al.,* 2007). As such, due to the frequent use of acid-HVP, DCP has been found as a primary member of the chemical contaminants group, most notably in acid-HVPs from savory foods and soy sauces (Codex Commission on Food Additives and Contaminants, 2006; Fu *et al.,* 2007).

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[1] $BMDL_{10}$ 3.3 mg/kg body weight/day/UF of 100 x 70 kg body weight x 1,000 µg/mg = 2,310 µg/day

Surveys have been conducted by the United States (U.S. FDA, 2002) to determine the national occurrence of DCP in soy sauces and soy-based products. Based on the occurrence data for individual samples of 39 different soy sauce and soy sauce-based products in the U.S., the average concentration of DCP was found to be 0.62 mg/kg. The average was calculated by assigning a value of half the reporting limits to the 64% of samples of which the reported value was less than the limit of 0.025 mg/kg.

Based on consumption data of soy sauce and soy sauce-based products in the U.S., potential exposures to DCP were estimated to be 7 µg/person/day and 14 µg/person/day, at the mean and 90th percentile intake of the soy products, respectively. In the survey conducted in the U.S., the intake of DCP from foods other than soy sauce was estimated to be approximately 0.1 µg/person/day (JECFA, 2002).

A national estimate of dietary intake of DCP was provided by JECFA for Australia and member states of the European Union (JECFA, 2007). Table 4-1 provides a summary of the estimated dietary intake of DCP from various food sources, including soy-based products, for the countries surveyed.

Table 4-1 Estimated Dietary Intake of 31,3-Dichloro-2-Propanol from Various Food Sources, Including Soya Sauce and Soy Sauce-Based Products [1]

Country	Population Group	Intake of 1,3-Dichloro-2-Propanol (µg/kg body weight/day) [2]	
		Mean	P95[3]
Australia	All (≥ 2 years)	0.041	0.105
	2 to 12 years	0.051	0.136
	13 to 19 years	0.035	0.094
	≥ 20 years	0.039	0.101
Denmark	Adult	0.040	NR[4]
Finland	Adult	0.010	NR[5]
France	≥ 18 years	0.018	0.038
	3 to 14 years	0.031	0.064
Germany[4]	Adult	0.008	0.026
	14 years	0.011	0.036
Ireland	Adult	0.048	0.077
Netherlands	Adult	0.021	0.053
	Children	0.036	0.099
Sweden	Adult	0.011	0.025
United Kingdom[4]	≥ 18 years	0.016	0.041
	1.5 to 4.5 years	0.035	0.133

[1] Table reproduced from JECFA (2007)
[2] Only 5% of consumers had exposure above this level.
[3] 95th Percentile; Estimated dietary intakes of 1,3-dichloro-2-propanol for European countries were assessed by JECFA (2007) based on available food consumption data and a fixed weighted concentration of 1,3-dichloro-2-

propanol for food categories found to contain 1,3-dichloro-2-propanol in the European Union report (European Union, 2004) (soy sauce and soy sauce-based products) and in the Australian report for the other foods group (meat and fish products. Standard average body weight of 65 kg for adults, 30 kg for children and 15 kg for young children were used.
[4] Consumers only.
[5] Not reported.

These estimated dietary intakes were calculated by correlating individual consumption data with mean occurrence data, using the body weight of the consumer as reported in the consumption survey. As such, the results showed that the intake estimates from various food sources including soy sauce and soy sauce-based products ranged from 0.008 to 0.051 µg/kg body weight/day for the average in the general population and a range of 0.025 to 0.136 µg/kg body weight/day for consumers at the 95th percentile, including young children. Thus, based on the national estimated ranges, the Committee concluded that the level of 0.051 µg/kg body weight/day of DCP could be taken to represent the average intake of DCP for the general population and the intake of 0.136 µg/kg body weight/day of could be taken to represent consumers with a high intake (95th percentile). However, it should be noted that these numbers were actually the maximum intakes by population group and correspond to the mean and 95th percentile intakes from the Australian survey for children aged 2 to 12 years of age. To determine medium or average exposure over a 70 year lifetime, it would be more appropriate to use the Australian data for all ages (≥ 2 years) which is 0.041 µg/kg body weight/day (or ~2.87 µg/person/day) for mean consumption and 0.105 µg/kg body weight/day or ~7.35 µg/person/day for 95th percentile intakes. These intake estimates are still higher than the average DCP intakes for most of the other jurisdictions indicated in the EU survey (Table 4-1).

The level of exposure to DCP found in foods other than soy sauce is infrequent; thus, the level of consumption of DCP from foods other than soy sauce is relatively low. As such, it can be expected that the distribution of residual DCP present in soy sauce heavily skews the level of DCP exposure and therefore, exposures to DCP 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”.

Intakes of DCP are highest among consumers of soy sauce. For U.S. populations, DCP exposure from soy sauce consumption was calculated to be 7 µg/person/day at the mean or average consumption (the 90th percentile level of soy sauce consumption is 14 µg/person/day).

In Europe and Australia, intakes of DCP at a level of 0.041 µg/kg body weight/day (~2.87 µg/person/day) from a variety of foods including soy sauce and soy sauce-containing food products for all ages was considered representative of average consumption over a 70 year lifetime (the 95th percentile estimate for DCP intake was 0.105 µg/kg body weight/day or ~7.35 µg/person/day).

The Safe Harbor Level of 53 µg/day is 8 to 18 times higher that the average DCP intake estimates for U.S. (7 µg/person/day) and Australia/European (2.87 µg/person/day) populations, respectively. The Safe Harbor Level also is higher than the intakes of DCP estimated for heavy consumers.

In the re-evaluation of DCP, JECFA (2007) calculated margins of exposure between the lowest $BMDL_{10}$ (3.3 mg/kg body weight/day) based on the incidence data on tumor bearing animals for all treatment-affected locations and the estimated exposures from the diet determined for Europe. Given that the $BMDL_{10}$ was several orders of magnitude higher than anticipated exposures to DCP from the diet, JECFA concluded that DCP intakes from the diet were of low concern for human health.

6.0 SUMMARY

Based on the results of a chronic study in rats, DCP was concluded to be carcinogenic to rats. Increased tumor incidences were observed in the liver, kidneys, tongue, and thyroid for male and female rats. With the exception of follicular adenomas of the thyroid in mid-dose male rats, the tumors were statistically significantly increased only in the high dose groups. The genotoxicity results for DCP were generally positive in *in vitro* assays but negative *in vivo*.

There are data to support that the mechanism of carcinogenicity may be threshold based. These include *in vivo* genotoxicity assays that were negative, rat tumor incidence data showing statistically significant increased generally only at the high doses, and supported non-genotoxic mechanistic data for some of the tumor types. However, as a non-genotoxic mechanism could not definitively be supported for the tongue tumors (an irritation based mechanism has been hypothesized but no research data are available), a Safe Harbor Level (NSRL) was derived assuming a linear dose-response.

The risk characterization results indicated that, even assuming a conservative linear response relationship, the NSRL for DCP of 53 µg/day was in excess of intakes of DCP even at the 90th and 95th percentile levels of consumption.

Consequently, based on this assessment, it is not expected that any product would ever need to be labeled with a Proposition 65 warning as it would not exceed the Safe Harbor Level.

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