Food and Chemical Toxicology 48 (2010) S57–S62

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Application of the margin of exposure (MoE) approach to substances in food that are genotoxic and carcinogenic Example: (CAS No. 96-23-1) 1,3-Dichloro-2-propanol (DCP)

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ARTICLE INFO

Article history:
Received 8 June 2009
Accepted 27 October 2009

ABSTRACT

1,3-Dichloro-2-propanol (DCP) is formed in foods under a variety of conditions. It was positive in a variety of *in vitro* genotoxicity tests, but was negative in two *in vivo* studies. DCP produced neoplasms at several sites in rats. Kidney tumours in male rats were selected as the critical tumour type. Dose–response modelling of the data for DCP gave a $BMDL_{10}$ for combined kidney carcinomas and adenomas in male rats of 9.62 mg/kg-body weight (bw)/day. The exposure of humans was estimated at an average of 0.00009 mg/kg-bw/day and a high exposure of 0.000136 mg/kg-bw/day. The MOEs for these exposures were 100,000 and 70,000, respectively.

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1. Toxicological data

1,3-Dichloro-2-propanol (DCP) is formed when chloride ions react with lipid components in foods under a variety of conditions including food processing, cooking and storage.

1.1. Genotoxicity

1,3-Dichloro-2-propanol (DCP) was positive in a variety of *in vitro* genotoxicity tests, but was negative in two *in vivo* studies, a rat bone marrow micronucleus assay and a rat hepatocyte DNA repair assay using oral administration (JEFCA, 2007). In the micronucleus assay, rats received up to 60 mg/kg-body weight (bw)/day for 2 days while in the DNA repair assay, they received single doses up to 100 mg/kg-bw.

1.2. Carcinogenicity

1.2.1. Rats

Groups of 80 male and 80 female Wistar KFM/Han rats, 4 weeks of age were acclimatised for 10 days and then were administered DCP (purity, 99%) in their drinking-water at concentrations of 0, 27, 80, or 240 mg DCP/L, corresponding to intakes of 0, 2.1, 6.3, and 19 mg DCP/kg-bw/day for males and 0, 3.4, 9.6, and 30 mg/kg-bw/day for females, for up to 104 weeks (RCC, 1986). The drinking-water was prepared daily, and the stability, concentration, and homogeneity of DCP were determined regularly. The rats were fed *ad libitum* a pelleted diet, which was tested regularly for contaminants and found to contain low, biologically insignificant levels of aflatoxin, estrogen, pesticides, and heavy metals. The mortality rates of the groups of 50 rats that were exposed throughout the study were higher for males (32/50) and females (27/50) at the high dose than for controls (males, 18/50; females, 13/50) (statistics not reported). The mortality rates were 11/50 males and 9/50 females at the low dose and 16/50 males and 14/50 females at the intermediate dose. DCP produced increases in kidney, liver, thyroid and tongue tumours in males and liver, thyroid and tongue tumours in females.

1.3. Mode of action

DCP was genotoxic *in vitro*, but not *in vivo*. No mechanistic data are available on which to assess the mode of action in the target tissues of carcinogenicity, but increases in neoplasia at several sites suggests genotoxicity.

1.4. Epidemiological data

No study was available.

1.5. Dose–response relationships

In the RCC study (RCC, 1986), as shown in Table 1, in male rats there were dose-related increases in combined kidney tubular

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doi:10.1016/j.fct.2009.10.038

Table 1
Number of male rats bearing tumours after receiving drinking-water containing 1,3-dichloro-2-propanol for 2 years.

Tumour site	Concentration (mg/kg)			
	0	2.1	6.3	19
Kidney				
Tubular adenoma	0/50	0/50	3/50	9/50
Tubular carcinoma	0/50	0/50	0/50	1/50
Combined	0/50	0/50	3/50	9/50
Liver				
Hepatocellular adenoma	1/50	0/50	0/50	0/50
Hepatocellular carcinoma	0/50	0/50	2/50	8/50
Combined	1/50	0/50	2/50	8/50
Thyroid gland				
Follicular adenoma	0/50	0/50	2/50	3/48
Follicular carcinoma	0/50	0/50	2/50	1/48
Combined	0/50	0/50	4/50	4/48
Tongue				
Papilloma	0/50	1/50	0/49	6/50
Carcinoma	0/50	0/50	0/49	6/50
Combined	0/50	1/50	0/49	12/50

From RCC (1986).

Table 2
Number of female rats bearing tumours after receiving drinking-water containing 1,3-dichloro-2-propanol for 2 years.

Tumour site	Concentration (mg/kg)			
	0	3.4	9.6	30
Liver				
Hepatocellular adenoma	1/50	1/50	1/50	5/50
Hepatocellular carcinoma	0/50	0/50	1/50	36/50
Combined	1/50	1/50	2/50	41/50
Thyroid gland				
Follicular adenoma	1/50	0/50	3/50	3/49
Follicular carcinoma	0/50	0/50	0/50	2/49
Combined	1/50	0/50	3/50	5/49
Tongue				
Papilloma	0/50	0/50	0/50	7/49
Carcinoma	0/50	1/50	1/50	4/49
Combined	0/50	1/50	1/50	11/49

From RCC (1986).

adenoma and carcinomas and combined hepatocellular adenomas and carcinomas and combined tongue papillomas and carcinomas.

In females (Table 2), there were dose-related increases in combined hepatocellular adenomas and carcinomas and combined tongue papillomas and carcinomas.

1.6. Data quality, uncertainties and limitations

The RCC carcinogenicity study (RCC, 1986) met current standards.

2. Human dietary exposure analysis

2.1. Sub-populations of interest

No information is available on specific exposures of sub-populations or sensitivity of sub-populations.

2.2. Concentration in food

DCP concentrations in food were available from several countries (Table 3, JEFCA, 2007). DCP was only quantified in samples of soy sauce, acid-hydrolysed vegetable proteins (HVPs), malt products, minced beef (dry-fried, raw or cooked), pork ham, sausage meat (raw or cooked), and fish fillets (battered and fried). Average concentrations in samples of soy sauce-based products ranged from 0.09 mg/kg for soy oyster sauce to 0.6 mg/kg for soy mushroom sauce. Average concentrations were 0.0025 mg/kg in samples of fish product, 0.019 mg/kg in samples of meat products, and 0.008 mg/kg in samples of malt products.

With the exception of certain meat products, DCP was detected only in samples that also contained 3-chloro-1,2-propanediol (MCP). In one report, for 50 meat samples, DCP and MCP were found together in 18 of the samples, with the concentrations of DCP generally higher than those of MCP.

JECFA noted that DCP is found in samples of soy sauce and soy sauce-based products where the concentration of MCP exceeded 0.4 mg/kg. These limited data suggest that there is a linear relationship between the concentration of MCP and DCP in any given food, but there was considerable scatter in the data at low concentrations was and also some variation among different types of products. Additional occurrence data would be needed to confirm these relationships, before they could be used to predict the concentrations of DCP based on measured concentrations MCP in food.

2.3. Dietary exposures

2.3.1. National estimates

According to the recent JECFA evaluation (JEFCA, 2007), mean dietary exposure estimates for DCP in various foods, including soy sauce and soy-sauce products, were reported to range from 0.008 to 0.051 μg/kg-bw/day in the general population. For those with a dietary exposure at a high percentile (95th), including young children, intake estimates ranged from 0.025 to 0.136 μg/kg-bw/day (Table 4).

These national estimates of dietary exposure to DCP were provided by one country, with additional estimates for European Union (EU) Member States assessed by the JECFA Committee based on available occurrence data provided both by EU Member States and Australia. Dietary exposures were calculated by linking individual food consumption data with mean DCP concentrations, using the actual body weight of the consumer as reported in consumption surveys.

Meat products are the main contributor to dietary exposure in all the national estimates, ranging from 45% to 99% depending on the country. Soy sauce and soy sauce-based products contributed up to 30% in all the national estimates. Other food groups contributed up to 10% of the total dietary exposure.

JECFA Committee based on available food consumption data and a fixed weighted concentration of DCP for food categories found to contain DCP in the Scoop European Union report (soy sauce and soy sauce-based products) and in the Australian report for the other foods group (meat and fish products). Standard average body weights of 65 kg for adults, 30 kg for children and 15 kg for small children were used.

2.3.2. International estimates

International mean dietary exposure estimates range from 0.008 to 0.090 μg/kg-bw/day for the 13 GEMS/Food cluster diets, assuming a body weight of 60 kg (Table 5) (JEFCA, 2007). These estimates were prepared using distribution-weighted concentrations of DCP in soy sauce and soy sauce-based products, as well as in other foods and food ingredients from various countries. The data were compiled from 2001 to 2006. Those data reported as the best available occurrence data (described in Table 3) have been used in these estimates.

Meat and meat products made the greatest contribution to total dietary exposure in all cluster diets except for clusters C, G, K and L,

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