This is provisional English translation of an excerpt from the original full report.

Risk Assessment Report

Dimethyl dicarbonate

(Food Additives)

Food Safety Commission of Japan (FSCJ)
January 2019

ABSTRACT

FSCJ conducted a risk assessment of dimethyl dicarbonate (CAS No. 4525-33-1), an additive used as a food disinfectant, based on results from various studies.

The data used in the assessment include tokicokinetics, genotoxicity, acute toxicity, repeated dose toxicity, carcinogenicity, reproductive developmental toxicity, and human data on the following test substances; that are dimethyl dicarbonate (DMDC), DMDC containing beverages, methanol which is hydrolysate of DMDC, products of chemical reaction of DMDC with components in beverages such as methoxycarbonyl compounds (MCC), ethyl methyl carbonate (MEC) and methyl carbamate (MC). The test substances also include dimethyl carbonate (DMC) which is a side product of the manufacturing process as well as a product of decarboxylation of DMDC in beverages.

Regarding the findings related to food safety of DMDC as an additive, data of pharmacokinetic study of DMDC have not been presented and data of the toxicological study are also limited.

When DMDC is appropriately used as an additive following the draft standard for use, DMDC is hydrolyzed into carbon dioxide and methanol in the beverage and also reacts with components in the beverage producing various MCC, MEC, MC and DMC. As the result, DMDC content in the final product becomes below the detection limit (0.05 mg/L). While, DMC is also produced during the manufacturing process of DMDC as a side product thus remains in the final product.

Concerning carbon dioxide, FSCJ decided not to evaluate its food safety since the amount of carbon dioxide in beverages derived from the added DMDC was considered to be considerably low compared to the amount of CO_2 ingested through ordinal food consumption.

Consequently, FSCJ decided to comprehensively assess the safety risk of an additive, dimethyl dicarbonate, based on the data of not only DMDC but also methanol, MCC, MEC, MC and DMC. In addition, FSCJ included the data of beverages to which DMDC was added for the comprehensive assessment, since such beverages contain various DMDC-related compounds including MCC.

1. Dimethyl dicarbonate (DMDC)

On the basis of the data concerning the stability of DMDC, FSCJ considered that DMDC in foods was totally hydrolyzed within several hours and the concentration in the final products became below the detection limit.

FSCJ considered that DMDC-added beverages were of no genotoxic concern relevant to human health.

The NOAEL of DMDC was not specified because FSCJ considered it inappropriate to determine the NOAEL of DMDC based on the results from relevant studies on DMDC-added beverages where the actual exposure to DMDC was unknown. However, none of toxicity was observed in the studies on repeated dose toxicity, combined repeated dose toxicity and carcinogenicity, and reproductive developmental toxicity of the DMDC-added beverages.

FSCJ calculated the EDI (Estimated Daily Intake) of DMDC after it was designated as an additive and the standards and specification were established, substituting the content in the final production for the detection limit, based on the Approach for the Risk Assessment of Processing Aids (Food Disinfectants and Extractants), Supplement of the Guideline for Assessment of the Effect of Food on Human Health Regarding Food Additives. Thus FSCJ specified the EDI of DMDC for the national average (over one year old population) and for children of 1 ~ 6 years old to be 0.00051 mg/kg bw/day and 0.00074 mg/kg bw/day, respectively.

Hence, FSCJ concluded that DMDC has no safety concern as long as the additive “dimethyl dicarbonate” was used appropriately as an additive.

2. Methanol

As for toxicokinetics of methanol, FSCJ considered that methanol was promptly absorbed from digestive tracts, oxidized in the liver into formaldehyde then to formic acid, and into carbon dioxide to be excreted. The oxidation rate of formic acid, which determines the sensitivity to methanol, is thought to be extremely slow in the primates compared to that in the rodents resulting in the very high sensitivity to the toxicity of methanol in the primate compared to in the rodents.

According to the WHO (1997), formic acid is not accumulated more than the amount normally contained in the body even if methanol is orally ingested at the dose below 20 mg/kg body weight. JECFA (1991) has reported that humans with ordinal eating habit metabolize 1,000 ~ 2,000 mg of methanol a day. FDA (1988) and SCF (2001) have suggested that healthy humans are able to metabolize 1,500 mg of methanol per an hour with no difficulty.

FSCJ considered that methanol has no genotoxic concern relevant to human health.

The NOAEL of methanol could not be determined because toxic findings were observed even at the lowest dose (1,000 mg/kg bw) in the reproductive developmental toxicity study in rabbits (Youssef et al., 1997), though FSCJ examined results of acute toxicity study and of reproductive developmental toxicity study.

No finding of the carcinogenicity of methanol was available.

Toxicity of methanol is mainly attributed to its metabolic product, formic acid. In methanol intoxication, metabolic acidosis and dysfunction of central nervous system are exerted generally as the intake increases. Further intoxication sometimes may result in visual impairment leading to blindness and even death. Although the adverse effect level and lethal dose of methanol in human is unknown, the lowest lethal dose in human has been estimated as 1 g/kg bw by Röe (1982).

While, FDA (1993) specified the ADI of methanol to be 7.1 ~ 8.4 mg/kg bw/day, applying a safety factor 10 to the NOAEL of 71 ~ 84 mg/kg bw/day obtained in the human studies.

Methanol is also contained in foods and drinks such as fruits, vegetables, fruit juice and fermented beverages. If the estimated daily intake (EDI) of methanol from fruit juice and alcoholic beverages is calculated using the reported concentration of methanol in fruit juice and the standard for methanol level in alcoholic beverages in Japan, 1.93 mg/kg bw/day and 1.14 mg/kg bw/day are calculated as a national average and as for children, respectively. However, actual intake of methanol from foods possibly exceeds this estimation if methanol intake from fruits and vegetables are taken into consideration.

FDA estimated the 90 percentile upper limit of the daily intake of methanol which are contained in fruit juice and wine and methanol derived from DMDC as 59 mg/person/day. EFSA (2015) estimated the sum of methanol taken from regular dietary life and endogenous methanol to be 8.4 ~ 18.9 mg /kg bw/day as an average.

FSCJ specified the estimated daily intake of methanol derived from DMDC to be 1.21 mg/kg bw/day and 1.79 mg/kg bw/day as the national average and as for children, respectively.

Considering that methanol derived from DMDC is absorbed, metabolized and excreted similarly to methanol derived from ordinal foods, as well as taking in to consideration human data, methanol intake from ordinal eating habits and the ADI specified by FDA, FSCJ concluded that methanol has no safety concern as long as the additive “dimethyl dicarbonate” is appropriately used as an additive.

3. Methoxycarbonyl compounds (MCC)

Data on the toxicokinetics of MCC indicated that metabolism of N-methooxycarbonylated amino acids (N-MCC-AA) varies depend on the amino acid moiety. For example, a N-MCC-AA originated from an aliphatic amino acid is easily hydrolyzed relative to that of N-MCC-AA derived from the other amino acids in the presence of enzyme mixture prepared from the liver or kidney of human or pigs. And N-methoxycarbanyl aspartame was promptly hydrolyzed in the rat liver homogenate.

FSCJ could not specify the NOAEL of MCC because available data for it was only the data of acute toxicity study of N-MCC-AA. In a repeated dose study, a combined repeated dose toxicity and carcinogenicity study and a reproductive developmental toxicity study of various DMDC added beverages, no toxic finding was observed.

The estimated daily intake of MCC derived from DMDC was determined to be 0.051 mg/kg bw/day for the national average and 0.074 mg/kg bw/day for children.

FSCJ concluded that MCC produced from DMDC added to the beverages of target of the draft standards for use had no safety concern as long as the additive “dimethyldicarbonate” is used appropriately as an additive, taking into consideration the fact that no toxicity was observed in the studies with DMDC added beverages.

4. Ethyl methyl carbonate (MEC)

As a toxicokinetics finding of MEC, MEC was hydrolyzed in the mixture with enzyme solution derived from the pig livers.

Although no result of genotoxicity studies on MEC was available, FSCJ considered that MEC has no genotoxicity relevant to human health, based on the results of a combined repeated dose toxicity and carcinogenicity study with DMDC-added wine, the results of genotoxicity study and a combined repeated dose toxicity and carcinogenicity study with DMDC-added orange juice, a genotoxicity study of MC that resembles MEC in the structure.
As for the acute toxicity, repeated dose toxicity and developmental toxicity of MEC, no toxicity was observed even at the highest dose in a 3-month repeated dose study in rats (BayerAG internal document (Löser (1973))) and developmental toxicity study in rats (BayerAG internal document (Machemer (1976))). FSCJ specified NOAEL of MEC to be 1.0 % (1,094 mg/kg bw/day in male) based on the results of the 3-month repeated dose study where the lowest NOAEL was obtained.
No sign of carcinogenicity was observed.

The estimated daily intake of MEC derived from DMDC was determined to be 0.0052 mg/kg bw/day for the national average and 0.00012 mg/kg bw/day for children.

Margin between NOAEL of MEC, 1,094 mg/kg bw/day, and the estimated daily intake foe the national average and for children were ca. 210,000 and ca. 9,100,000, respectively. FSCJ concluded that MEC produced from DMDC added to the beverages had no safety concern as long as there was a sufficient margin and the additive "dimethyldicarbonate" is used appropriately as an additive.

5. Methyl carbamate (MC)
According to a study on toxicokinetics of MC in mice and rats (Ioannou et al. (1988)), the orally administered MC after absorbed was excreted unchanged or as the metabolite, carbon dioxide. The rate of excretion as carbon dioxide in rats is lower than that in mice suggesting that the distribution in the tissues is higher in rats than in mice. Thus, the higher sensitivity of Fischer344 rats to toxicity of MC than that of mice seems to attribute to such a difference in tissue distribution.
FSCJ considered that MC has no genotoxicity relevant to human health.
Among the results of acute toxicity studies and repeated dose toxicity studies, suppressed body weight and hepatitis (necrosis, hyperchromasia and atypia of nuclei, abnormal mitosis) in Fischer 344 rats of both sexes were observed in 13-week oral administration study in rats (Quest et al. (1987) and NTP (1987)). FSCJ specified a NOAEL in this study to be 200 mg/kg bw/day for male and 250 mg/kg bw/day for female based on these results.
In a 103-week carcinogenicity study by NTP (1987), total number of female Fisher344 rats showing development of neoplastic nodule or hepatocellular carcinomas was increased. FSCJ, based on this result, considered that MC was carcinogenic to the liver in female Fisher344 rats at the dose of 200 mg/kg bw/day but non-carcinogenic at the dose of 100 mg/kg bw/day. As MC has no genotoxicity, the carcinogenic mechanism is unlikely attributed to the genotoxicity mechanism, thus FSCJ considered that a threshold can be specified for the carcinogenicity of MC. No carcinogenicity was observed in mice.

The estimated daily intake of MC derived from DMDC was determined to be 0.00025 mg/kg bw/day for the national average and 0.00037 mg/kg bw/day for children.
The highest value of the estimated daily intake of MC contained in wine was 0.003 μg/L of wine which was about one hundredth of that of MC derived from DMDC, calculating based on the wine consumption of the national average.

The lowest NOAEL obtained in 13-week oral administration studies with rats by Quest et al. (1987) and NTP (1987) was 200 mg/kg bw/day. The margin between this lowest NOAEL and the estimated daily intake of the national average and children were about 800,000 and about 540,000, respectively.
In addition, the dose of 100 mg/kg bw/day was considered to be non-carcinogenic in the 13-week carcinogenicity study in rats by NTP (1987). The margin between this lowest NOAEL and the estimated daily intake of the national average and children were about 400,000 and about 270,000, respectively.
Hence, FSCJ concluded that MC derived from the additive "dimethyl dicarbonate" had no concern relevant to human health as long as the additive "dimethyl dicarbonate" was used appropriately as an additive, since there was sufficient margin between the estimated daily intake and the abovementioned NOAEL of 200 mg/kg bw/day or between the estimated daily intake and the abovementioned non-carcinogenic dose of 100 mg/kg bw/day.

6. Dimethyl carbonate (DMC)
As a toxicokinetics finding of DMC, DMC was hydrolyzed in the mixture with enzyme solution derived from the pig livers.
Although no result of genotoxicity studies on DMC was available, FSCJ considered that DMC has no genotoxicity relevant to human health, based on the results of genotoxicity study and a combined repeated dose toxicity and carcinogenicity study with DMDC-added orange juice, a genotoxicity study of MC that resembles in the structure.
As for the acute toxicity and repeated dose toxicity of DMC, no toxicity was observed even at the highest dose in a 3-month oral administration study in rats (BayerAG internal document (Eiben et al. (1982))). Consequently, FSCJ specified NOAEL of DMC to be 10,000 ppm (890 mg/kg bw/day for male).
No sign of carcinogenicity was observed.

The estimated daily intake of DMC derived from DMDC was determined to be 0.0051 mg/kg bw/day for the national average and 0.0074 mg/kg bw/day for children.

The margin between the NOAEL of DMC and the estimated daily intake of the national average and children were about 170,000 and about 120,000, respectively. Hence, FSCJ concluded that DMC derived from the additive "dimethyl dicarbonate" had no concern relevant to human health as long as the additive "dimethyl dicarbonate" was used appropriately as an additive, since there was sufficient margin between the estimated daily intake and the abovementioned NOAEL.

FSCJ concluded, based on the abovementioned evaluation of DMDC and DMDC-related compounds, that the additive “dimethyl dicarbonate” had no concern relevant to human health as long as it was used appropriately as an additive.