APPENDIX B

**OEHHA FINAL REVISED HEALTH ASSESSMENT FOR
DIMETHYL CARBONATE**

November 18, 2010

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Office of Environmental Health Hazard Assessment

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M E M O R A N D U M

TO: Richard Corey, Chief
              Research and Economic Studies Branch
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              Air Resources Board

FROM: Melanie A. Marty, Ph.D., Chief
              Air Toxicology and Epidemiology Branch

DATE: December 8, 2009

SUBJECT: REVISED ASSESSMENT OF HEALTH EFFECTS OF EXPOSURE TO
              DIMETHYL CARBONATE, A CHEMICAL PETITIONED FOR
              EXEMPTION FROM VOC RULES

Recently the Research Division sent the Office of Environmental Health Hazard
Assessment (OEHHA) an application for VOC Exempt Status in the State of California
for Dimethyl Carbonate. This was submitted by Kowa Corporation, who propose use of
from 2 to possibly 5 million pounds of dimethyl carbonate per year as a niche solvent in
California, if dimethyl carbonate is exempted from VOC regulations. In response to a
request from the Division, OEHHA recently provided you a review of the health effects
of dimethyl carbonate. This has now been revised to correct a typographical error
which resulted in a difference in the proposed value of the interim chronic Reference
Exposure Level (REL). Our revised assessment is attached.

Exposure to workers and to the general public near facilities in California using dimethyl
carbonate will occur if it is exempted. Dimethyl carbonate is an ester of methanol and
carbon dioxide. For ambient exposures, the concern is the internal levels of methanol,
formaldehyde, and formic acid (or formate ion) in solution due to metabolism of dimethyl
carbonate, not the external air concentrations of the chemicals. At dose levels likely to
be achieved due to environmental exposures of the general public by inhalation, these
concerns appear to be relatively minor. OEHHA has estimated interim acute and chronic
RELs for dimethyl carbonate. Although derived by approved methodology, the RELs for
dimethyl carbonate have not undergone external peer-review or review by the Scientific
Review Panel on Toxic Air Contaminants.

If you have questions about our review, or would like additional information, please call
Dr. Jim Collins, of my staff, at 510-622-3146.

Attachment

California Environmental Protection Agency

The energy challenge facing California is real. Every Californian needs to take immediate action to reduce energy consumption.
B-3
♻ *Printed on Recycled Paper*
Draft Staff Report with Appendices for
Draft Amendments to Rule 1020

Richard Corey
2009
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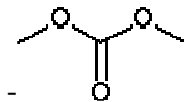
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Dimethyl Carbonate
(CAS# 616-38-6)
(Synonyms: Carbonic acid, methyl ester; methyl carbonate)

1   Introduction

Dimethyl carbonate has been used as a reagent in methylation reactions (HSDB, 2009), and has possible uses in paints, coatings, and adhesives. On January 13, 2009 the United States Environmental Protection Agency (U.S. EPA) granted a Volatile Organic Compound (VOC) exemption to dimethyl carbonate (USEPA, 2009) since it makes a negligible contribution to tropospheric ozone formation. In a letter dated March 2, 2009, Kowa American submitted to the California Air Resources Board (ARB) an Application for VOC Exempt Status for dimethyl carbonate in California. The application contains limited toxicological information. As part of its consideration of exempt status for a VOC, ARB asked the Office of Environmental Health Hazard Assessment (OEHHA) to review the toxicology of dimethyl carbonate.

Dimethyl carbonate does not have a Threshold Limit Value (TLV) for worker exposure. U.S. EPA also does not have any health values for exposure of the general public to dimethyl carbonate. OEHHA notes that increased public exposure is likely if dimethyl carbonate is exempted from VOC regulation, and its use becomes more widespread in California. Thus we developed an interim Reference Exposure Level (REL) for dimethyl carbonate to compare to estimated exposures from use in California. Additionally, we discuss formation and toxicity of possible dimethyl carbonate metabolites.

2   Physical and Chemical Properties of Dimethyl Carbonate (HSDB, 2009)

Description	Colorless liquid; pleasant odor
Molecular formula	C3-H6-O3
Molecular weight	90.08
Density	1.0636 @ 25°C/15°C
Boiling point	90-91ºC
Melting point	0.5ºC
Vapor pressure	55.364 mm Hg @ 25ºC
Odor threshold	Not found
Log Kow	0.23 (estimated) (Meylan and Howard, 1995; SRC, 2009)
Bioconcentration factor	3.16 (estimated) (Kowa American, 2009)
Solubility	Miscible with alcohol and ether; Insoluble in water (HSDB, 2009); Solubility = 13.9 g/100 g water (Kowa American, 2009)
Flammability	Highly flammable
Conversion factor	3.68 µg/m^3 per ppb @ 25ºC

3   Toxicity of Dimethyl Carbonate

3.1   Metabolism of Dimethyl Carbonate

Dimethyl carbonate is readily hydrolyzed to carbon dioxide and methanol in the environment and presumably in the body via esterases (Kowa America, 2009). Methanol is metabolized to formaldehyde, which is then further oxidized to formic acid.

3.2   Animal Toxicity of Dimethyl Carbonate

The International Uniform Chemical Information Database (IUCLID) dataset (European Commission, 2000) indicates the following data gaps for dimethyl carbonate: chronic toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, neurotoxicity, immunotoxicity, aquatic toxicity, and toxicity to terrestrial organisms.

The IUCLID dataset lists a rat 4 hour LC_{50} of > 140 mg/L (> 38,000 parts per million (ppm)).

The IUCLID dataset reports that dimethyl carbonate is slightly irritating to the rabbit eye and not irritating to rabbit skin. No dose information is stated.

In a 10-day developmental toxicity study (Exxon, 1992; Bevan and Beyer, 1995), mated female CD-1 mice (96 per dose level) were exposed by inhalation to 0, 300, 1000, or 3000 ppm dimethyl carbonate during gestational days (gd) 6 through 15 for 6 h/day. The females were euthanized on gd 18, and the fetuses from the first 30-32 pregnant dams were weighed, sexed, and examined for external, visceral, and skeletal alterations. Maternal body weights and body weight gains were significantly reduced at 3000 ppm (Table 1).

Table 1. Maternal body weights on gestation days 0, 15, and 18

Dimethyl carbonate	0 ppm	300 ppm	1000 ppm	3000 ppm
Day 0	28.38±1.36 (32)	29.24±1.82 (31)	28.63±1.56 (30)	28.78±1.72 (32)
Day 15	43.47±2.60 (32)	43.03±3.66 (31)	42.80±2.54 (30)	39.23±3.55* (30)
Day 18	51.92±3.40 (30)	51.23±4.69 (30)	51.67±3.11 (30)	45.92±4.90* (30)

* $p < 0.01$ vs. control. Values are mean ± 1 SD (number of dams)

Food consumption was significantly reduced at 1000 and 3000 ppm, indicating an adverse effect on the mothers. Gestational parameters affected at 3000 ppm included post-implantation loss due to increased resorptions, and altered sex ratio (fewer males surviving). Fetal body weights/litter were reduced at 3000 ppm indicating a gross adverse effect on the fetus (Table 2) and the number of growth-stunted fetuses (<1 g body weight) was increased.

Table 2. Fetal body weight as a function of dimethyl carbonate concentration

Dimethyl carbonate	0 ppm	300 ppm	1000 ppm	3000 ppm
Males	1.24±0.10 (193)	1.27±0.12 (154)	1.24±0.10 (179)	1.12±0.14* (137)
Females	1.10±0.10 (157)	1.19±0.12 (181)	1.20±0.10 (155)	1.07±0.15* (140)

* $p<0.01$ vs. control. Values are mean ± 1 SD (number of fetuses)

Total incidences of fetal malformations were significantly increased at 3000 ppm and included cleft palate (Table 3), multiple malformations of the bones of the skull, and fused vertebral arches. Skeletal variations, including misshapen sternebrae (breastbones), rudimentary cervical ribs, and well-formed cervical or lumbar ribs, were also increased at 3000 ppm. The No Observed Adverse Effect Level (NOAEL) for maternal and developmental toxicity was 1000 parts per million (ppm) (Exxon, 1992; Bevan and Beyer, 1995). In a developmental toxicity in mice, the NOAEL for inhaled methanol was also 1000 ppm (Rogers et al., 1993).

Table 3. Some significantly increased external malformations

Dimethyl carbonate	0 ppm	300 ppm	1000 ppm	3000 ppm
Total fetuses (total litters)	350 (30)	337 (30)	334 (30)	277 (29)
External malformations				
Cleft palate	3 (2)	0	1 (1)	140 (26)**
Microtia (small ear)	0	0	0	24 (5)*
Low set ear(s)	0	0	0	13 (5)*
Imperforate anus	0	0	0	5 (3)*
Ectrodactyly#	0	0	0	4 (2)*

* $p < 0.05$ vs. control; ** $p < 0.01$ vs. control. Values are number of fetuses
   with malformations (number of litters affected).
complete or partial absence of one or more digits

Song et al. (2002) tested three gasoline oxygenates, dimethyl carbonate, ethanol anhydrous, and methyl tertiary butyl ether (MTBE) in the single cell gel electrophoresis (Comet) assay in L-929 mouse fibroblasts. They reported that dimethyl carbonate did not cause DNA damage in the assay (MTBE was positive in the assay). No other studies of genotoxicity were identified. Thus there is a gap in direct data on genotoxicity for dimethyl carbonate.

3.3   Human Toxicity of Dimethyl Carbonate

Dimethyl carbonate is mildly toxic by ingestion and moderately toxic by the intraperitoneal route (Lewis, 1996, in Sax's Dangerous Properties of Industrial Materials: HSDB, 2009). No data were available in the peer-reviewed literature for chronic exposure of humans to dimethyl carbonate. Since so little toxicity information on dimethyl carbonate itself is available, the toxicity of its metabolites is summarized in the following sections.

4 Toxicity of the Metabolites of Dimethyl Carbonate (Methanol, Formaldehyde, and Formic Acid)

Since dimethyl carbonate breaks down to methanol and carbon dioxide, and methanol is metabolized to formaldehyde and formic acid, we briefly review the toxicity of the metabolites. In response to Health and Safety Code Section 44300 *et seq*., OEHHA reviewed the toxicology of formaldehyde and methanol and developed acute and chronic RELs for formaldehyde and methanol (OEHHA 1999; OEHHA, 2000; OEHHA, 2008) and an inhalation cancer unit risk factor for formaldehyde (OEHHA, 2005).   The current health values are tabulated below (Table 4).

Table 4. Reference Exposure Levels and cancer inhalation unit risk values

Chemical	*Acute REL*	*Chronic REL*	*Unit Risk (cancer)*
Methanol	28,000 μg/m^3	4000 μg/m^3	None
Formaldehyde	55 μg/m^3	9 μg/m^3	6 x 10^{-6} (μg/m^3)$^{-1}$

4.1   Toxicity of Methanol

The National Toxicology Program reviewed methanol, concentrating on its reproductive and developmental toxicity (NTP-CERHR, 2003). An expert panel judged that the human data were insufficient to evaluate the developmental toxicity of methanol but concluded, based on data from rodents, that developmental toxicity was the most sensitive reproductive endpoint of concern for humans from methanol exposure. Other general reviews of methanol toxicity include Roe (1955) and Kavet and Nauss (1990).

Inhalation of methanol by humans is associated with headache and narcosis due to methanol itself. Ingestion of methanol induces blindness in humans (Roe 1955). Medinsky and Dorman (1995) reviewed the disposition of methanol and of formate, its first metabolite, in humans, non-human primates, and rodents after neurotoxic doses

Formate is also formed endogenously from serine and is detoxified to CO_2 and H_2O by a tetrahydrofolate(THF)-dependent pathway. Rodents detoxify formate more rapidly than primates. Species (e.g., rodents) with high liver THF levels are less sensitive to neurotoxicity due to large doses of methanol than species with low THF levels (e.g., humans and non-human primates). The capacity of primates to detoxify formate from low level methanol inhalation can be extrapolated to assess human risk from methanol.

Cynomolgus monkeys exposed to 10-200 ppm [^{14}C]methanol for 2 hours have blood levels of methanol-derived formate that are 100- to 1000-fold *lower* than endogenous levels of formate (Dorman et al., 1994). Healthy human volunteers exposed at rest or during exercise to 200 ppm methanol for 6 hours (Lee et al., 1992) or exposed to 20 mg/kg orally have elevated blood levels of methanol, but blood formate levels are not significantly increased above endogenous levels. Deficiencies in THF may prolong elevated blood levels of formate and increase the likelihood of

toxicity. Monkeys with low THF levels exposed to 900 ppm [^{14}C]methanol for 2 hours had methanol-derived blood formate levels below endogenous levels (Dorman et al., 1994). Medinsky and Dorman (1995) suggested that humans may not be at added risk of neurotoxicity from low level methanol exposure by inhalation.

Since dimethyl carbonate is metabolized in the body to methanol, we reviewed a study of methanol by the oral route. Sprague-Dawley rats (30 animals/sex/dose) were gavaged daily with 0, 100, 500, or 2500 mg/kg/day methanol (U.S. EPA, 1986). At six weeks, 10 rats/sex/dose group were subjected to interim necropsy and the other 20 were dosed until necropsy at 90 days. No differences between dosed and controls were found for body weight gain, food consumption, and gross or microscopic evaluations. There were elevated levels of serum glutamate pyruvate transaminase (SGPT, alanine aminotransferase), serum alkaline phosphatase (SAP), and increased, but not statistically significant, liver weights in both male and female rats at the highest dose. These effects could be treatment-related although there were no liver lesions detected by histopathology. In addition, brain weights in both high-dose males and females were significantly less than control group. The U.S. EPA considered 500 mg/kg/day of methanol a NOAEL for rats (U.S. EPA, 2008).

4.2   Toxicity of Formaldehyde

Formaldehyde gas is listed under Proposition 65 as a chemical known to the State to cause cancer. In 2006, the International Agency for Research on Cancer (IARC) classified formaldehyde as carcinogenic to humans (Group 1) (IARC, 2006). Although the listing under Proposition 65 relates to inhalation exposure, the IARC classified formaldehyde as carcinogenic to humans with sufficient evidence in humans and in experimental animals, without reference to route of exposure. IARC noted tumors in rat studies by the oral route: statistically significant increases in forestomach papillomas in one study; statistically significant increases in gastrointestinal leiomyosarcomas in a drinking water study (which included transplacental exposure); and a statistically significant increase in haemolymphoreticular tumors [lymphomas and leukemias] in high dose males in another drinking water study. IARC also concluded that "there is strong but not sufficient evidence for a causal association between leukaemia and occupational exposure to formaldehyde." The Agency for Toxic Substances and Disease Registry has produced a comprehensive review of the toxicity of formaldehyde (ATSDR, 1999).

The non-cancer adverse health effects of airborne formaldehyde are due to its irritation of mucous membranes. As a result of its solubility in water and high reactivity, formaldehyde is efficiently absorbed into the mucus layers protecting the eyes and respiratory tract where it rapidly reacts, leading to localized irritation. Acute high inhalation exposure may lead to eye, nose and throat irritation, and in the respiratory tract, nasal obstruction, pulmonary edema and dyspnea. Prolonged or repeated exposures have been associated with allergic sensitization, asthma-like symptoms, histopathological changes in respiratory epithelium, and decrements in lung function. Children, especially those diagnosed with asthma, may be more likely to show impaired pulmonary function and symptoms of asthma than are adults following chronic exposure to formaldehyde. However, in the case of dimethyl carbonate exposure, formaldehyde would only be formed internally where it is rapidly metabolized to formate. Thus, respiratory

tract irritation from the formaldehyde metabolite is not an issue in this case.

4.3   Toxicity of Formic Acid

Formic acid has been used in workplaces for decades and has an acceptable workplace exposure level (TLV) of 5 ppm (ACGIH, 2007).

Since formic acid is one of the metabolites of methanol, staff looked for relevant toxicity studies on it in the open literature. Although much of the toxicity data is from inhalation exposure, in the present application the concern is the internal level of formic acid (or formate ion) in solution due to metabolism of dimethyl carbonate, not the external air concentrations of the chemicals. We did not find any informative studies of formate by ingestion. Nonetheless, we briefly describe the inhalation studies below.

Animal Toxicity of Formic Acid

Amdur (1960) exposed guinea pigs (n=7-16/level) by inhalation to 0.34, 1.0, 2.8, 6.6, 13.5, or 42.5 ppm formic acid for 1 hour. The LOAEL was 42.5 ppm and the NOAEL was 13.5 ppm for overt respiratory irritation (measured by decreased breaths per minute), but more subtle adverse effects on lung function were measured at all the lower concentrations.

NTP (1992) conducted 2- and 13-week toxicity studies in male and female F344/N rats and B6C3F$_1$ mice exposed by whole body inhalation exposure to formic acid vapors.

In 2-week studies, groups of 5 F344/N rats and 5 B6C3F$_1$ mice of each sex were exposed 6 hours/day, 5 days/week for two weeks, to 0, 31, 62.5, 125, 250, or 500 ppm. Deaths occurred in animals exposed to 500 ppm (rats and mice) and 250 ppm (1 female mouse).

In 13-week studies, F344/N rats and B6C3F1 mice (10 animals/group/sex) were exposed to 0, 8, 16, 32, 64, and 128 ppm formic acid 6 hours/day, 5 days/week. One male and one female mouse in the 128 ppm groups died. Body weight gain was significantly decreased in mice exposed to 64 and 128 ppm.

In both the 2-week and 13-week studies, microscopic lesions of squamous metaplasia, necrosis, and inflammation in the respiratory and olfactory epithelia were detected in rats and mice. These were observed at 62.5 ppm and above after 2 weeks, but only at 128 ppm after 13 weeks. NTP concluded that the effects of formic acid were consistent with those of other irritants administered by inhalation. The no-observed-adverse-effect level (NOAEL) for respiratory injury was 32 ppm in rats and mice. There was no significant evidence of systemic toxicity.

Formate inhibits cytochrome c oxidase activity in the electron transport chain in intact mitochondria and in submitochondrial particles. The inhibition increases with decreasing pH, indicating that HCOOH may be the inhibitory species. Formate is permeable through the inner mitochondrial membrane (Nicholls, 1976) and could inhibit oxidative phosphorylation.

In genetic toxicity tests *in vitro* with *Salmonella typhimurium*, formic acid was not mutagenic either with or without metabolic activation (NTP, 1992).

5   **Derivation of Interim Acute REL (1-hour exposure) for Dimethyl Carbonate**

Study	Bevan and Beyer, 1995; Exxon, 1992
Study population	Pregnant female CD-1 mice
Exposure method	Inhalation of 0, 300, 1000, or 3000 ppm
Exposure duration	6 hours/day on gestation days 6 to 15
Critical effects	Fetal malformations
NOAEL	1000 ppm
Extrapolation to 1 hour	not done with developmental study (see below)
Interspecies uncertainty factor	
Toxicokinetic UF_{A-k}	2 (default)
Toxicodynamic UF_{A-d}	$\sqrt{10}$ (default)
Intraspecies uncertainty factor	
Toxicokinetic UF_{H-k}	10 (default)
Toxicodynamic UF_{H-d}	$\sqrt{10}$ (default)
Cumulative uncertainty factor	200
Acute Reference Exposure Level	5 ppm (18 mg/m^3; 18,000 µg/m^3)

The interim acute REL for dimethyl carbonate is based on a developmental study in which pregnant mice were exposed 6 hours per day for 10 days. However, the resulting acute REL is a level not to be exceeded in any one hour period. The interim acute REL was developed using methodology published in 2008 (OEHHA, 2008). The methodology was modified from earlier methodology (OEHHA, 1999) due to a mandate to specifically insure that infants and children are protected from the adverse effects of chemicals. Because of the limited data available on dimethyl carbonate, default values were used for the uncertainty factors (UF).

The default interspecies UF_{A-k} of 2 was used for residual toxicokinetic differences in studies of non- primate species using the human equivalent concentration (HEC) approach. In this case the HEC adjustment factor was 1 since fetal malformations occur internally. The default interspecies UF_{A-d} of $\sqrt{10}$ was applied to compensate for the absence of data on pharmacodynamic differences between rodents and humans. The default intraspecies UF_{A-k} of 10 was used since there was no information on dimethyl carbonate metabolism at different stages of human development. The default interspecies UF_{A-d} of $\sqrt{10}$ was applied to compensate for the absence of data on pharmacodynamic differences among humans to the effects of dimethyl carbonate.

The acute REL of 18,000 µg/m^3 is somewhat more than half that for methanol (28,000 µg/m^3).

6   **Derivation of Interim Chronic REL for Dimethyl Carbonate**

No data are available on long term inhalation of dimethyl carbonate.   However, since one mole of dimethyl carbonate is degraded to two moles of methanol plus one mole of carbon dioxide, an interim chronic REL can be based on the chronic REL for methanol as a surrogate, assuming

100% conversion to methanol occurs during metabolism. The derivation of OEHHA's chronic REL, done by an earlier methodology (OEHHA, 2000), follows:

<div align="center">Methanol Chronic Reference Exposure Level</div>

Study	Rogers *et al.* (1993)
Study population	Pregnant mice
Exposure method	Inhalation of 0, 300, 1000, or 3000 ppm
Exposure duration	7 hours/day on gestation days 6 to 15
Critical effects	Abnormal cervical ribs, exencephaly, cleft palate
NOAEL	1000 ppm
Benchmark Concentration (BMC_{05})	305 ppm
Average experimental exposure	89 ppm at BMC_{05} (305 ppm x 7/24)
Human equivalent concentration	89 ppm at BMC_{05} (gas with systemic effects, based on RGDR = 1.0 using default assumption that lambda (a) = lambda (h))
Subchronic uncertainty factor	1
LOAEL uncertainty factor	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	30
Chronic Methanol Reference Exposure Level	3 ppm (4 mg/m^3; 4,000 μg/m^3)

Since, as noted above, one mole of dimethyl carbonate gives rise to two moles of methanol, it is reasonable to extrapolate from the methanol REL of 3 ppm to an interim chronic REL for dimethyl carbonate of 1.5 ppm. This is equivalent to 1.5 x 3.68 x 10^3 = 5500 μg/m^3. The chronic REL for methanol is derived from a developmental study in which the critical exposures were over a relatively short timescale, rather than a long-term study. However, unlike the situation for dimethyl carbonate, there are several long-term studies of other endpoints in both rodents and primates which confirm that the developmental endpoint is the most sensitive (see Section 5 and the toxicity summary for the methanol chronic REL [OEHHA, 2008]). The REL thus derived is therefore protective against these other effects, which included liver toxicity and neurological or neuromuscular effects. Use of the methanol REL as an indirect basis for the dimethyl carbonate REL is thus the preferred option, although alternatively it could be argued that a REL based on the developmental toxicity data for dimethyl carbonate should be similarly protective of chronic effects.

7   Data Gaps

Data gaps of concern to OEHHA staff include:

1. No lifetime inhalation study of dimethyl carbonate is available. The longest inhalation study available in the open literature is an abstract of a 10 day developmental toxicity study in mice (Bevan and Beyer, 1995). This is a serious data gap for a high production volume chemical.

2. A substantial developmental toxicity study with group sizes of 30-32 pregnant female mice was reported, but no multigenerational studies or other investigations addressing reproductive toxicity in either sex were available.

3. There are no data in neonatal animals of the effects of dimethyl carbonate or formic acid exposure. OEHHA has a mandate to determine if our health values adequately protect infants and children.

4. There are very few data on genotoxicity of dimethyl carbonate itself. This is a source of concern which is partially alleviated by the fact that the first metabolite, methanol, is not genotoxic. The subsequent metabolites include formate, which is not genotoxic, and formaldehyde which is. The genotoxicity of formaldehyde when it is generated internally is probably only important in high dose situations, in view of its role in intermediary metabolism and the generally negative profile of various compounds of which it is a metabolite, including methanol.

8   Conclusion

There are no carcinogenicity or long-term toxicity data on dimethyl carbonate. There is no evidence of carcinogenicity for methanol, the primary metabolite of dimethyl carbonate (along with carbon dioxide), despite a robust database on toxicity and a long history of human exposure.

Exposure to workers and the general public near facilities in California using dimethyl carbonate will occur if it is exempted. Dimethyl carbonate is an ester and would be expected to be less irritating to mucous membranes than formaldehyde or formic acid. In the present application the concern is the internal levels of methanol and its metabolites formaldehyde and formic acid (or formate ion) in solution due to metabolism of dimethyl carbonate, rather than the external air concentrations of the chemicals. The proposed interim acute REL of 18, 000 $\mu g/m^3$ and chronic REL of 5500 $\mu g/m^3$ are expected to be protective of anticipated adverse health effects, including the developmental toxicity observed in the key study (Bevan and Beyer, 1995; Exxon, 1992) reported for dimethyl carbonate.

These interim RELs have not undergone public and peer review, and thus are considered interim values. It should be noted that large data gaps exist for dimethyl carbonate.

9   References

ACGIH (2007). American Conference of Governmental Industrial Hygienists. TLVs® and BEIs®. Cincinnati: American Conference of Governmental Industrial Hygienists.

ATSDR (1999). Agency for Toxic Substances and Disease Registry. Toxicological Profile for Formaldehyde. PB/99/166654.

Amdur MO (1960). The response of guinea pigs to inhalation of formaldehyde and formic acid alone and with a sodium chloride aerosol. Int J Air Pollut. 3: 201-20.

Bevan C and Beyer B (1995). Developmental toxicity evaluation of dimethylcarbonate by inhalation in CD-1 mice. International Toxicologist, 7(1): AB# 74-P-2.

Dorman DC, Moss OR, Farris GM, Janszen D, Bond JA, Medinsky MA (1994). Pharmacokinetics of inhaled [^{14}C]methanol and methanol-derived [^{14}C]formate in normal and folate-deficient cynomolgus monkeys. Toxicol Appl Pharmacol. 128(2): 229-38.

European Commission (2000). Dimethyl carbonate. IUCLID Dataset. European Chemicals Bureau. Available online at: http://ecb.jrc.ec.europa.eu/iuclid-datasheet/616386.pdf

Exxon Biomedical Sciences (1992). Inhalation development toxicity study in mice with dimethylcarbonate. Final report. Project number 107334. E. Millstone, NJ.

HSDB (2009). Hazardous Substances Data Bank. Available online at: http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB Last accessed March 4, 2009.

IARC (2006). Formaldehyde, 2-Butoxyethanol and 1-*tert*-Butoxypropan-2-ol. IARC Monographs. Vol. 88. Lyon: International Agency for Research on Cancer.

Kavet R and Nauss KM (1990). The toxicity of inhaled methanol vapors. Crit Rev Toxicol. 21(1): 21-50.

Kowa American (2009). Dimethyl carbonate information request. Submitted by Mark K. Smith.

Lee EW, Terzo TS, D'Arcy JB, Gross KB, Schreck RM (1992). Lack of blood formate accumulation in humans following exposure to methanol vapor at the current permissible exposure limit of 200 ppm. Am Ind Hyg Assoc J. 53(2):99-104.

Lewis RJ (1996). Sax's Dangerous Properties of Industrial Materials. 9th ed. Volumes 1-3. New York, NY: Van Nostrand Reinhold, p. 2205.

Medinsky MA, Dorman DC (1995). Recent developments in methanol toxicity. Toxicol Lett. 82-83:707-11.

Meylan WM, Howard PH (1995). Atom/fragment contribution method for estimating octanol-water partition coefficients. J Pharm Sci. 84(1):83-92.

NTP (1992). National Toxicology Program. Toxicity Studies of Formic Acid (CAS No. 64-18-6) Administered by Inhalation to F344/N Rats and B6C3F$_1$ Mice. Tox-19. NIH Publication 92-3342.

NTP-CERHR (2003). National Toxicology Program. Center for the Evaluation of Risks to Human Reproduction. Monograph on the Potential Human Reproductive and Developmental Effects of Methanol. NIH Publication No. 03-4478.

Nicholls P (1976). The effect of formate on cytochrome aa3 and on electron transport in the intact respiratory chain. Biochim Biophys Acta. 9;430(1):13-29

OEHHA. (1999). Air Toxics Hot Spots Program Risk Assessment Guidelines Part I. The
    Determination of Acute Reference Exposure Levels for Airborne Toxicants. Office of
    Environmental Health Hazard Assessment, California Environmental Protection Agency.

OEHHA. (2000). Air Toxics Hot Spots Program Risk Assessment Guidelines Part III Technical
    Support Document for the Determination of Noncancer Chronic Reference Exposure Levels.
    Office of Environmental Health Hazard Assessment, California Environmental Protection
    Agency.

OEHHA (2005). Office of Environmental Health Hazard Assessment. Air Toxics Hot Spots Risk
    Assessment Guidelines. Part II. Technical Support Document for Describing Available
    Cancer potency Factors. Available on-line at
    http://www.oehha.ca.gov/air/hot_spots/pdf/TSDNov2002.pdf

OEHHA. (2008). Air Toxics Hot Spots Risk Assessment Guidelines. Technical Support
    Document for the Derivation of Noncancer Reference Exposure Levels. Air Toxicology and
    Epidemiology Branch, Office of Environmental Health Hazard Assessment, California
    Environmental Protection Agency. Available on-line at
    http://www.oehha.ca.gov/air/hot_spots/rels_dec2008.html

Röe O (1955). The metabolism and toxicity of methanol. Pharmacol Rev. 7(3):399-412.

Rogers JM, Mole ML, Chernoff N, Barbee BD, Turner CI, Logsdon TR, and Kavlock JV (1993).
    The developmental toxicity of inhaled methanol in the CD-1 mouse, with quantitative dose-
    response modeling for estimation of benchmark doses. Teratology 47:175-188.

Song C, Zhang Z, Chen X, Zhang Y, Wang C, Liu K (2002). [Study on three kinds of gasoline
    oxygenates-induced DNA damage in mice fibroblasts] [Chinese] Zhonghua Lao Dong Wei
    Sheng Zhi Ye Bing Za Zhi. 20(5):362-4.

SRC (2009). Syracuse Research Corporation on-line database. Accessed at
    http://www.syrres.com/what-we-do/databaseforms.aspx?id=386

U.S. EPA (1986). Rat oral subchronic toxicity study with methanol. Office of Solid Waste,
    Washington, DC.

U.S. EPA (2008). Methanol. Integrated Risk Information System. Available online at:
    http://www.epa.gov/iris/subst/0305.htm

USEPA. (2009). Air Quality: Revision to Definition of Volatile Organic Compounds -
    Exclusion of Propylene Carbonate and Dimethyl Carbonate. Federal Register 74(12):3437-
    41.

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