UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

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MEMORANDUM

SUBJECT: ***Formaldehyde/paraformadehyde*** - Report of the Antimicrobials Division Toxicity Endpoint Selection Committee (ADTC).

FROM: Timothy F. McMahon, Ph.D., Chair, ADTC
Antimicrobials Division (7510C)

TO: Sharon Carlisle, Chemical Review Manager
Mark Hartman, Branch Chief
Regulatory Management Branch II
Antimicrobials Division (7510C)

And

Timothy F. McMahon, Ph.D., Risk Assessor
Antimicrobials Division (7510C)

PC Code: 043001; 043002

On January 29, 2008, the Antimicrobials Division's Toxicity Endpoint Selection Committee (ADTC) evaluated the toxicology data base of **formaldehyde,** and selected toxicological endpoints appropriate for the currently registered uses of formaldehyde and paraformaldehyde. The conclusions of this meeting are presented in this report.

Committee Members in Attendance

Members present were: John Redden; Stephen Dapson, Ph.D.; Jonathan Chen, Ph.D., Michelle Centra, Najm Shamim, Ph.D; Timothy F. McMahon, Ph.D.; Roger Gardner; Jenny Tao.

I. INTRODUCTION

Formaldehyde is used primarily as a fumigant in agricultural premises such as poultry and swine farms and processing plants as well as in citrus and mushroom houses. It is used as a hard surface disinfectant in commercial premises, industrial premises and veterinary clinics. Formaldehyde containing products are also used in oil drilling wells for preservation of processing waters. There are no dietary uses of formaldehyde.
Paraformaldehyde is a white crystalline solid formed by polymerization of formaldehyde.
Presently there are 2 active products under a single PC Code 043002. Steri-Dri™Fumigant is used as a bacteriostat, fungicide, and sanitizer in hair/beauty salons and barber shops, and Sun Pac is used as mildewcide for closets, cupboards, dresser drawers, trunks, suitcases, lockers, golf bags, trailers, bathroom and kitchens, and mobile homes.

II. HAZARD IDENTIFICATION

A1. Acute Reference Dose (aRfD) [general population including infants and children]

There are no expected dietary exposures to formaldehyde or paraformaldehyde from the currently registered uses. Therefore an acute reference dose value is not needed.

A2. Acute Reference Dose (females 13-49)

There are no expected dietary exposures to formaldehyde or paraformaldehyde from the currently registered uses. Therefore an acute reference dose value is not needed.

B. Chronic Reference Dose (cPAD)

There are no expected dietary exposures to formaldehyde or paraformaldehyde from the currently registered uses. Therefore a chronic reference dose value is not needed. There is an existing chronic reference dose value in the current EPA IRIS assessment for formaldehyde, but for registered antimicrobial uses this value is not needed.

C. Incidental Oral Exposure

The committee determined that an incidental oral endpoint was not needed for formaldehyde. Formaldehyde is highly volatile with a low percentage of active ingredient in those products with residential exposures (laundry detergents, general household cleaners) and residues available for incidental oral exposure are not expected to occur. An accidental ingestion is considered a misuse and is not a regulatory endpoint. Therefore, no incidental oral endpoint was selected.

D. Dermal Exposure

There are available studies on the dermal irritancy and dermal sensitization potential of formaldehyde (Krivanek et al., Flyvholm et al, 1997). These data demonstrate irritancy and sensitization potential of formaldehyde, which is well known. However, the committee determined that dermal endpoints are not needed for formaldehyde for the registered antimicrobial uses. Residential uses do not involve purposeful contact with the skin. Use in laundry detergents and household cleaners is not expected to result in any significant dermal exposure based on the high water solubility of formaldehyde and the volatility of the active ingredient.

E. Inhalation Exposure (all durations)

The committee considered the data set forth in the 2001 ACGIH publication on formaldehyde as relevant for selection of a non-cancer inhalation endpoint for use in risk assessment. Inhalation is the major route of exposure to formaldehyde and thus hazard and risk need to be addressed from inhalation exposures.

As noted in the ACGIH document, "A TLV-Ceiling of 0.3 ppm (0.37 mg/m^3) is recommended for occupational exposure to formaldehyde. This value is recommended to minimize the potential for sensory irritation, chiefly eye and upper respiratory tract. Although the recommended TLV is intended to protect nearly all workers, ACGIH recognizes that the value may not safeguard that portion of the worker population (10-20%) reported to be responsive to low ambient concentrations (< 0.25 ppm), of the chemical…"

Additional published literature on human exposure to formaldehyde via inhalation (Ballarin, C. at al., Mutat. Res. 280(1), 1992; Akbar-Khanzadeh F., Am. J. Ind. Med. 26(1), 1994; Dally, KA et al., Arch. Environ. Health 36(6), 1981; Alexandersson and Hedenstierna, Arch. Environ. Health 43(3), 1988; Alexandersson and Hedenstierna, Arch. Environ. Health 44(1), 1989) show effects of formaldehyde on pulmonary function and irritation of the eye and nasal passages at similar concentrations. The level of formaldehyde causing such symptoms does not appear to vary regardless of exposure duration (i.e. hours to years).

In 2005, the Registration Division, in conjunction with the Antimicrobials Division, issued an emergency exemption for use of paraformaldehyde to decontaminate microbiological containment areas and equipment. In this assessment, the NOAEL of 0.1 ppm was selected from the epidemiology study of Horvath et al. (JAMA 259(5), 1988), who recorded complaints of eye, nose, and throat irritation in particle board workers at concentrations of formaldehyde from 0.4 – 1.0 ppm. Four additional studies were cited in the 2005 assessment as co-critical in support of the selected NOAEL value.

For occupational exposures, the committee felt that the 0.1 ppm inhalation endpoint was appropriate. No uncertainty factor was applied for occupational assessments. However, for residential and children's inhalation exposure, an uncertainty factor of 10x was applied to the 01 ppm endpoint. The common effects of formaldehyde exposure are various symptoms as a result of irritation of the mucosa in the eyes and upper airways. In the non-industrial indoor environment, sensory reactions are typical effects, but there are large individual differences in the normal population and between hyperreactive and sensitized people. Thus, the committee concluded that in order to protect sensitive subpopulations (children, older people and/or sensitized persons), an extra safety factor of 10X is applied to address this concern.

F. Recommendation for Aggregate Risk Assessments

Inhalation exposures are appropriate for aggregate risk assessment.

I. CLASSIFICATION OF CARCINOGENIC POTENTIAL

Formaldehyde has been extensively investigated for carcinogenic potential and several regulatory organizations including the government of Australia and IARC have reviewed the available carcinogenicity data in animals and humans with respect to formaldehyde. A detailed review is not necessary here but links to the documentation are: www.nicnas.gov.au for the Australian review, and http://monographs.iarc.fr/ for the IARC publication. The U.S. EPA National Center for Environmental Assessment (NCEA) is also in the process of updating the carcinogenic assessment for formaldehyde. Information from the draft document is reproduced here with permission.

The Agency is currently reevaluating the carcinogenic potential of formaldehyde. The historical and ongoing development of an inhalation unit risk value to assess the carcinogenic potential of formaldehyde is briefly summarized below. Contributors to this summary included scientists from several EPA program offices (OPP, OPPT, ORD, OAR, and NHEERL)

- In 1991 IRIS published a weight-of-evidence characterization for carcinogenicity of formaldehyde, classifying formaldehyde as a B1 probable human carcinogen with a potency factor of 1.3 E-5 per ($\mu g/m^3$)) on the basis of squamous cell nasal tumors observed in a two-year study in rats (Kerns et al., 1983).
- In 1999 the Chemical Industry Institute of Toxicology (CIIT) developed a health risk assessment for formaldehyde based upon the animal toxicology data (CIIT, 1999). This document presented the dose-response modeling of these data in two distinct parts: 1). based upon a biologically-based dose response (BBDR) model , 2) benchmark dose models that were based upon point of departures at various response levels of the tumor and precursor data. Both these approaches made extensive use of the available time-to-tumor and mechanistic information. The 1999 assessment was subsequently published in various articles in peer-reviewed journals (2001, 2002, 2003, 2004).

- In 1999, the U.S. EPA's Office of Air and Radiation and Office of Research and Development, in conjunction with Health Canada, conducted an external peer review workshop for the CIIT BDDR model as well as an external written peer review and public comment period for their assessments. While the review was largely positive on the overall approach in the assessment, reviewers also pointed to the potential for significant uncertainty due to model mis-specification and uncertainties in key parameters involved in the BBDR model

- Based on the peer review of the CIIT model, OAR determined in 2004 that the CIIT model was the most appropriate tool for risk assessment for formaldehyde. OAR has subsequently used the formaldehyde cancer potency derived using the CIIT model for a number of risk assessments involving formaldehyde emissions to the atmosphere such as the Plywood and Composite Wood Products National Emission Standard for Hazardous Air Pollutants (final rule 2004, reconsidered final rule 2006, remanded to EPA by court 2007); Control of Hazardous Air Pollutants from Mobile Sources (Final Rule 2007); and Proposed Rule for National Emission Standard for Combustion Turbines (2004). Health Canada, Australia, the World Health Organization, and the German MAK Commission have also used the CIIT model. Model strengths include consideration of the mode of action data for formaldehyde and a conservative approach to account for potential direct DNA interaction and mutation induction. Model uncertainties include variability for some of the parameters of the model (e.g., cell proliferation) which can affect predictions of risk (Subramanian et al 2007; 2008 [in press]).

- In 2004, NCEA convened a panel of experts, including scientists from CIIT, to provide advice on these and other critical biological and statistical uncertainties. The strength of the CIIT model is its consideration of mode of action and extensive mechanistic information.

- Although current OAR assessments still use the CIIT model, these assessments now acknowledge previously unknown uncertainties with the CIIT model when characterizing the risk results.

- In 2004, the International Agency for Research on Cancer (IARC) characterized formaldehyde as a human carcinogen based on their review of the current literature (IARC, 2004), including data in humans on nasopharyngeal cancer, cancer of the nasal cavity and paranasal sinuses,and leukemia. It should be noted that some epidemiology studies did not find a reported association between formaldehyde exposure and carcinogenicity. For example, Coggon et al, 2003 studied over 14,000 workers exposed to formaldehyde in industrial workplaces and reported no excesses of either leukemia or nasal and nasopharyngeal cancer.

- In 2005, the Scientific Review Panel (SRP) of the California Office of Environmental Health Hazard Assessment responded to the CA Air Resources Board request to reevaluate the carcinogenic potential of formaldehyde. The Panel noted in this 2005 review that OEHHA's November 2002 evaluation of a petition had included the 1999 report on the CIIT model and other information, and that California's OEHHA had concluded that "*the evidence…(1) did not change the determination that formaldehyde is a carcinogen; (2) presented information that considered the possibility of non-linear dose response relationships, but presented no clear grounds to review the original "no threshold"*

determination; and (3) did not provide any new epidemiology or bioassays supporting a change in potency. In addition, there was insufficient information to fully evaluate the CIIT model, issues such as model uncertainty were not adequately addressed…." The Scientific Review Panel's overall conclusion in 2005 was, *"The Panel concluded that there was not sufficient new data to support the petition to review the [OEHHA's earlier 1992] formaldehyde risk assessment. In addition, the newly published studies represented relevant new information, but they did not allow determination of a causal relationship between formaldehyde exposure and leukemia. These studies deserve further evaluation over time given their potential importance."* Froines (2005).

- EPA is currently completing a new IRIS assessment and unit risk value for formaldehyde; the reassessment is scheduled to start internal peer review in May 2008 and begin independent external peer review in January 2009 (http://cfpub.epa.gov/ncea/iristrac/index.cfm?fuseaction=viewChemical.showChemical&sw_id=1031). EPA anticipates that the peer review of the formaldehyde assessment will be a longer process then that of EPA's reregistration process scheduled to conclude in September 2008.

Based of the on going development of the science to predict carcinogenic potential of formaldehyde, OPP has decided to present the formaldehyde cancer risks for the pesticidal uses using both the existing 1991 IRIS cancer unit risk of 1.3 E-5 per ($\mu g/m^3$) and the CIIT BBDR model until any new cancer estimates are fully peer reviewed. OPP also acknowledges the wide range in cancer risks using these approaches and will coordinate with other offices in EPA on the outcome of the upcoming peer review process on the carcinogenicity of formaldehyde. Because formaldehyde air concentrations approach those associated with ocular and respiratory tract irritation, the risk mitigation measures to be implemented in the meantime for the pesticidal uses will be based on mitigating the non-cancer effects at a limit of 0.01 ppm. It is believed that this level will reduce exposures sufficiently such that the cancer risks would not be of concern. The EPA process of regulating pesticides allows for reevaluation at any time if new information from the peer review process of the carcinogenic potential of formaldehyde warrants.

II. MUTAGENICITY

Formaldehyde's mutagenicity has been examined in a variety of in vitro and in vivo test systems. In a bacterial reverse mutation test (MRID 00132156), formaldehyde (2%) was tested at concentrations of 0.001, 0.01, 0.10, 1.0, or 5.0 µL and found to be negative. In a second submitted study (MRID 00132157), formaldehyde (2%) was tested at concentrations of 3.0, 15.0, 75.0, 150, or 300 µg/plate and found to be positive in the bacterial reverse mutation assay. Formaldehyde caused a positive response (3.2-fold increase) on tester strain TA98 without metabolic activation. A 1.9-fold increase was observed on TA98 with metabolic activation. Also, increases of 2.2-fold and 1.7-fold were observed on tester strain TA100 with and without activation, respectively. In an in vitro mammalian chromosome aberration test (MRID 00132168), formaldehyde (37% formalin), was tested on Chinese hamster ovary cells at concentrations of 28.43, 37.91, or 50.55 nL/mL. The test article caused a significant dose-dependant increase in the frequencies of chromosome aberrations in the Chinese Hamster Ovary cells, both with and without S-9 activation. One submitted study (MRID 00132169), tested formaldehyde (37%) for Unscheduled DNA synthesis (UDS) in Primary rat liver hepatocytes. The test material was tested at concentrations of 0.0005, 0.001, 0.005, 0.01, 0.02, or 0.04 µL/mL and found to cause no significant increase in UDS in rat hepatocytes.

In published studies, formaldehyde has shown both positive and negative results in the Ames Salmonella assay (Donovan et al., 1983; Connor et al., 1983, 1985; Frei et al., 1984; Fiddler et al., 1984; Oerstavik and Hongslo, 1985; Takahashi et al., 1985; Schmid et al., 1986; Zielenska and Guttenplan, 1988; Le Curieux et al., 1993; O'Donovan and Mee (1993) Watanabe et al., 1996; Dillon et al., 1998; Ryden et al., 2000; Wilcox et al., 1990; Jung et al., 1992; Marnett et al., 1985; Mueller et al., 1993).

Temcharoen and Thilly (1983) examined the capacity of formaldehyde to induce forward mutations to 8-azaguanine resistance in S. typhimurium TM 677, a his^+ revertant of TA 1535. Both toxicity and mutagenicity were obtained at formaldehyde concentrations of 0.17 mM in the absence of S9 and 0.33 mM in the presence of S9 Dillon et al. (1998) employed Salmonella strains TA102 and TA104 because they are more sensitive to oxidative mutagens. Formaldehyde was mutagenic in both strains, as well as in TA100. However, the authors reported that the mutagenic activity was not reduced in TA104 in the presence of S9 from either Aroclor-induced male Fischer F 344 rats or male $B6C3F_1$ mice.

In another study, formaldehyde induced forward mutations to trifluorothymidine resistance in mouse lymphoma L5178Y $tk^{+/-}$ cells both in the absence and presence of rat liver S9 (higher concentrations required for effect with S9). Both toxicity and mutagenicity were abolished when formaldehyde dehydrogenase was incorporated in the exposure medium (Blackburn et al., 1991).

Ross and Shipley (1980) used a [^{14}C]-thymidine-incorporated mouse L1210 cell line to monitor formaldehyde-induced DNA strand breaks and DPX. Single strand breaks (SSB) and DNA-protein cross links were induced by formaldehyde, with SSB at concentrations greater than 200 □M and a reduction of radiation-induced breaks (indirect measure of DPX) at 50 □M.

Formaldehyde-induced DPX were repaired 24 hours after the compound was removed from the culture.

In vivo, no treatment-related increase in either micronuclei or chromosome aberrations were observed following intraperitoneal exposure to formaldehyde at 0, 6.25, 12.5, or 25 mg/kg. (Natarajan et al. (1983)). Similarly, chromosomal analysis of spermatocytes at metaphase I did not reveal any chromosomal lesions in Q strain mice injected intraperitoneally with 50 mg/kg of the compound (Fontignie-Houbrechts, 1981). Exposure of male and female Fischer F-344 rats to 0.5, 6, or 15 ppm (0.6, 7.4, 18.5 mg/m^3) formaldehyde by inhalation for 6 hours/day for 5 days showed no increases in either SCE or chromosome aberrations at any dose level (Kligerman et al. (1984)) .

III. FQPA CONSIDERATIONS

There are no tolerances for formaldehyde or paraformaldehyde and the use patterns considered for the reregistration eligibility decision do not involve dietary exposure. As a result, a FQPA safety finding is not applicable.

IV. DATA GAPS / REQUIREMENTS

There are no acceptable repeat dose dermal toxicity studies for formaldehyde. Although currently there are no dermal endpoints selected, a dermal toxicity study is considered a data gap with respect to the dermal concentration of formaldehyde that causes systemic effects and whether any systemic effects are precluded by the irritancy and/or sensitization potential of the chemical.

VII. ACUTE TOXICITY

Acute Toxicity data for Formaldehyde technical a.i.				
Guideline Number	**Study Type/ Test substance (% a.i.)**	**MRID Number/ Citation**	**Results**	**Toxicity Category**
870.1100 (§81-1)	Acute Oral – Guinea Pig Purity 37.3% - Formaldehyde	00058054	LD_{50} = 260 mg/kg	II
870.1200 (§81-2)	Acute Dermal – Rat Purity 37.3% - Formaldehyde	00058054	LD_{50} = 300 mg/kg	II
870.1200 (§81-2)	Acute Dermal – Rabbit Purity 37.3% - Formaldehyde	00058054	LD_{50} = 240 mg/kg	II
870.1200 (§81-2)	Acute Dermal – Dog Purity 37.3% - Formaldehyde	00058054	LD_{50} = 550 mg/kg	II
870.1300 (§81-3)	Acute Inhalation – Mouse and Rat	See Open Literature studies in Toxicity Profile for Formaldehyde		
870.2400 (§81-4)	Primary Eye Irritation - Purity 37.3% - Formaldehyde	00058054	Severe eye irritant	I
870.2500 (§81-5)	Primary Dermal Irritation Purity 37.3% - Formaldehyde	00058054	Formation of vesicles with superficial necrosis or nodules.	I
870.2600 (§81-6)	Dermal Sensitization – Guinea pigs Purity 40.0% - Formaldehyde	40161103	Extreme Sensitizer	NA

VIII. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION FOR OF FORMALDEHYDE

Exposure Scenario	Dose Used in Risk Assessment (mg/kg/day)	Target MOE, UF, Special FQPA SF* for Risk Assessment	Study and Toxicological Effects
Dietary Risk Assessments			
Acute Dietary (general population including infants and children)	An acute dietary assessment is not needed for the registered antimicrobial uses of formaldehyde.		
Chronic Dietary (all populations)	A chronic dietary assessment is not needed for the registered antimicrobial uses of formaldehyde.		
Non-Dietary Risk Assessments			
Incidental Oral	An incidental oral risk assessment is not required for the registered antimicrobial uses of formaldehyde.		
Dermal (all durations)	A dermal risk assessment is not required for the registered antimicrobial uses of formaldehyde.		
Inhalation (all durations)	**NOAEL** (human) = 0.1 ppm	**UF = 1 (occupational)** **UF = 10 (residential)**	ACGIH 2001 publication on formaldehyde Horvath, E.P. et al. (1986): JAMA 259(5): 701-707. Based on complaints of eye, nose, and throat irritation in particle board workers at concentrations of formaldehyde from 0.4 – 1.0 ppm. Redden, J. (2005): Section 18 Emergency Exemption for the use of Paraformaldehyde: U.S. Army Medical Research Institute of Infectious Diseases.

Exposure Scenario	Dose Used in Risk Assessment (mg/kg/day)	Target MOE, UF, Special FQPA SF* for Risk Assessment	Study and Toxicological Effects
Cancer	Formaldehyde is currently classified as a B1 (probable human carcinogen) in EPA's IRIS assessment. IARC has classified formaldehyde as "carcinogenic to humans." The Agency has decided to present the formaldehyde cancer risks for the pesticidal uses using both the existing 1991 IRIS cancer unit risk of 1.3 E-5 per ($\mu g/m^3$) and the CIIT BBDR model until any new cancer estimates are fully peer reviewed		