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ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

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MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agency wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Formaldehyde
CAS number(s):   50-00-0
Date: April 20, 1999
Profile status: Final
Route: [X] Inhalation [ ] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Key to figure: 15
Species: Human

MRL: 0.04 [ ] mg/kg/day [X] ppm [ ] mg/m^3

Reference: Pazdrak, K, Gorski, P, Krakowiak, A and Urszula, R (1993). Changes in Nasal Lavage Fluid Due to Formaldehyde Inhalation. Int Arch Occup Environ Health 64: 515-519.

Experimental design: This study investigated the effects of formaldehyde exposure on the severity of symptoms of nasal and eye irritation and the cellular makeup of nasal discharge in occupationally exposed patients with skin hypersensitivity to formaldehyde and unexposed (control) patients. The study was comprised of 2 study groups, all of whom were non-smokers. Group 1 consisted of 7 male and 3 female volunteers, all of whom suffered from skin hypersensitivity to formaldehyde; group 2 consisted of 11 healthy males with no history of allergic diseases, normal serum IgE levels, and negative skin tests to common allergens. Nasal washings were performed in both groups immediately before and after a 2-hour exposure to 0 (placebo) and 0.5 mg/m^3 (0.4 ppm) formaldehyde, and at 4 and 18 hours after completion of the 2-hour exposure periods. Washings were analyzed for eosinophil, neutrophil, basophil, and mononuclear cells, and albumin content. Symptoms of irritation (number of sneezes, degree of mucosal edema, rhinorrhea, and itchy eyes) were evaluated through the exposure period and through 4- and 18-hour periods after the exposure period. A symptom score was compiled for each subject by summation of points assigned to the following symptoms (maximum score = 7): sneezing (0 points/0 sneezes; 1 point/1-4 sneezes; 2 points/ > 4 sneezes); rhinorrhea (0 points /none; 1 point/mild; 2 points/abundant); mucosal edema (0 points/none; 1 point/mild; 2 points/nasal block); and itching (0 points/none; 1 point/itchy eyes).

Effects noted in study and corresponding doses: In both groups, placebo inhalation periods were without effects on nasal wash cellular contents or symptom score. During exposure to 0.4 ppm formaldehyde, both groups showed statistically significantly increased average symptom scores compared with average placebo scores (about 4 versus <0.5). Symptom scores were no longer elevated 18 hours after exposure. In both groups, eosinophil counts were elevated at all time points after 0.4 ppm formaldehyde exposure, while the proportion of epithelial cells declined after formaldehyde exposure. Albumin levels also increased in both groups after formaldehyde exposure, but remained elevated only briefly (10 minutes). There were no significant differences between allergic and healthy patients in nasal washing characteristics after formaldehyde exposure. No changes in basophil numbers were noted in either patient group and there was no evidence of mast cell degranulation. The authors concluded that the symptoms observed were the result of a non-specific, non-allergic process in response to low-level formaldehyde vapor exposure. The authors also noted that further study is required to understand the significance of the increased release of eosinophils noting that eosinophils may have both protective (e.g., they can neutralize histamine) and damaging (e.g., they may liberate mediators that damage epithelial surfaces) properties.

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Dose and end point used for MRL derivation:

The only concentration tested, 0.4 ppm, is a minimal LOAEL for nasal and eye irritation

[ ] NOAEL [X] LOAEL

Uncertainty factors used in MRL derivation:

[X]   3 for use of a minimal LOAEL- the observed symptoms of irritation were mild and reversible,
        and the clinical significance of the changes in nasal lavage fluid content is uncertain at present .
[ ]   10 for extrapolation from animals to humans
[X]   3 for human variability - the observed symptoms of irritation were observed in a potentially
        sensitive group of subjects (they displayed dermal sensitivity to formaldehyde).

Was a conversion factor used from ppm in food or water to a mg/body weight dose?

NA

Was a conversion used from intermittent to continuous exposure?

NA

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:

NA

Other additional studies or pertinent information that lend support to this MRL:

The Anderson and Molhave (1983) study identified an apparent effect level (0.2 ppm), based on subjective reports of irritation that is lower than the effect levels (0.35-0.4 ppm) in the studies by Pazdrak et al. (1993), Krakowiak et al. (1998), and Bender et al. (1993), which used more objective measures of acute irritation (eosinophil counts and protein concentrations in nasal lavage fluid or time to first reporting of irritation: see section 2.2.1.2 Systemic Effects - Respiratory Effects Acute Controlled Exposure Human Studies.) Because of the use of objective measures of toxicity and the general weight of the available data indicating that some people will not experience eye or upper respiratory tract irritation from formaldehyde even at 1 ppm (see Day et al. 1984; Kulle et al. 1987, Weber Tschopp et al. 1977, and Witek et al. 1986), the Pazdrak et al. (1993) LOAEL of 0.4 ppm was considered a minimal LOAEL in a group of potentially sensitive individuals (some subjects had dermal hypersensitivity to formaldehyde) and selected as the basis of the acute MRL.

Agency Contact (Chemical Manager): Sharon Wilbur

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Formaldehyde
CAS number: 50-00-0
Date: April 20, 1999
Profile status: Final
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Key to figure: 49
Species: Cynomolgus Monkey

MRL: <u>0.03</u>   [ ] mg/kg/day [X] ppm [ ] mg/m^3

Reference: Rusch, G, Clary, JJ, Rinehart WE and Bolte, HF (1983). A 26 Week Inhalation Toxicity Study with Formaldehyde in the Monkey, Rat and Hamster. Toxicol Appl Pharmacol 68: 329-343.

Experimental design: Groups of 6 male Cynomolgus monkeys were exposed to 0, 0.19±0.02, 0.98±0.08, or 2.95±0.18 ppm for 22 hours per day, 7 days per week for 26 weeks. All monkeys were weighed and clinically assessed weekly. At sacrifice, adrenals, kidneys, liver, and heart were weighed. Sections of lung, nasal turbinate, trachea, and any other tissue with gross abnormalities were prepared for histologic examination.

Effects noted in study and corresponding doses: Body weights in the monkeys were normal in all groups throughout the study. Monkeys in the 2.95-ppm group exhibited increasing hoarseness, nasal congestion, and nasal discharge, especially during the last 13 weeks of the study. While some nasal symptoms were noted in the 0.19- and 0.98-ppm groups, they were observed to be inconsistent and were not substantiated histologically. All organ weight data were unremarkable. No treatment-related effects were noted in internal organs upon gross inspection. A statistically significant increased incidence of squamous metaplasia and hyperplasia of the nasal epithelium was clearly observed in the 2.95-ppm group, but no significant increase in the incidence of epithelial squamous metaplasia/hyperplasia was found in the 0.19 and 0.98-ppm groups. The response was seen most clearly in the mid-region of the nasoturbinates. No ultrastructural changes were noted in other sections of the turbinates, trachea, or lungs at any of the doses of formaldehyde tested.

Dose and end point used for MRL derivation:

Clinical signs of nasopharyngeal irritation (hoarseness and nasal congestion and discharge) and lesions in the nasal epithelium (squamous metaplasia and hyperplasia) were observed at 2.95 ppm; no effects were observed at 0.98 ppm. Thus, the NOAEL and LOAEL for nasopharyngeal irritation are 0.98 and 2.95 ppm, respectively.

[X] NOAEL [ ] LOAEL

Uncertainty factors used in MRL derivation:

[   ]   10 for use of a LOAEL
[X]   3 for extrapolation from animals to humans - an uncertainty factor of 3 was used, instead of 10, because similar nasal effects have been reported at similar concentrations in different species and different studies indicating few pharmacodynamic differences in species susceptibility

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[X]   10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose?

NA

Was a conversion used from intermittent to continuous exposure?

The exposure concentration was not adjusted to a continuous exposure basis based on evidence that concentration is more important than the product of concentration and duration of exposure in determining the severity of formaldehyde-induced epithelial damage in the upper respiratory tract (Wilmer et al. 1987).

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:

In the absence of reference nasal cavity surface areas and minute ventilations for Cynomolgus monkeys, a default regional gas dose ratio of 1 was assumed (EPA 1994).

Other additional studies or pertinent information that lend support to this MRL:

Although there are numerous human studies of acute inhalation toxicity from formaldehyde (controlled-exposure and occupational exposure studies) and numerous investigations of toxic effects from chronic occupational exposures, studies of humans exposed for intermediate durations were not located. In contrast, the database for studies of animals (including primates) exposed by inhalation to formaldehyde is rich, providing data describing exposure-response relationships for formaldehyde-induced effects on the upper respiratory tract system in several species (rats, mice, hamsters, and monkeys) . The study by Rusch et al. (1983) examined a number of species and identified the lowest effect level among the available sets of data. Given this observation, the absence of human intermediate-duration data, and the putatively greater relevance of monkeys, compared with rodents, to humans, the monkey NOAEL of 0.98 ppm and LOAEL of 2.95 ppm for clinical signs of nasopharyngeal irritation were selected as the basis of the intermediate-duration MRL.

Agency Contact (Chemical Manager) : Sharon Wilbur

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Formaldehyde
CAS number: 50-00-0
Date: April 20, 1999
Profile status: Final
Route: [X] Inhalation [ ] Oral
Duration: [] Acute [ ] Intermediate [X] Chronic
Key to figure: 86
Species: Human

MRL: 0.008   [ ] mg/kg/day [X] ppm [ ] mg/m^3

Reference: Holmstrom M, Wilhelmsson B, Hellquist H, et al. 1989c. Histological changes in the nasal mucosa in persons occupationally exposed to formaldehyde alone and in combination with wood dust. Acta Otolaryngol (Stockh) 107:120-129.

Experimental design: Holmstrom et al. (1989c) examined histological changes in nasal tissue specimens from a group of 70 workers in a chemical plant that produced formaldehyde and formaldehyde resins for impregnation of paper, a group of 100 furniture factory workers working with particle board and glue components, and a nonexposed, control group of 36 office workers in the same village as the furniture factories. Mean durations of employment in the groups were 10.4 years (SD 7.3, range 1–36 years) for the chemical workers and 9.0 years (SD 6.3, range 1–30 years) for the furniture workers. Estimates of personal breathing zone air concentrations ranged from 0.04 to 0.4 ppm (median 0.24±0.13 ppm) for the chemical workers, from 0.16 to 0.4 ppm (median 0.20±0.04 ppm) for the furniture workers, and from 0.07 to 0.13 ppm in the late summer for the office workers with a year-round office worker median reported as 0.07 ppm with no standard deviation. The mean wood dust concentration in the furniture factory was reported to have been between 1 and 2 mg/m^3. Nasal mucosa specimens were taken from the medial or inferior aspect of the middle turbinate. Histology scores were assigned to each specimen based on a 0–8 scale, identical to the scale used by Edling et al. (1988; described previously). Nasal mucosal biopsy sections for each subject were examined and assigned scores as follows: 0 - normal respiratory epithelium; 1- loss of ciliated epithelium cells; 2 - mixed cuboid/squamous epithelium, metaplasia; 3 - stratified squamous epithelium; 4 - keratosis; 5 - budding of epithelium; 6 - mild or moderate dysplasia; 7 - severe dysplasia; and 8 - carcinoma.

Effects noted in study and corresponding doses: Nasal histology scores ranged from 0 to 4 (mean 2.16; n=62) for the chemical workers, from 0 to 6 (mean 2.07; n=89) for the furniture workers, and from 0 to 4 (mean 1.46; n=32) for the office workers. The mean histological score for the chemical workers, but not the furniture workers, was significantly different from the control score, thus supporting the hypothesis that the development of the nasal lesions is formaldehyde-related and not obligatorily related to possible interaction between formaldehyde and wood dust. The most severe epithelial change found (light or moderate epithelial dysplasia) was found in two furniture workers. Among the chemical workers (not exposed to wood dust), loss of cilia, goblet cell hyperplasia and cuboidal and squamous cell metaplasia replacing the columnar epithelium occurred more frequently than in the control group of office workers. Within both groups of formaldehyde-exposed workers, no evidence was found for associations between histological score and duration of exposure, index of accumulated dose, or smoking habit.

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Dose and end point used for MRL derivation:

Clinical symptoms of mild irritation of the eyes and upper respiratory tract and mild damage to the nasal epithelium were observed in workers exposed for 10.4 years (range 1-36 years) to an average TWA concentration of 0.24 ppm (range: 0.04 to 0.4 ppm). The LOAEL of 0.24 ppm is considered to be a minimal LOAEL.

[ ] NOAEL [X] LOAEL

Uncertainty factors used in MRL derivation:

[X]   3 for use of a LOAEL - the exposed histological effects are considered to be mild and subclinical
        in nature, suitable for 0.24 ppm to be designated as a minimal LOAEL
[ ]   10 for extrapolation from animals to humans
[X]   10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose?

NA

Was a conversion used from intermittent-to-continuous exposure?

The exposure concentration was not adjusted to a continuous exposure basis based on evidence that concentration is more important than the product of concentration and duration of exposure in determining the severity of formaldehyde-induced epithelial damage in the upper respiratory tract (Wilmer et al. 1987).

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:

NA

Other additional studies or pertinent information that lend support to this MRL:

Several cross-sectional studies of groups of formaldehyde-exposed workers chronically exposed to estimated concentrations ranging from about 0.1 to 0.6 ppm (Holmstrom et al. 1989c; Edling et al. 1988; Boysen et al. 1990; Ballarin et al. 1992) have found histological evidence for mild damage to nasal epithelial tissue such as the damage described for exposed workers in the Holmstrom et al. (1989c) study. The observed effects were consistently mild, but each study reported a statistically significant, albeit small, increase in average histological score (increasing scores indicating increasing severity of change) for exposed groups compared with nonexposed control groups: 2.8 exposed versus 1.8 on an 8-point scale (Edling et al., 1988); 2.16 versus 1.46 on an 8-point scale (Holmstrom et al., 1989c); 1.9 versus 1.4 on a 5-point scale (Boysen et al., 1990); and 2.3 versus 1.6 on a 6-point scale (Ballarin et al., 1992). The Holmstrom et al. (1989c) study was selected as the basis of the MRL from among these four cross-sectional studies (they each examined equivalent endpoints and are of similar quality of design) primarily because the statistically significant effects were found in a group exposed to formaldehyde in the absence of potentially confounding exposures to wood dust. A full uncertainty factor of 10 was used to account for human variability because the observed mild effects were seen in groups of chronically exposed workers that were otherwise in apparent good health; a healthy worker effect may have operated causing sensitive individuals to avoid employment in the studied workplaces.

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Additional supporting evidence for mild histological changes to the nasal epithelium with chronic exposure to concentrations below 1 ppm comes from rat studies. Although several studies of rats exposed for life (generally with an exposure protocol of 6 hours/day, 5 day/week) found no statistically significant increases in incidences of nonneoplastic lesions in the nasal epithelium of rats exposed to 0.1 to 2 ppm [Kerns et al. 1983b (F344 rats); Monticello et al. 1996 (F344 rats); Woutersen et al. 1989 (Wistar rats)], Kamata et al. (1997) reported that some F344 rats, after 28 months of exposure, displayed a mild response at 2 ppm and even at 0.3 ppm. A statistically significantly increased incidence for nasal epithelial squamous metaplasia without hyperplasia was observed in rats exposed to 2 ppm compared with control rats (5/32 versus 0/32); the incidence for nasal epithelial cell hyperplasia with squamous metaplasia was also significantly elevated compared with controls (7/32 versus 0/32). In rats exposed to 0.3 ppm, incidences of the same respective nasal epithelial lesions were also greater than control incidences (1/32 versus 0/32 and 4/32 versus 0/32), but not to a statistically significant degree.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name(s):   Formaldehyde
CAS number(s):   50-00-0
Date: Aprile 20, 1999
Profile status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Key to figure: 17
Species: Rat

MRL: 0.3   [X] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: Til HP, Woutersen RA, Feron VJ, Clary JJ (1988b). Evaluation of the oral toxicity of acetaldehyde and formaldehyde in a 4-week drinking-water study in rats. Fd. Chem. Toxic 26: 447–452.

Experimental design: Groups (10 males and 10 females) of weanling, SPF-bred rats (Cpb:WU; Wistar random) received 0, 5, 25, or 125 mg/kg/day formaldehyde in their drinking water for 4 weeks. Fresh formaldehyde dosing solutions were made once per week; however, the authors did not provide information on if or how often the dosing solutions were analyzed for actual formaldehyde content. Due to this procedural discrepancy, it is unclear how much formaldehyde each animal actually received in the drinking water, since polymerization, oxidation, or evaporation may have occurred during the study. Control groups (20 males and 20 females) were given unsupplemented tap water. A water-restricted group (10 males and 10 females) received the same amount of unsupplemented drinking water as the amount of liquid consumed by the group given the highest dose of formaldehyde. Rats were weighed weekly and observed daily for condition and behavior. Food and water intake were measured over weekly periods throughout the study. Hematological parameters (hemoglobin concentration, packed-cell volume, erythrocyte and leucocyte counts) were determined. Whole blood from fasted animals was examined for glucose. Blood samples were analyzed for alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total protein, albumin, total bilirubin, urea, creatinine and calcium, inorganic phosphate, chloride, and sodium and potassium. In week 4 of treatment, rats were deprived of water for 24 hours and of food for 16 hours. Urine was collected during the last 16 hours of the deprivation period. Density and volume of urine were determined. The rats were killed in week 5, organs (adrenals, brain, liver, heart, kidneys, spleen, testes, thymus, thyroid, and ovaries) were weighed and organ-to-body weight ratios determined. Histopathological examination was performed on the liver, kidneys, tongue, pharynx, esophagus, stomach, and nose. The fur of rats receiving 125 mg/kg/day formaldehyde showed yellowish discoloration from week 3 onward. Food intake was significantly reduced at all dose levels for female rats. At 125 mg/kg/day formaldehyde, water intake was significantly reduced in both sexes; body weight was not affected. There was no effect on the density (except that in 5 mg/kg treated males and water-restricted males, density significantly decreased) or volume of the urine collected. Hematological parameters showed no significant changes in animals treated with formaldehyde at any dose level. Male rats given 125 mg/kg/day formaldehyde showed statistically significant decrease in plasma protein and albumin concentrations. Female rats given 25 mg/kg/day formaldehyde showed statistically significant decrease in plasma alkaline phosphatase; alanine aminotransferase activities also decreased but was not significant. At 125 mg/kg, kidney weights in females were significantly increased. There were no other organ weight changes observed at any dose level, treatment-related, or histopathological changes in any of the tissues examined except the stomach. Necropsy findings revealed thickening of the limiting ridges and hyperkeratosis in the forestomach and focal atrophic inflammation in the glandular stomach in animals given the high concentration of formaldehyde. Moderate papillomatous hyperplasia was seen in one female given a high concentration of formaldehyde. Types of lesions in

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males given 125 mg/kg formaldehyde are as follows: slight-to-moderate focal hyperkeratosis of forestomach, slight-to-moderate focal gastritis (location in stomach not reported), and slight-to-moderate submucosal mononuclear-cell infiltrate (location in stomach not reported). Types of lesions in females given 125 mg/kg formaldehyde are as follows: very slight, slight-to-moderate focal hyperkeratosis of forestomach; very slight, slight-to-moderate focal gastritis (location in stomach not reported); focal papillomatous hyperplasia (location in stomach not reported); and polymorphonuclear leucocytic infiltration.

Effects noted in study and corresponding doses:

25 mg/kg/day: NOAEL for gastrointestinal effects.

125 mg/kg/day: Thickening of the limiting ridges and hyperkeratosis in the forestomach and focal atrophic inflammation in the glandular stomach; slight-to-moderate focal hyper-keratosis of forestomach. Slight-to-moderate focal gastritis, and slight-to-moderate submucosal mononuclear-cell infiltrate in males (location in stomach not reported); very slight, slight-to-moderate focal hyperkeratosis of forestomach. Very slight, slight-to-moderate focal gastritis and focal papillomatous hyperplasia (location in stomach not reported). Polymorphonuclear leucocytic infiltration in females, moderate papillomatous hyperplasia in one female (less serious LOAEL).

Dose end point used for MRL derivation: NA

[X] NOAEL [ ] LOAEL 25 mg/kg/day

Uncertainty factors used in MRL derivation:

[X] 1 [ ] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [ ] 3 [X] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [X] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain: None

Was a conversion used from intermittent to continuous exposure?
If so, explain: None

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: NA

Other additional studies or pertinent information that lend support to this MRL : Gastrointestinal irritation and damage have been observed in both humans and animals after ingestion of formaldehyde. In human poisoning studies, effects observed include: ulceration and sloughing of the soft palate and posterior pharyngeal wall; ulceration of the epiglottis, pyriform fossae and arytenoids; edematous and ulcerated esophageal mucosa with patches of black, sloughed tissue along the entire length; hyperemic areas of the stomach; and superficial ulceration in the distal body and antrum after a single dose of 234 mg/kg formaldehyde (Kochhar et al. 1986); abdominal pain and retching; hard, white and leathery stomach after a dose of 517 mg/kg (Burkhart et al. 1990), or abdominal pain at 624 mg/kg (Eells et al. 1981). In human poisoning studies in which the dose of formaldehyde is not known, gastrointestinal symptoms including mucosal damage, ulceration and bleeding of the buccal cavity and tonsils, and dysphagia due to esophageal mucosal damage (Freestone and Bentley 1989), necrosis of the esophagus and stomach, extensive congestion, peptic plaques in esophagus and stomach, colitis, congestion, diffuse necrosis and

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hemorrhage of gastric and duodenal mucosa, burns in gastrointestinal mucosa, and ileitis (Koppel et al. 1990). In animals, gastrointestinal irritation and damage (Til et al. 1989; Tobe et al. 1989), and neoplastic lesions (Soffritti et al. 1989; Takahashi et al. 1986a) have been observed in other studies in which formaldehyde was administered orally for longer periods of time. Vargova et al. (1993) reported immunological effects related to formaldehyde exposure (increased relative lymph node weight and a decrease in combined IgM and IgG titers), while Dean et al. (1984) failed to produce observable changes in immunological parameters. The Vargova et al. (1993) study was not used for MRL calculation because actual individual IgG and IgM titers were not significantly reduced until the dose reached 40 mg/kg/day, and because it used a gavage method of dosing, which is less relevant to human exposure than the drinking water study of Til et al. (1988b). It appears from the available data that immunological changes resulting from formaldehyde exposure are unclear and perhaps not a viable toxicological endpoint for determining formaldehyde toxicity. Thus, gastrointestinal effects appear to be an appropriate indicator of an adverse reaction to oral exposure to formaldehyde.

Agency Contact (Chemical Manager) : Sharon Wilbur

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name(s):   Formaldehyde
CAS number(s):   50-00-0
Date: April 20, 1999
Profile status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Key to figure: 38
Species: Rat

MRL: 0.2   [X] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: Til HP, Woutersen RA, Feron VJ, Hollanders VHM, Falke HE, Clary JJ (1989). Two-year drinking-water study of formaldehyde in rats. Fd. Chem. Toxic 27: 77-86.

Experimental design: Target concentrations of 5, 25, and 125 mg/kg/day formaldehyde (95% paraformaldehyde) were administered to groups of weanling SPF-bred rats (Cpb:WU; Wistar random) in their drinking water for 2 years. Actual formaldehyde concentrations reported in this study were 0, 1.2, 15, or 82 mg/kg/day for males and 0, 1.8, 21, or 109 mg/kg/day for females when adjusted for body weight. Fresh formaldehyde dosing solutions were made once per week; however, the authors did not provide information on if or how often the dosing solutions were analyzed for actual formaldehyde content. Due to this procedural discrepancy, it is unclear how much formaldehyde each animal actually received in the drinking water, since polymerization, oxidation, or evaporation may have occurred during the study. Daily observations were made of the condition and behavior of the rats. Body weights were recorded at the start of the study, at weekly intervals in the first 12 weeks, and once every 4 weeks thereafter. Water intake was measured over weekly periods throughout the study and food intake was determined over weekly periods during the first 12 weeks, then over 2-week periods every 3 months. Hematological parameters (hemoglobin concentration; packed-cell volume; erythrocyte, leucocyte, and thrombocyte counts) were determined in weeks 26 and 103 from 10 rats/sex/group. Whole blood taken from 10 rats/sex/group after overnight fasting in weeks 27, 52, 78, and 104 was examined for glucose. Blood samples taken from 10 rats/sex/group on weeks 26, 53, 79, and 105 were analyzed for alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total protein, albumin, total bilirubin, urea, creatinine, cholesterol, g-glutamyl transferase and calcium, inorganic phosphate, chloride, sodium, and potassium. Urinalysis was performed from pooled urine samples collected in weeks 27 and 104 and observed for protein, glucose, occult blood, ketones, urobilinogen, and bilirubin. pH determinations were carried out in weeks 27, 52, 78 and 104. Surviving rats of the first (10 rats/sex/group), second (10 rats/sex/group) and third (50 rats/sex/group) subsets were killed in weeks 53, 79, and 105, respectively. Organs (adrenals, brain, heart, kidneys, liver, ovaries, pituitary, spleen, testes, and thyroid) were weighed and organ-to-body weight ratios determined. Microscopic examination was performed on the these organs and samples of the skin, skeletal muscle, mammary glands (females), Harderian and exorbital lachrymal glands, nose, lungs, aorta, parotid, submandibular and sublingual salivary glands, esophagus, forestomach, glandular stomach, small and large intestine, pancreas, urinary bladder, epididymides, prostate, uterus, sternum, mesenteric and axillary lymph nodes, spinal cord, sciatic nerve, and eye in control and high-dose groups. The liver, lungs, stomach, and nose of the low- and mid-dose groups were examined as well as the adrenals, kidneys, spleen, testes, thyroid, ovaries, and pituitary and mammary glands (females) of the third subset killed in week 105. Necropsies were performed on rats found dead or killed when moribund in the course of the study. A slight yellowing of the fur in the rats given mid- and high-dose levels were observed from week 3 onward; this effect was more pronounced in the high-dose group. Liquid consumption decreased 40% in high-dose animals of both sexes; in mid-dose groups,

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liquid consumption decreased as compared to controls, but the differences were not statistically significant. Food consumption at the high dose was significantly decreased in males but showed a less pronounced effect in females. The mean body weights of the high-dose group were decreased from week 1 onward in males and from week 24 onward in females. At the end of the study, there had been a 15% decrease in body weight in males at the 82 mg/kg/day dose and a 10% decrease in females at the 109 mg/kg/day dose. There were no significant differences in the hematological parameters monitored. In the high-dose groups, increased urine density and decreased volume of urine in males (in weeks 27 and 52) and females (in week 27) were observed. Occult blood was found in males of all dose groups in week 27 and in females of the mid- and high-dose groups in week 104. Clinical chemistry variables evaluated between groups during weeks 53 and 105 showed no statistically significant differences and, therefore, no toxicological significance was attached to the slight changes in plasma alkaline phosphatase activity, total plasma protein content, plasma urea level, cholesterol levels, and plasma potassium concentration in weeks 27 and 79 of the study. Absolute heart and liver weights in high-dose males were significantly decreased in weeks 79 and 105, testes weight in week 79, and kidney weight in week 105. These decreases in weight were attributed to lower body weights of animals in this group. Relative kidney weight in females increased in the high-dose group in weeks 53, 79, and 105. Relative brain weight significantly increased in high-dose males in weeks 53, 79, and 105 and in females in week 105. Relative testes weight increased in the high-dose groups in week 105. Necropsy findings of high-dose rats killed in weeks 53, 79, and 105 revealed a raised and thickened limiting ridge of the forestomach. The limiting ridge of the forestomach was raised and thickened in most male and female rats of the high-dose group, and in some males and females of the other groups, including the control group. Also, several rats in the high-dose groups showed irregular mucosal thickenings in the forestomach and/or glandular stomach. These changes were also found in rats of the other groups as well as the control groups. The incidence of discoloration and an irregular surface of the kidneys, which was frequently accompanied by enlarged parathyroids, was lower in males of the high-dose group (12%) than in the controls (33%) in week 105. The incidence of testicular atrophy in the high-dose group (6%) was also remarkably low as compared to controls (24%). In high-dose animals, histopathological examination revealed gastric changes including papillary epithelial hyperplasia accompanied by hyperkeratosis and focal ulceration in the forestomach, and focal chronic atrophic gastritis, occasionally accompanied by ulceration and/or glandular hyperplasia, in the glandular stomach. Histopathological examinations of the kidneys showed that the incidence and degree of renal papillary necrosis increased in week 105 in high-dose animals. Non-neoplastic lesions found in organs other than the stomach or kidneys were not treatment-related. There were no gastric tumors observed apart from two benign papillomas, one in the male of the low-dose group and one in a female control rat.

Effects noted in study and corresponding doses:

15 mg/kg/day: NOAEL for gastrointestinal effects in males.

82 mg/kg/day: gastric changes including papillary epithelial hyperplasia accompanied by hyperkeratosis and focal ulceration in the forestomach and focal chronic atrophic gastritis, occasionally accompanied by ulceration and/or glandular hyperplasia, in the glandular stomach (less serious LOAEL in males), and renal papillary necrosis.

Dose end point used for MRL derivation: NA

[X] NOAEL [ ] LOAEL 15 mg/kg/day

Uncertainty factors used in MRL derivation:

[X] 1 [ ] 3 [ ] 10 (for use of a LOAEL)

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[ ] 1 [ ] 3 [X] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [X] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain: None

Was a conversion used from intermittent to continuous exposure?
If so, explain: None

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: NA

Other additional studies or pertinent information that lend support to this MRL : Gastrointestinal irritation
and damage have been observed in both humans and animals after ingestion of formaldehyde. In human
poisoning studies, effects observed include: ulceration and sloughing of the soft palate and posterior
pharyngeal wall; ulceration of the epiglottis, pyriform fossae and arytenoids; edematous and ulcerated
esophageal mucosa with patches of black, sloughed tissue along the entire length; hyperemic areas of the
stomach; and superficial ulceration in the distal body and antrum after a single dose of 234 mg/kg
formaldehyde (Kochhar et al. 1986); abdominal pain and retching; hard, white and leathery stomach after
a dose of 517 mg/kg (Burkhart et al. 1990), or abdominal pain (Eells et al. 1981). In human poisoning
studies, in which the dose of formaldehyde is usually not known with any accuracy, the gastrointestinal
symptoms include mucosal damage, ulceration and bleeding of the buccal cavity and tonsils, and
dysphagia due to esophageal mucosal damage (Freestone and Bentley 1989). In addition, necrosis of the
esophagus and stomach, extensive congestion, peptic plaques in esophagus and stomach, colitis,
congestion, diffuse necrosis and hemorrhage of gastric and duodenal mucosa, burns in gastrointestinal
mucosa, and ileitis (Koppel et al. 1990) have also been reported. In animals, gastrointestinal irritation and
damage also occurs, which includes thickening of the limiting ridges and hyperkeratosis in the
forestomach and focal atrophic inflammation in the glandular stomach. In addition, slight-to-moderate
focal hyperkeratosis of forestomach, slight-to-moderate focal gastritis, slight-to-moderate submucosal
mononuclear-cell infiltrate (males), focal papillomatous hyperplasia, polymorphonuclear leucocytic
infiltration (females), and moderate papillomatous hyperplasia in one female were noted in rats after
administration of 125 mg/kg/day formaldehyde in the drinking water for 4 weeks (Til et al. 1988b). Tobe
et al. (1989) noted forestomach hyperkeratosis in rats given 50 mg/kg/day formaldehyde in the drinking
water for 15–24 months; neoplastic lesions (Soffritti et al. 1989; Takahashi et al. 1986a) have been
observed in other studies in which formaldehyde was administered orally for longer periods of time.
Thus, gastrointestinal effects appear to be an appropriate indicator of an adverse reaction to oral exposure
to formaldehyde.

It was also noted that the data showed that at 104 weeks of administering 15 mg/kg/day formaldehyde, 27
male rats in the 15 mg/kg group died, which differed significantly from corresponding control values.
However, the deaths were not dose-related, since deaths at 82 mg/kg/day were not significantly different
from control animals. Otherwise, no toxicologically significant difference in mortality was found
between controls and treated animals. This study was also used to derive the EPA Reference Dose (RfD)
of 0.2 mg/kg/day, which is the same number as this chronic oral MRL.

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