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Provisional Peer-Reviewed Toxicity Values for

Formic Acid
(CASRN 64-18-6)

Superfund Health Risk Technical Support Center
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ACRONYMS AND ABBREVIATIONS

BMC	Benchmark Concentration
BMD	Benchmark Dose
BMCL	Benchmark Concentration Lower bound 95% confidence interval
BMDL	Benchmark Dose Lower bound 95% confidence interval
HEC	Human Equivalent Concentration
HED	Human Equivalent Dose
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
LOAEL	lowest-observed-adverse-effect level
$LOAEL_{[ADJ]}$	LOAEL adjusted to continuous exposure duration
$LOAEL_{[HEC]}$	LOAEL adjusted for dosimetric differences across species to a human
NOAEL	no-observed-adverse-effect level
$NOAEL_{[ADJ]}$	NOAEL adjusted to continuous exposure duration
$NOAEL_{[HEC]}$	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional reference concentration (inhalation)
p-RfD	provisional reference dose (oral)
POD	point of departure (oral)
RfC	reference concentration (inhalation)
RfD	reference dose
UF	uncertainty factor
UF_A	animal to human uncertainty factor
UF_C	composite uncertainty factor
UF_D	incomplete to complete database uncertainty factor
UF_H	interhuman uncertainty factor
UF_L	LOAEL to NOAEL uncertainty factor
UF_S	subchronic to chronic uncertainty factor
WOE	weight of evidence

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR FORMIC ACID (CASRN 64-18-6)

BACKGROUND

HISTORY

On December 5, 2003, the U.S. Environmental Protection Agency's (EPA) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1) EPA's Integrated Risk Information System (IRIS).
2) Provisional Peer-Reviewed Toxicity Values (PPRTVs) used in EPA's Superfund Program.
3) Other (peer-reviewed) toxicity values, including
   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
   - California Environmental Protection Agency (CalEPA) values, and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in EPA's IRIS. PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the EPA IRIS Program. All provisional toxicity values receive internal review by a panel of EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multiprogram consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a 5-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV documents conclude that a PPRTV cannot be derived based on inadequate data.

DISCLAIMERS

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and Resource Conservation and Recovery Act (RCRA) program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV document and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

QUESTIONS REGARDING PPRTVS

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

Formic acid occurs naturally in a variety of plants, fruits, mammalian tissues, and insect venoms, and is used in the preparation of a variety of pharmaceuticals, dyes, and chemicals. Formic acid has been identified as the toxic intermediate (formate) in methanol poisoning (NTP, 1992). The empirical formula for formic acid is CH_2O_2 (see Figure 1).

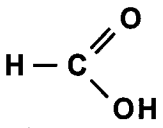

Figure 1. Formic Acid Structure

The U.S. Environmental Protection Agency (U.S. EPA, 2002) Integrated Risk Information System (IRIS) has a listing for formic acid, but no RfD, RfC, or cancer assessment is included. IRIS notes that the RfD was withdrawn in 1990. Formic acid was not included in the Drinking Water Standards and Health Advisories List (U.S. EPA, 2006). The U.S. EPA (1997) Health Effects Assessment Summary Tables (HEAST) listed subchronic and chronic oral RfD values of 2 mg/kg-day for formic acid based on a freestanding NOAEL of 200 mg/kg-day (a LOAEL was not identified). The NOAEL point of departure (POD) in the HEAST assessment was from a multigeneration rat drinking water study of calcium formate (Malorny, 1969) and included an uncertainty factor (UF) of 100 (10 for animal-to-human extrapolation and 10 for intrahuman variability). The source of this derivation was a Health and Environmental Effects Document (HEED) for Formic Acid (U.S. EPA, 1990). Neither the HEAST nor the HEED reported an inhalation toxicity value for formic acid. The HEED classified formic acid in carcinogenicity group D, "Not classifiable as to carcinogenic potential in humans," while no carcinogenicity classification or quantitative assessment of risk was reported in the HEAST. The

Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1991, 1994a) did not report any documents relevant to the toxicity of formic acid other than the HEED (U.S. EPA, 1990).

Neither the Agency for Toxic Substances and Disease Registry (ATSDR, 2008) nor the International Agency for Research on Cancer (IARC, 2008) published documents on formic acid. The World Health Organization (WHO) summarized information on formic acid in the WHO Food Additive Series No. 5 (WHO, 1974). A subsequent WHO (1996) review of ethyl formate concluded an "acceptable daily intake" of up to 3 mg/kg-day for all sources of formic acid. The American Conference of Governmental Industrial Hygienists (ACGIH, 2007), the National Institute for Occupational Safety and Health (NIOSH, 2005), and the Occupational Safety and Health Administration (OSHA, 2008) all adopted 8- to 10-hour per day, time-weighted average (TWA) occupational exposure limits of 5 ppm (9.4 mg/m^3) for formic acid. ACGIH (2001, 2007) also recommended a 15-minute short-term exposure limit of 10 ppm (19 mg/m^3) to protect against skin, eye, mucous membrane, and respiratory tract irritation. Formic acid is on the list of materials used in food packaging and the subsequent, indirect addition to human food that were "generally recognized as safe" (GRAS) by the US Food and Drug Administration (FDA, 1983, 2007; Tracor Jitco, 1974).

Literature searches for studies relevant to the derivation of provisional toxicity values for formic acid (CASRN 64-18-6) were conducted in MEDLINE, TOXLINE special, and DART/ETIC (1960's−September 2010); BIOSIS (2000−August 2008); TSCATS/TSCATS2, RTECS, CCRIS, HSDB, and GENETOX (not date limited); and Current Contents (June−September 2010).

REVIEW OF PERTINENT DATA

HUMAN STUDIES

Oral Exposure

Only one study was located that investigated the effects of repeated exposures of humans to formic acid. Lebbin (1916) reported there were no treatment-related effects in men (number not reported) administered approximately 8 mg/kg-day of formic acid in lemonade for 4 weeks. At unreported doses higher than this, "local actions," presumably effects related to acid irritation, were observed. The secondary sources (Sollmann, 1920; Tracor Jitco, 1974) for the Lebbin (1916) data did not specify duration of exposure at the higher dose and provided no other relevant information. The dose of 8 mg/kg-day might have been a human oral NOAEL for 4-week ingestion of formic acid, but insufficient data were provided.

Rost (1917) reported that 2−4 g of sodium formate daily did not produce toxic effects in human subjects, including an unidentified number with kidney disease. The secondary source of these data (WHO, 1974) noted that a daily therapeutic intake of 2−4 g "could be tolerated for months" without adverse effects.

Numerous case reports of accidental or intentional ingestion of formic acid provided information regarding the adverse effects of acute, high-dose exposure on humans (Westphal et al., 2001; Verstraete et al., 1989; Moore et al., 1994; Rajan et al., 1985; Rosewarne,

1983; Jefferys and Wiseman, 1980; Naik et al., 1980). These reports indicated that ingestion of formic acid can produce irritant and corrosive effects, including ulceration and perforation to the gastrointestinal tract. Systemic effects have included internal hemorrhagic, hemolytic, hematologic, and cardiovascular effects; altered blood chemistry; metabolic acidosis; renal failure; liver toxicity; and CNS depression. The threshold oral dose for formic acid-induced acute mortality ranged from approximately 30 to 45 g (429 to 643 mg/kg, assuming a body weight of 70 kg), with mortality occurring in one of six people exposed to this dose range (Jefferys and Wiseman, 1980). Three surviving subjects developed acute, though reversible, renal failure; all subjects developed hematemesis and exhibited evidence of liver impairment. No deaths occurred in 23 subjects who ingested 5−30 g formic acid; 16 of these subjects developed superficial oropharyngeal burns; 5 had additional symptoms including abdominal pain, dyspnea, and dysphagia; and 2 resulted in more serious localized effects. Oral exposure to single doses greater than 45 g resulted in nearly 100% mortality. Nine of the fourteen deaths reported resulted from corrosive perforations of the abdominal viscera or gastrointestinal hemorrhage. Acute renal failure contributed to the other five deaths in this highly exposed group (Jefferys and Wiseman, 1980).

Inhalation Exposure

Studies on the effects of subchronic or chronic inhalation exposure of humans to formic acid were not found. A case study of a 39-year old man exposed briefly to an aerosol produced from a 98% solution of formic acid reported burns of the face, mild supraglottic erythema, dyspnea, and cough (Yelon et al., 1996).

Liesivuori et al. (1992) investigated the effects of an 8-hour-airborne exposure of 12 male farmers, aged 38 ± 14 years (mean ± SD), to formic acid during silage-making. The study authors measured Formic acid concentrations in the air from samples collected in each farmer's breathing zone. The 8-hour TWA exposures ranged from approximately 75 to 225 nmol/L, equivalent to 3.5 to 10.4 mg formic acid/m^3 (data reported graphically). Other exposures were not reported. Urine samples were collected immediately and 15 and 30 hours following exposure and were analyzed for pH, formic acid, creatinine, ammonium (NH_4^+), and calcium (Ca^{++}). A group of 9 unexposed men, with ages ranging from 26 to 46 years, served as the control group; the criteria used in their selection were not reported.

Urinary excretion of formic acid immediately following exposure was similar to controls, but it was significantly increased 15 and 30 hours after the end of exposure (see Table 1; Liesivuori et al., 1992). Urinary NH_4^+ and Ca^{++} excretion was significantly elevated compared to controls at 30, but not 15, hours after the end of exposure. Urine pH was not affected by formic acid at any time point. No information on any other endpoints was reported. Liesivuori et al. (1992) speculated that increased urinary excretion of NH_4^+ and Ca^{++} resulted from exposure to formic acid because of its inhibition of cytochrome oxidase and the resulting effects on oxidative metabolism of renal tubular cells. However, increased urinary excretion of NH_4^+ is a normal physiological response to an increase in absorbed acids (Suki et al., 2000). Although the study authors presented no evidence to support this hypothesis, Baker and Gullo (1994) and Eells et al. (1996) provided evidence that (1) formic acid inhibits cytochrome oxidase activity at the end of the mitochondrial respiratory chain and (2) this inhibition is the toxicological basis of formic acid toxicity. Liesivuori et al. (1992) reported no clinical signs or other effects.

Table 1. Urinalysis Parameters in Farmers Exposed to Airborne Formic Acid for 8 Hours[a]

Group and Hours After End of Exposure Period	Urine Formic Acid (mmol/mol creatinine)	Urine pH	Urine NH_4^+ (mmol/mol creatinine)	Urine Ca^{++} (mmol/mol creatinine)
Control (*n* = 9)	26 ± 14[b]	5.8 ± 0.5	1.4 ± 0.4	227 ± 72
Workers (*n* = 12)				
0 hrs	31 ± 17 (119)	5.9 ± 0.5 (102)	1.5 ± 0.6 (107)	226 ± 129 (100)
15 hrs	65 ± 45 (250)[c]	5.9 ± 0.5 (102)	1.7 ± 0.6 (121)	241 ± 122 (106)
30 hrs	104 ± 60 (400)[d]	6.0 ± 0.8 (103)	2.3 ± 0.8 (164)[d]	370 ± 175 (163)[c]

[a]Liesivuori et al. (1992).
[b]Means ± SD, (percent of control)
[c]$p \leq 0.05$
[d]$p \leq 0.01$

ANIMAL STUDIES

Oral Exposure

The effects of oral formic acid exposure in animals have not been well studied. About 50 mg/kg in 10% aqueous solution given orally to dogs or 6 mg/kg given subcutaneously to rabbits produced methemoglobinemia lasting about 10 days (Croner and Selligmann, 1907). Daily doses of 0.5 g formic acid in the food had no apparent effects on dogs (Dick, 1909). However, the secondary sources for these data (WHO, 1965, 1974) did not provide study details, such as the duration of treatment, or clearly describe dosing frequency.

Sollmann (1920) administered formic acid in drinking water to groups of 3−6 rats (gender and strain not specified) at the following concentrations, durations, and related average doses reported in the study:

- 0.01% for 11 or 14 weeks, 8.1 or 10.25 mg/kg-day
- 0.1% for 15 weeks, 90 mg/kg-day
- 0.01% (8.1−10.25 mg/kg-day) for 12 weeks, followed by 0.25% for 15 weeks, 160 mg/kg-day
- 0.5% for 9 weeks, 360 mg/kg-day; after 17 weeks at 90 mg/kg-day

Weights of treated animals were compared with "normal weight," which appeared to have come from control groups. Variables measured included food and water consumption, and growth rate assessed by body weight gain over the observation period. One rat of six died in the 8.1 mg/kg-day group and 1/4 died in the 160 mg/kg-day group. Sollmann (1920) reported no meaningful effects on body weight or food consumption at doses up to 160 mg/kg-day. In rats exposed to the highest dose, 360 mg/kg-day, there was a 29% decrease in food consumption and a decrease of 56% or 58% in body weight relative to "normal weight." No treatment-related effects on water consumption were observed throughout the study. No other details were reported. Although there is an incomplete list of toxicological endpoints considered and noting the study's incomplete reporting, this study identified a subchronic NOAEL of 160 mg/kg-day and a LOAEL of 360 mg/kg-day for decreased weight gain among rats treated with formic acid in drinking water. However, the authors noted the weight gain reduction might have resulted

from "failure of appetite," but also could have been related to "local action on digestion" or a "profound disturbance of the acid-base equilibrium."

Bolduan et al. (1988) fed groups of 9−12 weanling pigs diets containing 0, 0.3, 0.35, 1, or 1.2% formic acid for 35 days. Based on initial body weights, average daily weight gains, and average food consumption, the study authors estimated average daily doses to be 0, 121, 159, 437, or 581 mg/kg-day for the 0, 0.3, 0.35, 1, or 1.2% groups, respectively. No adverse effects on body weight gain were observed. In a follow-up study, groups of 3−4 weanling pigs were fed diets containing 0, 0.3, 0.35, 1, or 1.2% formic acid; duration of exposure was not reported. Bolduan et al. (1988) noted no changes in relative liver weight but reported no other organ weight data. Concentrations of organic acids in the stomach appeared not to vary with exposure level. No histologic alterations of the mucosa of the stomach occurred; other histologic endpoints, if evaluated, were not reported. The testing protocol and reporting detail in this study are inadequate for establishing a NOAEL or LOAEL.

Sporn et al. (1962) fed groups of eight young white rats, weighing approximately 40 g (gender and strain not specified), casein-based diets containing 0.5 or 1.0% formic acid for 5 weeks (Replicate 1) or 6 weeks (Replicate 2) to determine effects on growth and "protein efficiency." Estimated daily doses of 500 and 1000 mg/kg-day of formic acid were calculated by assuming daily food intakes equivalent to 10% of body weight for rats in a subchronic study. Control rats received the basal diet without added formic acid. Terminal body weights were slightly (1−8%) lower in treated groups than in controls, but the changes were minimal, did not increase with dose, were not consistent across replicates in the high-dose group, and were not statistically significant. The testing protocol in this study is inadequate for establishing a NOAEL or LOAEL.

In a second experiment, Sporn et al. (1962) administered formic acid in drinking water at 0, 0.5, and 1% concentrations for 7 days to adult white male and female rats. Estimated daily doses of 680 and 1360 mg/kg-day were calculated using reference values for body weight and daily drinking water intake for adult Fischer rats (U.S. EPA, 1988). Sporn et al. (1962) evaluated organ weights (not specified), liver nitrogen and lipids, ascorbic acid content of suprarenal glands, hemoglobin, and blood catalase coefficients. Sporn et al. (1962) concluded that liver nitrogen and suprarenal (adrenal) gland weights were significantly lower than controls in the low-dose (680 mg/kg-day) rats. The reported details are insufficient for establishing a NOAEL or LOAEL.

In a third experiment, Sporn et al. (1962) administered formic acid in drinking water at 0 or 1% for 7 months to 10 male and 50 female adult white rats divided into the following groups:

- I—untreated controls
- II—females only on formic acid throughout the experiment (mated with untreated males)
- III—males only on formic acid throughout the experiment (mated with untreated females)
- IV—both males and females on formic acid throughout the experiment
- V—females on formic acid during lactation.

Two replicates of the experiment were performed but additional details were not available from the secondary source (Tracor Jitco, 1974) for these data. Using body weight and daily drinking water intake reference values for adult Fischer rats (U.S. EPA, 1988), treated rats ingested an estimated average dose of 1360 mg/kg-day. Sporn et al. (1962) evaluated endpoints that included reproductive performance, hematology, liver nitrogen content, and adrenal ascorbic acid content. Evaluations were conducted after 1, 3, and 7 months of exposure. There were decreases in the number of offspring born alive (Replicate 2) and offspring alive 7 days (Replicate 1) and 21 days (Replicate 2) after birth, and in Groups II and IV (i.e., the groups with maternal exposure throughout the experiment) in both replicates (see Table 2). No statistical analysis of these data was available; the secondary source for these data (Tracor Jitco, 1974) provided insufficient details to permit analysis for this review. Hyperchromic anemia, basophilic neutropenia, slight lymphocytosis, and leukocytosis also were observed in rats exposed to formic acid. However, quantitative data were not reported and additional study details were not available. The dose of 1360 mg/kg-day appeared to be a freestanding subchronic LOAEL for reproductive and hematological effects, but the study could not be fully evaluated without review and analysis of the original study report.

Table 2. Effects of Formic Acid in Drinking Water[a] on Reproduction of White Rats[b]

Group	Pregnant Females	Mean Offspring Born	Mean Offspring Born Alive	Mean Offspring Alive at 7 Days	Mean Offspring Alive at 21 Days
Replicate 1					
Controls	6	6.6	6.3	5.0	5.0
Females	6	5.5	5.0	0.5	0.5
Males	8	6.3	6.1	3.8	3.8
Males	5	6.0	5.4	2.2	2.2
Females[c]	6	7.3	7.0	5.5	5.5
Replicate 2					
I	6	6.0	4.0	4.0	4.0
II	6	4.1	2.8	2.1	2.1
III	6	6.3	6.0	6.0	6.0
IV	3	4.0	1.0	0.0	0.0
V	7	6.3	5.7	4.7	4.7

[a]Dose of 1360 mg/kg-day estimated for this review from exposures of 1% formic acid in drinking water
[b]Sporn et al. (1962).
[c]Exposed only during lactation

Malorny (1969) investigated the toxicity of oral formic acid in Wistar rats in a series of three studies. In the first study, 8 males and 24 females were exposed to 0.2% calcium formate in the drinking water; Malorny (1969) calculated daily doses of 150−200 mg calcium formate/kg (equivalent to approximately 104−138 mg formate/kg), based on fluid intake and body weight measurements. A control group of 8 animals (gender not specified) was used. Exposure of the F1 offspring was continued through 5 generations over a 3-year period. This study was poorly reported, including little information on methodology and limited quantitative data on measured endpoints. No treatment-related effects on fertility (specific endpoints not reported), fetal development (fetal weight and length; internal and external malformations), growth, or organ function (details not specified) were reported in any generation of animals. Histopathologic

examination (generation not specified) revealed slightly increased phagocytosis in "moderately proliferated" reticuloendothelial and reticulohistiocytic "elements" of the lungs, spleen, and abdominal lymph nodes; Malorny (1969) described these effects as compensatory rather than toxic. Malorny (1969) attributed no other effects to chronic oral administration of calcium formate. Examination of the digestive tract, liver, kidneys, and "other tissues" revealed no evidence of carcinogenicity; however, it is unclear if a comprehensive examination of all organs and tissues was performed. This study establishes a NOAEL of 104−138 mg/kg-day in Wistar rats.

The second study (Malorny 1969) was identical to the first, except the drinking water concentration of calcium formate was increased to 0.4% and the data were reported for two generations over a 2-year period. Malorny (1969) estimated daily doses as 300−400 mg calcium formate/kg (equivalent to approximately 208−277 mg formate/kg), based on drinking water and body weight measurements. No mortality or treatment-related effects on reproduction, growth, or organ function were observed in any of the exposed animals (data not reported). No histopathologic changes or evidence of cancer were reported, resulting in an apparent freestanding chronic NOAEL of 208−277 mg/kg-day.

In the third study, Malorny (1969) exposed the same number of rats to 1% sodium formate in drinking water for 1−1.5 years and estimated the daily intake as 730 mg sodium formate/kg (equivalent to 450 mg formate/kg). The study appeared to be ongoing at the time of publication and there was no clear statement of results specific to this study. The data are insufficient for establishing a NOAEL or LOAEL.

Dorman et al. (1995) evaluated the neuro-developmental effects of formic acid in CD-1 mice. Groups of 10 to 14 pregnant mice were administered 0 or 750 mg/kg formic acid (purity not reported) in water by gavage on Day 8 of gestation. Effects of exposure on fetal neural tube development were evaluated on Gestational Days 10 or 18. Comprehensive examinations of fetuses were not performed. No significant increase in open anterior neural tubes was observed in formic acid-exposed mice examined on Gestational Days 10 or 18. No information on maternal toxicity was reported. These data identified a single-dose freestanding NOAEL of 750 mg/kg for fetal neural tube development in mice.

Inhalation Exposure

NTP (1992) evaluated the effects of exposure to airborne formic acid in 2-week range-finding and 13-week toxicity studies in F344/N rats and $B6C3F_1$ mice. In the range-finding study, groups of 5 males and 5 females of each species were exposed, whole body, to 0, 31, 62.5, 125, 250, or 500 ppm (0, 58, 118, 235, 470, or 941 mg/m^3) formic acid vapor for 6 hours per day, 5 days per week. Animals were observed twice daily for mortality, moribundity, and clinical signs. Body weights were obtained on study Days 1 and 8 and at necropsy. NTP (1992) evaluated urinalysis, blood coagulation (prothrombin time and activated partial thromboplastin time), serum pH, and serum electrolyte levels at Day 3 and study termination. At death or sacrifice, a gross necropsy was performed on each animal, including histological examination of the lungs, trachea, larynx, bronchial lymph nodes, nose (three transverse sections), and all gross lesions.

In rats, in the 2-week study, 3/5 males and 1/5 females in the 941-mg/m^3 group died on Day 10 of exposure (NTP, 1992). Clinical signs typical of respiratory irritation, including nasal discharge, increased preening, hypoactivity, and labored breathing were observed in males and females in the 470 and 941 mg/m^3 groups (incidence data not reported). Corneal opacity was observed throughout the exposure period in males and females in the 941 mg/m^3 group but was only identified in one male from this group at the end of exposure. A dose-related decrease in body weight gain was observed in the 470 and 941 mg/m^3 groups; final mean body weights were decreased by 7−8% in males and females in the 470 mg/m^3 group and 24% in both males and females in the 941 mg/m^3 group compared to controls. NTP (1992) noted no treatment-related changes were in blood coagulation tests. A small but statistically significant increase in serum sodium level was seen in the high-dose female rats (data not reported); no other changes in serum electrolyte levels or blood pH were noted. Urinalysis revealed decreased urine volume in males and females exposed to 470 mg/m^3 and males exposed to 941 mg/m^3, but no other treatment-related changes.

Absolute and relative thymus weights were up to 50% lower in males and females in the 941 mg/m^3 group; NTP (1992) noted no other statistically significant changes in organ weights. Microscopic examination of the eyes revealed minimal inflammatory cell infiltrate (neutrophils) of the cornea and corneal opacity in the male rats exposed to 941 mg/m^3. Histologic lesions of the upper respiratory tract were similar in males and females, and showed dose-related increases in incidence and severity (see Table 3). Squamous metaplasia of the nose was seen in males and females exposed to $\geq$118 mg/m^3, with 100% incidence in the $\geq$235 mg/m^3 groups for both genders. Severity increased from minimal-to-mild at 118 mg/m^3 and to moderate at 941 mg/m^3. Both genders had nasal respiratory epithelial inflammation and olfactory epithelial necrosis at exposure levels $\geq$235 mg/m^3 and nasal respiratory epithelial necrosis at $\geq$470 mg/m^3. At the highest exposure concentration, squamous metaplasia of the larynx occurred in one male and one female rat. The severity of nasal lesions exhibited dose dependence; nasal lesions in the 971 mg/m^3 group were primarily of moderate severity. NTP (1992) considered lesions in the lower respiratory tract to be unrelated to treatment. These data identified a 6-hour/day, 5-day/week, 2-week NOAEL of 58 mg/m^3 and a LOAEL of 118 mg/m^3 for nasal lesions in male and female rats.

Based on the results of the 2-week range-finding study, NTP (1992) exposed groups of 20 male and 20 female rats, whole body, to formic acid vapor at concentrations of 0, 8, 16, 32, 64, or 128 ppm (0, 15, 30, 60, 120, and 241 mg/m^3) for 6 hours per day, 5 days per week, for 13 weeks. Of the 20 rats/gender/group, 10 rats/gender/group were evaluated after the 13-week exposure period (main study) and 5 rats/gender/group were sacrificed and evaluated for hematology and clinical chemistry after exposure Days 3 and 23. Animals were evaluated daily for mortality and clinical signs; body weights were recorded weekly. The following were evaluated at completion of exposure: hematology; clinical chemistry; sperm morphology and vaginal cytology in the 0, 15, 60, and 241 mg/m^3 groups; complete necropsy, including weights of thymus, heart, right kidney, lungs, liver and right testis; and histopathologic examination of comprehensive tissues in control and high-dose groups and of the upper and lower respiratory tract only (nose, lung, larynx, trachea, and bronchial and mediastinal lymph nodes) in all groups.

Table 3. Incidence of Histopathologic Lesions of the Upper Respiratory Tract in Groups of 5 F344/N Rats Exposed to Airborne Formic Acid, 6 Hours/Day, 5 Days/Week for 2 Weeks[a]

Lesion Location and Type	Exposure Group (mg/m^3)					
	0	58	118	235	470	941
Males						
Nose: respiratory epithelium squamous metaplasia	0/5	0/5	4/5 (1.3)[b]	5/5 (1.8)	5/5 (2.8)	5/5 (2.6)
Nose: respiratory epithelium inflammation	0/5	0/5	0/5	3/5 (1.0)	5/5 (2.4)	5/5 (3.0)
Nose: respiratory epithelium necrosis	0/5	0/5	0/5	0/5	5/5 (2.0)	5/5 (2.6)
Nose: olfactory epithelium necrosis	0/5	0/5	0/5	1/5 (1.0)	2/5 (2.5)	5/5 (2.6)
Larynx: squamous metaplasia	0/5	0/5	0/5	0/5	0/5	1/5 (1.0)
Larynx: inflammation	0/5	0/5	0/5	0/5	0/5	2/5 (1.5)
Females						
Nose: respiratory epithelium squamous metaplasia	0/5	0/5	3/5 (1.6)	5/5 (2.6)	5/5 (3.0)	5/5 (3.0)
Nose: respiratory epithelium inflammation	0/5	0/5	0/5	4/5 (1.3)	5/5 (2.0)	5/5 (3.0)
Nose: respiratory epithelium necrosis	0/5	0/5	0/5	0/5	3/5 (1.6)	5/5 (3.0)
Nose: olfactory epithelium necrosis	0/5	0/5	0/5	1/5 (1.0)	4/5 (1.5)	5/5 (3.0)
Larynx: squamous metaplasia	0/5	0/5	0/5	0/5	0/5	1/5 (1.0)
Larynx: inflammation	0/5	0/5	0/5	0/5	1/5 (1.0)	1/5 (2.0)

[a]NTP (1992).
[b]Incidence and severity score ( ) based on a scale of 1 to 4: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked. Severity scores are averages based on the number of animal with lesions from groups of 5.

NTP (1992) observed no mortalities, treatment-related changes in body weight or body weight gain, or clinical signs of toxicity in rats over the 13-week exposure period. Hematology and clinical chemistry results at Days 3 and 23 were unremarkable. At Week 13, there was evidence of mild hemoconcentration in treated females of all dose groups, including slight increases in red blood cell count, hemoglobin, mean cell volume, and mean cell hemoglobin concentration. All groups of treated rats also had statistically significant decreases in segmented neutrophil counts, including 33−46% decreases in males and 55−63% decreases in females, classified as mild-to-moderate by the study researchers (see Table 4). Decreases in neutrophil counts did not exhibit dose-dependence and were not accompanied by changes in the numbers of other immunological cells or overall white blood cell counts. NTP (1992) did not provide a comparison of neutrophil counts to historical control levels or normal values. However, our comparison of these data to contemporary NTP reports suggested that neutrophil levels in the treated rats at 13 weeks were below the normal control range for F344 rats. The only clinical chemistry changes of note at 13 weeks were statistically significant increases in serum alkaline phosphatase in males and females at 30 mg/m^3 and above (see Table 4). However, the increases were small and not clearly related to dose. There were no effects of formic acid exposure on measures of sperm motility or density, or the length of the estrous cycle in rats.

Table 4. Selected Hematological and Clinical Chemistry Parameters in Groups of 10 Male and Female F344/N Rats Exposed to Airborne Formic Acid, 6 Hours/Day, 5 Days/Week for 13 Weeks[a]

Parameter	Exposure Group (mg/m^3)					
	0	15	30	60	120	241
Males						
WBC count ($10^3/\mu L$)	6.99 ± 0.42[b]	5.51 ± 0.18[c]	5.67 ± 0.26[c]	6.60 ± 0.19	5.97 ± 0.23	5.69 ± 0.24
Segmented neutrophil count ($10^3/\mu L$)	1.51 ± 0.14	0.93 ± 0.07[d]	0.81 ± 0.06[d]	1.01 ± 0.09[d]	0.93 ± 0.10[d]	0.92 ± 0.11[d]
Alkaline phosphatase (IU/L)	325 ± 14	334 ± 11	356 ± 7[c]	354 ± 11	376 ± 7[d]	375 ± 6[d]
Females						
RBC count ($10^6/\mu L$)	9.10 ± 0.04	9.37 ± 0.05[c]	9.34 ± 0.06[c]	9.34 ± 0.10	9.23 ± 0.10	9.39 ± 0.06[c]
Hemoglobin (g/dL)	15.9 ± 0.1	16.5 ± 0.1[d]	16.3 ± 0.1	16.3 ± 0.2	16.1 ± 0.2	16.4 ± 0.1[c]
Mean cell volume (fL)	48.3 ± 0.2	48.2 ± 0.1	47.7 ± 0.2[c]	48.1 ± 0.1	48.1 ± 0.1	47.8 ± 0.1[c]
Mean cell hemoglobin concentration (g/dL)	36.1 ± 0.1	36.4 ± 0.1[d]	36.5 ± 0.1[d]	36.2 ± 0.1[c]	36.4 ± 0.1[c]	36.6 ± 0.1[d]
WBC count ($10^3/\mu L$)	5.57 ± 0.29	5.28 ± 0.26	4.78 ± 0.26	4.95 ± 0.26	4.96 ± 0.38	5.65 ± 0.50
Segmented neutrophil count ($10^3/\mu L$)	1.50 ± 0.15	0.61 ± 0.08[d]	0.56 ± 0.09[d]	0.68 ± 0.05[d]	0.56 ± 0.06[d]	0.64 ± 0.09[d]
Alkaline phosphatase (IU/L)	351 ± 9	375 ± 9	400 ± 11[d]	385 ± 9[d]	392 ± 14[c]	404 ± 13[d]

[a]NTP (1992).
[b]Means ± SE, 10 rats/group
[c]$p \leq 0.05$
[d]$p \leq 0.01$

Necropsy of rats exposed to formic acid for up to 13 weeks did not reveal any unusual gross lesions (NTP, 1992). Thymus weights, which had been markedly decreased at 941 mg/m^3 in the 2-week study, were only slightly decreased after 13-week exposure to 120 or 241 mg/m^3, and they were not affected at lower concentrations (see Table 5). The most prominent effects on organ weight were decreases in absolute and relative lung weight in all treated groups of male and female rats; however, the weight decreases were small and did not exhibit dose dependence. The only other organ weight changes of note were increases in absolute and relative liver weight in male rats, but, again, the changes were small and not dose-related, and no corresponding changes were seen in females. Treatment-related histopathologic changes were limited to minimal metaplasia of the respiratory epithelium and minimal degeneration of the olfactory epithelium of the nose, mainly in the most dorsal section of the dorsal meatus in the nose's anterior section; changes were observed primarily in males and females of the 241 mg/m^3 group, although minimal olfactory degeneration was observed in one male each in the 60 and 120 mg/m^3 groups (see Table 6). Mild inflammatory lesions of the lungs were seen in the control and 60 mg/m^3 exposure groups, but not in other exposure groups. Based on comparison of incidence and severity of upper respiratory lesions observed in the 2- and 13-week studies, there was no evidence that lesions progressed with exposure duration. In fact, NTP (1992) suggested that the data were consistent with an adaptive response to formic acid-induced irritant effects following the initial injury. Minimal effects present after 2 weeks of exposure to 118 mg/m^3 formic acid were not observed in male or female rats exposed to 120 mg/m^3 for 13 weeks and necrosis of the respiratory epithelium observed in rats after 2 weeks exposure to

235 mg/m^3 was not present in rats exposed to 241 mg/m^3 for 13 weeks. After 13 weeks, there was no evidence of hyperplasia, dysplasia or development of a superficial layer of keratinized epithelium in the areas of squamous metaplasia.

Table 5. Selected Organ Weights in Groups of 10 Male and Female F344/N Rats Exposed to Airborne Formic Acid, 6 Hours/Day, 5 Days/Week, for 13 Weeks[a]

Parameter	Exposure Group (mg/m^3)					
	0	15	30	60	120	241
Males						
Absolute liver weight (g)	10.57 ± 0.29[b]	11.74 ± 0.49[c]	11.59 ± 0.27[c]	12.41 ± 0.33[d]	12.46 ± 0.30[d]	11.15 ± 0.44[d]
Relative liver weight (mg organ wt/g body wt)	31.2 ± 0.60	32.7 ± 0.64	32.4 ± 0.57	33.8 ± 0.39[d]	34.1 ± 0.50[d]	33.3 ± 0.96[d]
Absolute lung weight (g)	1.97 ± 0.06	1.76 ± 0.06	1.74 ± 0.06	1.93 ± 0.06	1.66 ± 0.05[d]	1.61 ± 0.04[d]
Relative lung weight (mg organ wt/g body wt)	5.81 ± 0.18	4.90 ± 0.11[d]	4.87 ± 0.12[d]	5.28 ± 0.19[d]	4.54 ± 0.12[d]	4.81 ± 0.05[d]
Absolute thymus weight (g)	0.378 ± 0.010	0.353 ± 0.012	0.341 ± 0.010	0.400 ± 0.024	0.355 ± 0.010	0.325 ± 0.012[c]
Relative thymus weight (mg organ wt/g body wt)	1.12 ± 0.03	0.99 ± 0.03	0.95 ± 0.03	1.09 ± 0.07	0.97 ± 0.03[c]	0.98 ± 0.05[c]
Females						
Absolute liver weight (g)	6.28 ± 0.18	6.32 ± 0.27	6.07 ± 0.18	6.15 ± 0.20	6.29 ± 0.27	5.91 ± 0.19
Relative liver weight (mg organ wt/g body wt)	29.6 ± 0.68	30.2 ± 0.64	29.6 ± 0.63	29.8 ± 0.60	30.4 ± 1.02	29.3 ± 0.47
Absolute lung weight (g)	1.47 ± 0.06	1.24 ± 0.05[d]	1.20 ± 0.03[d]	1.25 ± 0.04[d]	1.17 ± 0.03[d]	1.24 ± 0.04[d]
Relative lung weight (mg organ wt/g body wt)	6.97 ± 0.30	5.96 ± 0.21[d]	5.85 ± 0.17[d]	6.06 ± 0.14[d]	5.68 ± 0.10[d]	6.18 ± 0.23[d]
Absolute thymus weight (g)	0.289 ± 0.019	0.280 ± 0.019	0.258 ± 0.008	0.267 ± 0.013	0.267 ± 0.010	0.272 ± 0.014
Relative thymus weight (mg organ wt/g body wt)	1.36 ± 0.08	1.34 ± 0.08	1.26 ± 0.05	1.30 ± 0.07	1.29 ± 0.04	1.34 ± 0.05

[a]NTP (1992).
[b]Means ± SE, 10 rats/group
[c]$p \leq 0.05$
[d]$p \leq 0.01$

Table 6. Incidence of Histopathologic Lesions of the Upper Respiratory Tract in Groups of 10 Male and Female F344/N Rats Exposed to Airborne Formic Acid, 6 Hours/Day, 5 Days/Week for 13 Weeks[a]

Lesion Location and Type	Exposure Group (mg/m^3)					
	0	15	30	60	120	241
Males						
Nose: respiratory epithelium squamous metaplasia	0	0	0	0	0	9 (1.0)[b]
Nose: olfactory epithelium degeneration	0	0	0	1 (1.0)	1 (1.0)	9 (1.2)
Females						
Nose: respiratory epithelium squamous metaplasia	0	0	0	0	0	6 (1.4)
Nose: olfactory epithelium degeneration	0	0	0	0	0	5 (1.0)

[a]NTP (1992).
[b]Incidence and severity score ( ) based on a scale of 1 to 4: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked. Severity scores are averages based on the number of animal with lesions from groups of 10.

NTP (1992) identified a NOAEL for formic acid vapor exposure of 120 mg/m^3 based on nasal lesions. Although NTP (1992) indicated that the 13-week study in rats provided no significant evidence of systemic toxicity, some systemic changes were observed. These included decreases in neutrophil counts, observed in both genders at the lowest concentration (30 mg/m^3), and increases in serum alkaline phosphatase levels observed at higher concentrations. All of these changes were found in most or all treated groups, and in both genders of rats; however, none exhibited dose dependence. Although the changes in lung weights were small in magnitude and there were no histological findings in the lung to support an effect on this organ, they were observed in both genders. In contrast, the decreases in neutrophil counts were relatively large (approximately 40−60%) and a brief review of other NTP 13-week studies suggested that neutrophil levels in treated rats were below the normal range observed in contemporaneous control F344 rats from those NTP studies. NTP considered potential causes of this neutropenia, including decreased production of neutrophils in bone marrow and increased margination or sequestration from the circulation into tissues in response to chemotactic factors released at sites of inflammation. Because histopathological examination of bone marrow did not reveal formic acid-induced abnormalities, neutropenia did not appear to be related to bone marrow toxicity or to increased alkaline phosphatase activity that also can be caused by bone disease. The potential mechanism of increased margination in response to inflammation also did not provide an adequate explanation for neutropenia because NTP (1992) did not observe upper airway inflammation after 13 weeks of exposure and did observe pulmonary inflammation only in the control and 60 mg/m^3 groups. Although the toxicological significance of the observed neutropenia is uncertain, the evidence for discounting this effect is inconclusive. In addition, increases in serum alkaline phosphatase appear to begin at the lowest exposure level. Therefore, based on neutropenia and increased serum alkaline phosphatase, the LOAEL for rats exposed to airborne formic acid for 13 weeks is identified as 15 mg/m^3; a NOAEL was not established.

The 2- and 13-week studies conducted by NTP (1992) in $B6C3F_1$ mice followed the same study design and methodology as those described above for the NTP (1992) studies in rats, except that blood was not analyzed for hematology or clinical chemistry in the mouse studies, and 3-day and 23-day sacrifices were not made in the 13-week study. In mice exposed to formic acid vapor at concentrations of 0, 31, 62.5, 125, 250, or 500 ppm (equivalent to 0, 58, 118, 235, 470, or 941 mg/m^3) for 2 weeks, 1 female in the 470 mg/m^3 group died on Day 4 and all mice in the 941 mg/m^3 group died during the first week of exposure. Necropsy of mice that died revealed that the gastrointestinal tract was distended with air, indicative of swelling and occlusion of the nasal passages and subsequent swallowing of air. During the exposure period, nasal discharge, increased preening, hypoactivity, and labored breathing were observed in mice exposed to $\geq$470 mg/m^3; clinical signs were not observed in other exposure groups (incidence data not reported). Corneal opacity was present in males and females exposed to 941 mg/m^3 (incidence data not reported). At the end of the 2-week exposure period, terminal body weights were significantly decreased by 19 and 16% in males and females, respectively, in the 470 mg/m^3 group compared to controls; there were no survivors in the 941 mg/m^3 group.

No gross lesions were observed in treated mice at study termination (NTP, 1992). Relative kidney weights were decreased by approximately 10% in males exposed to 118, 235, and 470 mg/m^3 and in females exposed to 470 mg/m^3 (actual weights not reported). Absolute and relative thymus weights were reduced, and relative lung weights were increased in mice exposed to 470 mg/m^3 (actual weights not reported). Histopathological examination of the upper respiratory tract showed lesions of the nasal respiratory epithelium in female mice exposed to $\geq$118 mg/m^3 and male mice exposed to $\geq$235 mg/m^3. Increasing exposure concentration resulted in increased severity of lesions, as well as lesions of the olfactory epithelium, larynx, and pharynx (see Table 7). Based on histologic alterations of the nasal respiratory epithelia in female mice exposed to formic acid 6 hr/day, 5 day/wk, for 2 weeks, NOAEL and LOAEL values were identified as 58 mg/m^3 and 118 mg/m^3, respectively.

Based on the results of the 2-week studies, groups of 10 male and 10 female mice were exposed to 0, 8, 16, 32, 64, or 128 ppm (0, 15, 30, 60, 120, or 241 mg/m^3, respectively) for 13 weeks (NTP, 1992). No mortality or clinical signs were associated with exposure of male and female mice to formic acid concentrations up to 241 mg/m^3. Body weights were significantly reduced, relative to controls, in male mice exposed to 241 mg/m^3 and in female mice exposed to 120 mg/m^3 or greater ($p \leq 0.01$). Changes in organ weights were limited mainly to increases in relative weights in animals in the 241 mg/m^3 groups, which the study authors suggested were due to lower body weights in the 241 mg/m^3 group, compared to controls. However, small increases in relative lung, liver, and kidney weights were seen sporadically in the 60 and 120 mg/m^3 groups. Sperm morphology and mobility, and vaginal cytology in formic acid groups were similar to controls. No treatment-related gross lesions were observed. Microscopic changes attributed to the toxicity of formic acid were limited to degeneration of the olfactory epithelium of the nose (in the dorsal portion of the dorsal meatus) in a few mice from the 120 mg/m^3 (2/10 females) and 241 mg/m^3 (2/10 males, 5/10 females) groups; in all cases, the lesions were of minimal (1.0) severity (see Table 8). For degeneration of the olfactory epithelium in female mice, 6 hr/day, 5 day/wk, 13-week NOAEL and LOAEL values of 60 mg/m^3 and 120 mg/m^3, respectively, were identified.

Table 7. Incidence of Histopathologic Lesions of the Upper Respiratory Tract in Groups of 10 Male and Female B6C3F$_1$ Mice Exposed to Airborne Formic Acid, 6 Hours/Day, 5 Days/Week, for 2 Weeks[a]

Lesion Location and Type	Exposure Group (mg/m^3)					
	0	58	118	235	470	941
Males						
Nose: respiratory epithelium squamous metaplasia	0	0	0	3 (1.3)	4 (1.3)	1 (1.0)
Nose: respiratory epithelium inflammation	0	0	0	2 (1.0)	4 (1.2)	5 (1.4)
Nose: respiratory epithelium necrosis	0	0	0	0	0	4 (3.5)
Nose: olfactory epithelium degeneration	0	0	0	0	3 (1.3)	1 (2.0)
Nose: olfactory epithelium necrosis	0	0	0	0	0	3 (2.0)
Larynx: squamous metaplasia	0	0	0	0	0	5 (2.8)
Larynx: inflammation	0	0	0	0	0	3 (1.0)
Pharynx: necrosis	0	0	0	0	0	3 (2.0)
Females						
Nose: respiratory epithelium squamous metaplasia	0	0	2 (1.0)	3 (1.3)	4 (1.0)	0
Nose: respiratory epithelium inflammation	0	0	0	2 (1.5)	5 (1.4)	5 (1.8)
Nose: respiratory epithelium necrosis	0	0	0	0	2 (1.5)	5 (3.6)
Nose: olfactory epithelium degeneration	0	0	0	0	2 (2.0)	0
Nose: olfactory epithelium necrosis	0	0	0	0	1 (1.0)	5 (1.8)
Larynx: squamous metaplasia	0	0	0	0	0	1 (2.0)
Larynx: inflammation	0	0	0	0	0	3 (1.0)
Larynx: necrosis	0	0	0	0	0	5 (2.2)
Pharynx: necrosis	0	0	0	0	0	2 (1.0)

[a]NTP (1992).
[b]Incidence and severity score ( ) based on a scale of 1 to 4: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked. Severity scores are averages based on the number of animal with lesions from groups of 5.

Table 8. Incidence of Histopathologic Lesions of the Upper Respiratory Tract in Groups of 10 Male and Female B6C3F$_1$ Mice Exposed to Airborne Formic Acid, 6 Hours/Day, 5 Days/Week, for 13 Weeks[a]

Lesion Location and Type	Exposure Group (mg/m^3)					
	0	15	30	60	120	241
Males						
Nose: olfactory epithelium degeneration	0	0	0	0	0	2 (1.0)[b]
Females						
Nose: olfactory epithelium degeneration	0	0	0	0	2 (1.0)	5 (1.0)

[a]NTP (1992).
[b]Incidence and severity score ( ) based on a scale of 1 to 4: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked. Severity scores are averages based on the number of animal with lesions from groups of 10.

No studies were found regarding the chronic, reproductive, or developmental effects of animal inhalation exposures to formic acid.

OTHER STUDIES

Genotoxicity Studies

Formic acid has tested negative for reverse mutation in *Salmonella typhimurium* strains TA97, TA98, TA100 and TA1535 (NTP, 1992; Zeiger et al., 1992) with and without metabolic activation, but positive for forward mutation in *E. coli* (Demerec et al., 1951). Negative results were obtained in a DNA inactivation assay in DNA donor strain *Bacillus subtilis* 60009 (Freese et al., 1967). Stumm-Tegethoff (1969) reported that formic acid was positive for mutations in *Drosophila*, both by vapor exposure and when added to the larval medium; however, the larval mutations might have been the result of low pH of the medium. Formic acid was negative for clastogenicity in Chinese hamster ovary cells, although reduced pH in vitro was found to be clastogenic, regardless of the source (Morita et al., 1990). Sipi et al. (1992) reported that formic acid was positive for sister-chromatid exchanges in human lymphocytes; the increases were small in magnitude but statistically significant.

Toxicokinetic Studies

Rauckman (2003) summarized evidence demonstrating that the formate ion is the primary determinant of systemic toxicity from formic acid and other formates, including sodium, calcium, and methyl formate. Nihlén and Droz (2000) developed a four-compartment toxicokinetic model for human inhalation exposure to methyl formate. The compartments identified included methyl formate, the metabolites, methanol and formic acid, and a urinary compartment from which formic acid could be reabsorbed. They demonstrated that the urinary reabsorption was saturable because urinary excretion increased more than marginally only following high exposures.

Lund (1948a,b, as cited in Pölönen, 2000) reported that rabbits excreted very little formic acid in urine after subcutaneous formic acid injections whereas dogs excreted 40%, suggesting large interspecies differences in renal elimination of formate. Croner and Selligmann (1907) observed that rabbits excreted no administered formate, whereas dogs excreted about half the

administered formate unchanged in the urine. However, the secondary source for these data (WHO, 1965, 1974) did not provide information on quantity or route of the dose. Citing these data and the relative amounts of formate excreted by man, dogs, and rabbits receiving methanol, WHO (1965, 1974) hypothesized that formate metabolism in human beings was between that found in dogs and rabbits.

None of the studies discussed above addressed the potential for optic nerve damage following internal formic acid exposure. It is well established that the formate metabolite is responsible for optic nerve and retinal toxicity following ingestion of large quantities of methanol (Tong, 1982; Sejersted et al., 1983; Timbrell, 2000; Fox and Boyes, 2001; Barceloux et al., 2002; Treichel et al., 2003).

Hanzlik et al. (2005) performed a study of calcium formate uptake and excretion in healthy young adult (age 19−33) women. After fasting for more than 10 hours, serum formate concentrations increased from 0.028 (± 0.013) to 0.050 (± 0.040) mM approximately 60 minutes after oral administration of 3900 mg calcium formate (2700 mg formate) in capsules. Serum concentrations then declined monoexponentially with a mean half life of 59 (± 7) minutes, returning to baseline values 225 minutes after dosing. By comparison, clinical case reports and experimental studies in nonhuman primates have suggested that irreversible damage to the optic nerve and retina occurred only when formate blood concentrations exceed 7 mM for at least 24 hours (Kavat and Nauss, 1990; Eells, 1992; Eells et al., 1996, 2000). Hayasaka et al. (2001) demonstrated that intravitreal injection of 100 microliters 1% formate into rabbit eyes resulted in no histological changes after one month. The data of Boeniger (1987), Yasugi et al. (1992), D'Alessandro et al. (1994), and Baumann and Angerer (1979) indicated that urinary formic acid concentrations vary widely but generally have been <20 mg/L among people without occupational exposure.

An additional issue for consideration, as discussed by NTP (1992), is that the rodent may not be the best model for the systemic toxicity of formic acid in humans. In primates, the primary system for formate metabolism is a folate-dependent pathway that converts formate and CO_2 to tetrahydrofolate. Activity of 10-formyl tetrahydrofolate dehydrogenase, the enzyme that catalyzes the conversion of 10-formyl tetrahydrofolate, an intermediate in the metabolism pathway, to CO_2 and tetrahydrofolate is much lower in primate livers than in rat livers. Hepatic metabolism of formate is, therefore, considerably faster in rodents than in primates, which may result in rodents being less sensitive to the effects of formic acid after oral exposure than humans or nonhuman primates. Evidence for this possibility comes from studies of methanol, for which the proximate toxicant is formate.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR FORMIC ACID

Human data on the subchronic or chronic oral toxicity of formic acid were limited to a single 4-week study of an unspecified number of male volunteers who received formic acid in lemonade (Lebbin, 1916). Although no adverse effects were reported, no information was available regarding the endpoints examined. The secondary source (Sollmann, 1920; Tracor Jitco, 1974) for these data indicated that doses higher than the initial 8 mg/kg-day dose resulted

in "local actions." However, those higher dose levels, durations of exposure, and specific findings were not reported. Case reports of acute oral exposure to formic acid provided descriptions of effects from fatal or near-fatal doses; these data are not useful for quantitative risk assessment (Westphal et al., 2001; Verstraete et al., 1989; Moore et al., 1994; Rajan et al., 1985; Rosewarne, 1983; Jefferys and Wiseman, 1980; Naik et al., 1980).

Available animal data on the oral toxicity of formic acid are of limited utility for risk assessment. The studies assessed a limited number of endpoints, and they were poorly described; in most cases, the numeric data were not presented and were insufficient for statistical analyses. Target organ effects were not identified in any of these studies. Nonspecific effects reported included decreases in growth rate and food consumption in rats exposed to 0.5% formic acid (360 mg/kg-day) in drinking water (Sollmann, 1920) and reduced postpartum survival of offspring of rats exposed to approximately 1360 mg/kg-day formic acid in drinking water (Sporn et al., 1962). However, the reliability of these data could not be assessed due to lack of details in the secondary source (Tracor Jitco, 1974) about study methodology and results. No other data were identified to support the plausibility of these effects. In addition, neither of these effects was found in the multigeneration rat drinking water study by Malorny (1969) in which rats received doses as high as 277 mg/kg-day. Malorny (1969) reported slightly increased phagocytosis in "moderately proliferated" reticuloendothelial and reticulohistiocytic "elements" of the lungs, spleen, and abdominal lymph nodes in rats exposed to 0.2% calcium formate (estimated dose of 104−138 mg formic acid/kg-day) throughout 5 generations over a 3-year period. Due to inadequate reporting, it is unclear which specific generation of rats exhibited effects in the 3-year study, when the rats were evaluated, or the magnitude or incidence of the effects. Similar findings were not observed in rats exposed to higher doses (208−277 or 450 mg formic acid/kg-day) for 1 to 2 years (Malorny, 1969); thus, the toxicological significance and relationship of findings to treatment could not be established.

Formate takes part in the metabolism of one-carbon compounds and its carbon may appear in methyl groups undergoing transmethylation. Using rabbits and dogs as animal models, Croner and Selligmann (1907) and Lund (1948a,b, as cited in Pölönen, 2000) reported large interspecies differences in the metabolism of formic acid.

Table 9 presents potential PODs from the oral data along with human lethality data. Each of these studies provided data that were not considered ideal for the derivation of p-RfDs. The highest degree of confidence is placed in the Malorney (1969) multigeneration study. This study provided a NOAEL of 277 mg/kg-day that is supported by chronic, developmental, and reproductive freestanding NOAELs of 138−450 mg/kg-day (Malorny, 1969), LOAELs of 680 and 1360 mg/kg-day (Sporn et al., 1962), and the NOAEL of 160 mg/kg-day (Sollmann, 1920) in rats.

Table 9. Potential Points of Departure for Oral Exposure to Formic Acid

Species	Study	Endpoint	Duration	NOAEL (mg/kg-day)	LOAEL (mg/kg-day)	Media
Humans	Lebbin, 1916	"local actions"	4 wks	8	NR[a]	Lemonade
Rats	Sollmann, 1920	Weight gain	9−15 wks	160 (0.25%)	360[b] (0.5%)	Water
Rats	Sporn et al., 1962	Weight gain	5−6 wks	1000 (1%)	------	Diet
Rats	Sporn et al., 1962	Liver nitrogen; suprarenal gland weight	7 days	------	680 (0.5%)	Water
Rats	Sporn et al., 1962	postpartum (7 days) survival; hyperchromic anemia[c]	7 months	------	1360 (1%)	Water
Rats	Malorny, 1969	Multiple	3 years	138	------	Water
Rats	Malorny, 1969	Repro, growth, organ function	2 years	277	------	Water
Weanling pigs	Bolduan et al., 1988	Organ and body weight	5 wks	581	------	Diet
Mice	Dorman et al., 1995	Fetal neural tube development	1 day	750	------	Gavage (water)

[a]Unspecified local effects were reported at unspecified higher doses.
[b]56−58% reduction in weight gain, accompanied by a 29% decrease in food consumption.
[c]Leucocytosis, basophil neutropenia, and slight lymphocytosis also were reported in individual treated rats.

To derive the subchronic p-RfD, the Malorny (1969) NOAEL of 277 mg/kg-day in a multigeneration reproduction study in rats was used as the POD, with a composite UF of 300, composed of the following:

- A UF of 10 was applied to account for potential differences between rats and humans.
- A UF of 10 was applied for human variability because of the lack of adequate data addressing sensitive human populations.
- A partial UF of 3 ($10^{0.5}$) was applied for database insufficiencies because, although limited, studies on developmental and reproductive toxicity are available

$$\textbf{Subchronic p-RfD} = \text{POD} \div \text{UF} = 277 \text{ mg/kg-day} \div 300 = \mathbf{0.9 \text{ or } 9 \times 10^{-1} \text{ mg/kg-day}}$$

To derive the chronic p-RfD, the NOAEL of 277 mg/kg-day in rats from the 2-year, multigeneration-reproduction/chronic-toxicity study by Malorny (1969) was used as the POD, with a composite UF of 300 composed of the following, as described for the subchronic derivation, above:

- A UF of 10 for extrapolation from animal data to humans.
- A UF of 10 for human variability.
- A UF of 3 for database uncertainties.

- A UF of 1 was applied for subchronic-to-chronic extrapolation because chronic toxicity data are available (Malorny et al., 1969) and do not suggest increasing toxicity with increasing exposure duration.

Chronic p-RfD = POD ÷ UF
= 277 mg/kg-day ÷ 300
= **0.9 or 9×10^{-1} mg/kg-day**.

For each oral derivation, confidence in the key study is low. The principal study (Malorny, 1969) in rats was both a multigeneration reproduction and chronic study, with the reproduction component representing the subchronic exposure period. The study seemed to have a comprehensive design for evaluating general reproductive and long-term toxicity, but was poorly reported. Confidence in the database is low, as other studies were very old and not well-reported. In addition, optic nerve and retinal toxicity resulting from formic acid as a metabolite of methanol, were not specifically studied. Low confidence in both the subchronic and the chronic p-RfD follows.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR FORMIC ACID

No human studies investigating the effects of subchronic or chronic inhalation exposure to formic acid were found.

Data on the effects of repeated airborne exposure of experimental animals to formic acid were limited to the 2- and 13-week NTP (1992) studies in rats and mice; chronic data were not available.

Histopathologic indications of irritation of the upper respiratory tract were observed in male and female rats and mice exposed to formic acid vapor for 2 or 13 weeks. In the 2-week studies, NTP (1992) reported NOAEL and LOAEL values of 58 and 118 mg/m^3, respectively, for squamous metaplasia of the respiratory epithelium in male and female rats (see Table 3) and female mice (see Table 7) (NTP, 1992). In the 13-week study, formic acid vapor NOAEL and LOAEL values of 60 and 120 mg/m^3 were reported for degeneration of the olfactory epithelium in female mice (see Table 9). Histopathological changes were not accompanied by clinical signs of respiratory irritation at any exposure concentration in the 2- or 13-week studies. The NTP (1992) studies showed that incidence and severity of lesions increased with exposure concentration, but not with exposure duration, indicating that tolerance to respiratory irritation may develop over a subchronic exposure period. NTP (1992) described this as an adaptive effect, similar to that seen with other respiratory tract irritants. The NTP (1992) study establishes 2-week and 13-week NOAELs of 58 and 60 mg/m^3, respectively, for respiratory lesions among male and female rats, and female mice.

Neutropenia was observed in male and female rats exposed for 13 weeks to formic acid at all concentrations, although decreases in neutrophil counts did not exhibit dose dependence (NTP, 1992). As shown in Table 4, segmented neutrophil counts were decreased by 33 to 46% in exposed male rats and 55 to 63% in exposed female rats. This finding could not be

corroborated in mice because the mouse study did not evaluate hematology (NTP, 1992). Potential causes of neutropenia have included decreased bone marrow production of neutrophils and increased margination or sequestration of neutrophils from the circulation into tissues, in response to chemotactic factors released at sites of inflammation. Because histopathological examination of bone marrow did not reveal formic acid induced abnormalities, neutropenia did not appear related to bone marrow toxicity. A potential mechanism of increased margination in response to inflammation also was unlikely to be related to the neutropenia, since upper airway inflammation was not observed in any 13-week exposure group and was observed only at concentrations of 241 mg/m^3 or greater after 2 weeks of exposure. Thus, other processes may have been involved in the development of neutropenia. Although neutropenia has been associated with an increased risk of infection, NTP (1992) did not report any specific information on the incidence of infection in rats exposed to inhaled formic acid for 13 weeks; however, no clinical signs of toxicity, including signs of infection, were observed. No additional information regarding possible effects of exposure to airborne formic acid on neutrophils or other immune cells was identified. Although the toxicological significance of decreased neutrophil counts observed in the NTP (1992) study was unclear, the study indicated a potential for airborne exposure to formic acid to produce adverse effects on neutrophils.

NTP (1992) observed liver, lung, and thymus weight changes, however, effects on liver and lung weights were not consistent. Absolute liver weights were increased in male rats (see Table 5) and absolute and relative weights were increased in male mice (see Table 8), but absolute weights were decreased in female mice (see Table 8). Absolute lung weights decreased in male rats (see Table 5) and male mice (see Table 8), as did absolute and relative lung weights in female rats (see Table 5). However, relative lung weights increased in female mice (see Table 8). NTP (1992) observed decreased relative thymus weights only in male rats (see Table 5), with no absolute or relative thymus weight changes observed in female rats or male or female mice. Histopathologic examination of livers, lungs, and thymus revealed no abnormalities. In rats, serum alkaline phosphatase activity was increased in both males and females starting at 15 mg/m^3 (see Table 4). No changes in serum activities of sorbitol dehydrogenase and alanine aminotransferase were observed in rats, and clinical chemistry was not evaluated in mice. Organ weight changes were small and did not exhibit a dose-response relationship. The organ weight changes also were inconsistent in direction (e.g., increased or decreased), and there was no histopathological evidence of toxicity in these organs.

In summary, for the NTP (1992) study, 15 mg/m^3 is considered to be a LOAEL for subchronic inhalation of formic acid based on neutropenia and increased serum alkaline phosphatase in male and female rats.

SUBCHRONIC p-RfC

The lesions of the upper respiratory tract in rats and mice and decreased neutrophil counts in rats were identified as potential critical effects for derivation of the subchronic p-RfC for formic acid. The NOAELs and LOAELs for both effects were converted to human equivalent concentrations (HEC).

To calculate the HECs for neutropenia, neutropenia was classified as an extrarespiratory effect and considered formic acid to be a category 3 gas. The upper respiratory tract lesions were considered to be an extrathoracic respiratory effect, treating formic acid as a category 1 gas as

defined in EPA (1994b). Thus, the 6 hour/day, 5 day/week exposure concentrations were first adjusted to reflect potential continuous exposure (see Table 10), using the following formula.

$$NOAEL_{[ADJ]} \text{ or } LOAEL_{[ADJ]} = NOAEL \text{ or } LOAEL \times 6/24 \times 5/7$$

For upper respiratory effects:

$$NOAEL_{[ADJ]} = 58 \text{ mg/m}^3 \times 6/24 \times 5/7$$
$$= 10.4 \text{ mg/m}^3 \text{ and}$$

$$LOAEL_{[ADJ]} = 118 \text{ mg/m}^3 \times 6/24 \times 5/7$$
$$= 21.1 \text{ mg/m}^3$$

For neutropenia:

$$LOAEL_{[ADJ]} = LOAEL \times 6/24 \times 5/7$$
$$= 15 \text{ mg/m}^3 \times 6/24 \times 5/7$$
$$= 2.7 \text{ mg/m}^3$$

Table 10. Human Equivalent Concentration (HEC) NOAELs and LOAELs for Upper Respiratory Tract Lesions in Rats and Mice Exposed to Airborne Formic Acid[a]

Species (Gender)	Duration	$NOAEL_{[ADJ]}$ (mg/m^3)	$LOAEL_{[ADJ]}$ (mg/m^3)	$RGDR_{ET}$	$NOAEL_{[HEC]}$ (mg/m^3)	$LOAEL_{[HEC]}$ (mg/m^3)
Rats (M)	2 weeks	10.4	21.1	0.113	1.2	2.4
Rats (F)	2 weeks	10.4	21.1	0.089	0.93	1.9
Mice (M)	2 weeks	21.1	42.0	0.133	2.8	5.6
Mice (F)	2 weeks	10.4	21.1	0.116	1.2	2.4
Rats (M)	13 weeks	21.4	43.0	0.162	3.5	7.0
Rats (F)	13 weeks	21.4	43.0	0.122	2.6	5.2
Mice (M)	13 weeks	21.4	43.0	0.174	3.7	7.5
Mice (F)	13 weeks	10.7	21.4	0.145	1.6	3.1

[a]NTP (1992)
M: males; F: females
NOAELs and LOAELs adjusted from 6 hr/day, 5 day/wk exposure to reflect average concentrations for continuous exposures.

The $NOAEL_{[HEC]}$ and $LOAEL_{[HEC]}$ values presented in Table 10 were calculated from the adjusted values, as follows, using average body weights for control male and female rats and mice in the 2- and 13-week NTP (1992) studies and U.S. EPA (1994b) default values for humans:

$NOAEL_{[HEC]}$ or $LOAEL_{[HEC]}$ = ($NOAEL_{[ADJ]}$ or $LOAEL_{[ADJ]}$) ($RGDR_{ET}$)

$$RGDR_{ET} = \frac{(Dose_{ET})_A}{(Dose_{ET})_H} = \frac{(V_E \div SA_{ET})_A}{(V_E \div SA_{ET})_H}$$

where:

$(V_E)_A$ = 116.9 cm^3/min [minute volume for male rat (0.148 kg body weight), 2-week study];
91.6 cm^3/min [minute volume for female rat (0.110 kg body weight), 2-week study];
27.6 cm^3/min [minute volume for male mouse (0.024 kg body weight), 2-week study];
24.0 cm^3/min [minute volume for female mouse (0.021 kg body weight), 2-week study];
167.3 cm^3/min [minute volume for male rat (0.299 kg body weight), 13-week study];
125.9 cm^3/min [minute volume for female rat (0.162 kg body weight), 13-week study];
36.1 cm^3/min [minute volume for male mouse (0.031 kg body weight), 13-week study];
30.0 cm^3/min [minute volume for female mouse (0.026 kg body weight), 13-week study]

$(V_E)_H$ = minute volume for 70 kg human (13,800 cm^3/min)

$(SA_{ET})_A$ = surface area of extrathoracic region for rat (15 cm^2) or mouse (3 cm^2)

$(SA_{ET})_H$ = surface area of extrathoracic region for 70 kg human (200 cm^2)

The values given for $(V_E)_H$, $(SA_{ET})_H$, and $(SA_{ET})_A$ are recommended as reference values in EPA (1994a). Values for $(V_E)_A$ were calculated from average body weights for control male and female rats and mice in the 2- and 13-week NTP (1992) studies using the EPA (1994b) scaling algorithm for rats and mice:

$$\ln(V_E)_A = -0.578 + 0.821 \cdot \ln(BW)$$

For extrarespiratory effects (neutropenia), formic acid was treated as a category 3 gas, as defined by EPA (1994b). The corresponding $LOAEL_{[HEC]}$ for extrarespiratory effects was calculated from the adjusted LOAEL using the following equation, where $(H_{b/g})_A$ and $(H_{b/g})_H$ are the blood/gas partition coefficients for formic acid in the animal (i.e., rat or mouse) and human, respectively. Because the blood-gas partition coefficients for formic acid were unknown in humans or rodents, the EPA (1994b) default value of 1.0 for the ratio of $(H_{b/g})_A \div (H_{b/g})$ was used. The $LOAEL_{[HEC]}$ of 2.7 mg/m^3 for neutropenia in male and female rats was calculated as follows:

$$LOAEL_{[HEC]} = LOAEL_{[ADJ]} \times (H_{b/g})_A \div (H_{b/g})_H$$
$$= 2.7 \text{ mg/m}^3 \times 1$$
$$= 2.7 \text{ mg/m}^3$$

A NOAEL was not established for neutropenia.

Based on the outcomes of the 2-week and 13-week studies, nasal lesions developed within 2 weeks of exposure to formic acid and persisted, with no apparent increase in severity, for up to 13 weeks. Therefore, exposure-response data for the lesions at both time points was modeled to estimate the BMCL for nasal lesions. The data for nasal lesions in rats and mice

exposed for 2 weeks (Tables 3 and 7) were evaluated for suitability for BMD analysis using BMD Modeling Software (BMDS, Version 1.3.2; U.S. EPA, 2000). The data set for nasal lesions in male mice was eliminated from consideration because nasal lesions occurred at a higher exposure levels, yielding a higher $NOAEL_{[HEC]}$ (see Table 10). The data set for nasal lesions (squamous metaplasia) in female mice was eliminated from consideration because of the nonmonotic nature of the response. Appendix B summarizes the results of BMD analysis for 2-week HECs of formic acid resulting in nasal lesions in rats. For nasal lesions in both male and female rats exposed for 2 weeks, the Log-Logistic model provided the best fit, yielding a $BMCL_{10[HEC]}$ values of 0.92 mg/m^{3}and 0.75 mg/m^3, respectively.

The data sets for nasal lesions in rats and mice exposed for 13 weeks (Tables 6 and 8) were evaluated to determine their suitability for BMD analysis using BMDS. The data sets for female rats and male mice were eliminated from consideration because the lesions were observed only at the highest concentration tested. Appendix B summarizes the results of the BMDS modeling for nasal lesions in male rats and female mice exposed to formic acid 6 hours/day, 5 days/week, for 13 weeks. For nasal lesions in male rats, the 4-degree multistage model provided the best fit, with a $BMCL_{10[HEC]}$ of 1.39 mg/m^3. For female mice, the log-probit model provided the best fit, with a $BMCL_{10[HEC]}$ of 1.5 mg/m^3.

The data sets for neutropenia in male and female rats (see Table 3) were analyzed using the Pearson (parametric) and Spearman (rank order) correlations to test independence of exposure group mean values for neutrophil counts and group exposure concentrations (Statgraphics version 15.0.04; StatPoint, Inc., 2007). Correlations were not significant ($p \geq 0.05$), indicating that means for segmented neutrophil counts were not significantly dependent on exposure concentration (i.e., there was no trend in neutrophil counts with changing exposure concentration). Because no trend was observed, the data sets were considered unsuitable for BMD analysis. In addition, neither of the data sets for increased serum alkaline phosphatase for male and female rats (see Table 4) could be fit adequately by any of the BMDS models. Thus, the $LOAEL_{[HEC]}$ of 2.7 mg/m^3 was used as the POD for neutropenia and increased serum alkaline phosphatase.

Table 11 summarizes the PODs derived for nasal lesions and neutropenia. For nasal lesions, $BMDL_{10[HEC]}$ PODs ranged from 0.29 mg/m^3 (female mice) to 0.91 mg/m^3 (male rats) after 2 weeks of exposure and 0.48 mg/m^3 (male rats) to 1.8 mg/m^3 (female mice) after 13 weeks of exposure. Similar $BMDL_{10[HEC]}$ values for 2 and 13 weeks exposure suggests that increasing exposure duration does not increase the magnitude of the response.

Table 11. Potential Points of Departure (POD) for the subchronic p-RfC[a]

Species/Gender	Exposure Duration	Effect	POD (mg/m^3)
Rats/Male	2 weeks	Nasal lesions	0.91 ($BMCL_{10[HEC]}$)
Rats/Female	2 weeks	Nasal lesions	0.75 ($BMCL_{10[HEC]}$)
Mice/Female	**2 weeks**	**Nasal lesions**	1.2 ($NOAEL_{[HEC]}$)
Rats/Male	13 weeks	Nasal lesions	1.39 ($BMCL_{10[HEC]}$)
Mice/Female	13 weeks	Nasal lesions	1.84 ($BMCL_{10[HEC]}$)
Rats/Male and Female	13 weeks	Neutropenia, increased serum alkaline phosphatase	2.7 ($LOAEL_{[HEC]}$)

[a]All data from NTP (1992).

Based on the critical effects of neutropenia and increased serum alkaline phosphatase in rats (NTP, 1992), the $LOAEL_{[HEC]}$ of 2.7 mg/m^3 is selected as the POD for the subchronic p-RfC for formic acid, which is derived as follows:

Subchronic p-RfC = $LOAEL_{[HEC]} \div UF$
= $2.7\ mg/m^3 \div 3000$
= **0.0009 or 9×10^{-4} mg/m^3**

The composite uncertainty factor of 3000 was derived as follows:

- A UF of 10 was applied for the lack of a NOAEL.
- A UF of 10 for human variability is applied to account for potentially susceptible individuals in the absence of quantitative information on the variability of response in humans. Individuals with rhinitis or other upper airway disorders may be more susceptible to inhaled irritants (Shusterman et al., 2005) such as formic acid.
- A partial UF of 3 ($10^{0.5}$) is applied to account for potential toxicodynamic differences between mice and humans; toxicokinetic differences were addressed by application of standard dosimetric adjustments in calculation of the HEC (U.S. EPA, 1994b).
- A UF of 10 is applied for database insufficiencies due to the lack of developmental toxicity and multigeneration reproduction studies for inhaled formic acid. Although limited developmental and reproductive toxicity data are available for oral exposure, the rapid metabolism of formic acid in the liver of rodents suggests a significant first-pass effect, which would preclude the use of oral exposure data as a surrogate for inhalation exposure data.

Confidence in the key study is medium. NTP (1992) evaluated appropriate and comprehensive endpoints in rats, but it did not include an investigation of hematological or clinical chemistry in mice. Although male and female rats and mice were tested at both 2 and 13 weeks, the study included only a small number of animals in each group. Confidence in the database is low. Subchronic inhalation studies have been conducted in two species and supporting subchronic oral studies were available, but all studies except one oral study were conducted in rodents, which may not be the best model for systemic toxicity of formic acid in humans due to species differences in metabolism. Developmental toxicity and multigeneration reproductive toxicity studies using the inhalation route of exposure have not been conducted, although a multigeneration oral study has been conducted in rats. Low confidence in the subchronic p-RfC results.

CHRONIC p-RfC

A chronic p-RfC is not derived because the composite uncertainty factor would be 10,000. However, a screening chronic p-RfC can be found in Appendix A.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR FORMIC ACID

WEIGHT-OF-EVIDENCE DESCRIPTOR

No studies evaluating the carcinogenic potential of oral or inhalation exposure to formic acid in humans were located. No evidence of carcinogenesis was observed in rats exposed by drinking water to 0.2% calcium formate (104−138 mg formate/kg-day) for 3 years, 0.4% calcium formate (208−277 mg formate/kg-day) for 2 years, or 1% sodium formate (450 mg formate/kg-day) for 1 to 1.5 years (Malorny, 1969). However, the Malorny (1969) study was poorly reported and did not provide sufficient information to determine if comprehensive tissues were examined for nonmalignant and malignant lesions. Cancer bioassays for formic acid have not been conducted in animals with inhalation exposure. Available genotoxicity assays of formic acid yielded mixed results that may be dependent on the ability of the assay to correct for formic acid-induced pH changes. Under the 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), there is "*Inadequate Information to Assess the Carcinogenic Potential*" of formic acid.

QUANTITATIVE ESTIMATES OF CARCINOGENIC RISK

The lack of suitable data precludes the derivation of quantitative estimates of cancer risk for formic acid.

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APPENDIX A. DERIVATION OF A SCREENING VALUE FOR FORMIC ACID

For reasons noted in the main PPRTV document, it is inappropriate to derive provisional toxicity values for formic acid. However, information is available for this chemical which, although insufficient to support derivation of a provisional toxicity value, under current guidelines, may be of limited use to risk assessors. In such cases, the Superfund Health Risk Technical Support Center summarizes available information in an Appendix and develops a "screening value." Appendices receive the same level of internal and external scientific peer review as the PPRTV documents to ensure their appropriateness within the limitations detailed in the document. Users of screening toxicity values in an appendix to a PPRTV assessment should understand that there is considerably more uncertainty associated with the derivation of an appendix screening toxicity value than for a value presented in the body of the assessment. Questions or concerns about the appropriate use of screening values should be directed to the Superfund Health Risk Technical Support Center.

In the absence of chronic toxicity data in humans or animals, the chronic p-RfC was based on the same POD as that used for derivation of the subchronic p-RfC ($LOAEL_{[HEC]}$ = 2.7 mg/m^3 for neutropenia and increased serum alkaline phosphatase [NTP, 1992]). The uncertainty factors are the same as for the subchronic p-RfC except for the addition of a 10-fold factor for extrapolation from subchronic to chronic exposure duration. This would result in a nominal 30,000-fold composite UF, but by convention the maximum UF for screening values is 10,000. Thus, the screening chronic p-RfC for formic acid is derived as follows:

$$\begin{aligned} \textbf{Screening Chronic p-RfC} &= LOAEL_{[HEC]} \div UF \\ &= 2.7\ mg/m^3 \div 10{,}000 \\ &= \mathbf{0.0003\ or\ 3 \times 10^{-4}\ mg/m^3} \end{aligned}$$

The composite UF of 10,000 is composed of the following:

- A UF of 10 was applied for the lack of a NOAEL.
- A UF of 10 for intraspecies differences is applied to account for potentially susceptible individuals in the absence of quantitative information on the variability of response in humans. Individuals with rhinitis or other upper airway disorders may be more susceptible than others to inhaled formic acid.
- A partial UF of 3 ($10^{0.5}$) is applied to account for potential toxicodynamic differences between mice and humans; toxicokinetic differences are addressed by application of standard dosimetric adjustments (U.S. EPA, 1994b).
- A UF of 10 is applied for extrapolation from subchronic to chronic exposure duration.
- A UF of 10 is applied for database insufficiencies due to the lack of developmental toxicity and multigeneration reproduction studies for inhaled formic acid
- The product of all individual UFs of 30,000 is reduced to 10,000 by convention for screening values.

Confidence in the key study is medium. NTP (1992) evaluated appropriate and comprehensive endpoints in rats, but it did not include investigation of hematological or clinical chemistry in mice. Although male and female rats and mice were tested at both 2 and 13 weeks,

the study included only a small number of animals in each group. Confidence in the database is low. Subchronic inhalation studies have been conducted in two species and supporting subchronic oral studies are available, but all the studies except one oral study have been conducted in rodents, which may not be the best model for systemic toxicity of formic acid in humans due to species differences in metabolism. Developmental toxicity and multigeneration reproductive toxicity studies by the inhalation route of exposure had not been conducted. Although limited developmental and reproductive toxicity data are available for oral exposure, the rapid metabolism of formic acid in the liver of rodents suggests a significant first-pass effect, which would preclude the use of oral exposure data as a surrogate for inhalation exposure data. Low confidence in the chronic p-RfC resulted.

APPENDIX B. BENCHMARK DOSE ANALYSIS OF NASAL LESIONS IN RATS AND MICE FOR POSSIBLE DERIVATION OF SUBCHRONIC AND CHRONIC p-RfCS

Nasal lesions in rats and mice following exposure to inhaled formic acid for 2 or 13 weeks were identified as a potential critical effect for derivation of the subchronic and chronic p-RfCs. To determine the POD for derivation of the p-RfC based on nasal lesions, data sets for squamous metaplasia of the respiratory epithelium in male and female rats and female mice exposed to inhaled formic acid for 2 weeks (see Table A-1) and degeneration of the olfactory epithelium in male rats and female mice exposed for 13 weeks (see Table A-2) were modeled using BMDS (Version 1.3.2) developed by the NCEA (U.S. EPA, 2000). In accordance with the EPA (2000) BMD methodology, the default benchmark response (BMR) of a 10% increase in extra risk was used as the basis for the BMC (BMC_{10}), with the $BMCL_{10}$ represented by the 95% lower confidence limit on the BMC_{10}. All available dichotomous models were fit to the incidence data for nasal lesions in rats and mice exposed to formic acid for 2 (see Table A-1) or 13 weeks (see Table A-2). The goodness-of-fit was evaluated using the Chi-square statistic calculated by the BMDS program. Acceptable global goodness-of-fit is a Chi-square *p*-value greater than or equal to 0.1. Models that did not meet this criterion were eliminated from consideration. Local fit was evaluated by visually comparing the observed and estimated results at each data point on the graphic output, and by comparing the Chi-square residual values nearest the BMR. Comparing across models, the model with the lowest Akaike's information criterion (AIC) initially was considered to provide a superior fit.

Table A-3 summarizes the results of the BMDS modeling for nasal lesions in male and female rats and female mice exposed to formic acid for 2 weeks. Note that the concentrations reported are not adjusted for continuous exposure duration; those adjustments were made later, in the main text of the PPRTV document. For nasal lesions in male rats, adequate fit to the data was observed for all dichotomous models in the BMDS except the Weibull. Comparing across models, the Log-Logistic model provided the lowest AIC (U.S. EPA, 2000), yielding a $BMCL_{10[HEC]}$ of 5.13 mg/m^3 (see Figure A-1). The 1-degree multistage model fit was rejected because of a poor fit to the lowest-dose data. Results are similar for female rats. Incidence data for nasal lesions in female rats were adequately fit by all models except the Weibull. Comparing across models, the Log-Logistic model provided the lowest AIC, yielding a $BMCL_{10[HEC]}$ of 4.19 mg/m^3 (see Figure A-2).

Table A-4 summarizes the results of the BMDS modeling for nasal lesions in male rats and female mice exposed to formic acid for 13 weeks. For nasal lesions in male rats, adequate fits to the data were observed for most models in the BMDS. Comparing across models, the logistic model provided the best fit, as indicated by the lowest AIC, yielding a $BMCL_{10[HEC]}$ of 11.62 mg/m^3 (see Figure A-4). For female mice, incidence data for nasal lesions were adequately fit by all dichotomous models in the BMDS. Comparing across models, the log-probit model provided the best fit, as indicated by the lowest AIC and yielded a $BMCL_{10[HEC]}$ of 8.55 mg/m^3 (see Table A-4).

Table A-1. Incidence of Nasal Lesions in Groups of Five Rats and Mice Exposed to Airborne Formic Acid, 6 Hours/Day, 5 Days/Week, for 2 Weeks[a]

Species/ Gender	Parameter	Exposure Group(mg/m^3)					
		0	**58**	**118**	**235**	**470**	**941**
Rats/ Male	HEC[b]	0	6.6	13.3	26.6	53.1	106.3
	Nasal respiratory epithelium squamous metaplasia	0	0	4	5	5	5
Rats/ Female	HEC[b]	0	5.2	10.5	20.9	41.8	83.7
	Nasal respiratory epithelium squamous metaplasia	0	0	3	5	5	5

[a]NTP (1992).
[b]HEC = (exposure in mg/m^3)x($RGDR_{ET}$); for male rats exposed for 2 weeks $RGDR_{ET}$ = 0.113; for female rats exposed for 2 weeks $RGDR_{ET}$ = 0.089; for female mice exposed for 2 weeks $RGDR_{ET}$ = 0.116

Table A-2. Incidence of Nasal Lesions in Groups of Ten Rats and Mice Exposed to Airborne Formic Acid, 6 Hours/Day, 5 Days/Week, for 13 Weeks[a]

Species/Gender (Duration)	Parameter	Exposure Group(mg/m^3)					
		0	**15**	**30**	**60**	**120**	**241**
Rats/Male	HEC[b]	0	2.4	4.9	9.7	19.4	39.0
	olfactory epithelium degeneration	0	0	0	1	1	9
Mice/Female	HEC[b]	0	2.2	4.4	8.7	17.4	34.9
	olfactory epithelium degeneration	0	0	0	0	2	5

[a]NTP (1992).
[b]HEC = (exposure in mg/m^3)x($RGDR_{ET}$); for male rats exposed for 13 weeks $RGDR_{ET}$ = 0.162; for female mice exposed for 13 weeks $RGDR_{ET}$ = 0.145

Table A-3. Goodness-of-Fit Statistics and BMC10s and $BMCL_{10}$s from Models of Incidence Data for Squamous Metaplasia of the Respiratory Epithelium in Male and Female Rats and Female Mice Exposed to Airborne Formic Acid, 6 Hours/Day, 5 Days/Week, for 2 Weeks[a]

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 *p*-Value[b]	AIC	$BMC_{10[HEC]}$ (mg/m^3)	$BMCL_{10[HEC]}$ (mg/m^3)
Male Rats—All Doses Included						
Gamma[c]	5	0.12	0.9997	7.23222	8.1011	4.63832
Logistic	4	0.00	1.0000	9.00402	12.1418	4.71754
Log-Logistic[d,e]	**5**	**0.00**	**1.0000**	**7.00417**	**10.8991**	**5.13021**
Multistage 1-Degree[f,]	5	4.72	0.4514	14.1972	1.27102	0.726551
Probit	4	0.00	1.0000	9.00402	11.1153	4.52629
Log-Probit[e]	4	0.00	1.0000	9.00402	10.6014	5.15996
Female Rats—All Doses Included						
Gamma[c]	5	0.04	1.0000	8.80227	7.21829	3.69697
Logistic	4	0.00	1.0000	10.7301	9.7774	3.86688
Log-Logistic[d,e]	**5**	**0.00**	**1.0000**	**8.73019**	**9.08643**	**4.19178**
Multistage 1-Degree[f,g]	5	3.97	0.5537	15.2989	1.20754	0.699013
Probit	4	1.63	1.0000	10.7301	9.13633	3.58282
Log-Probit[e]	4	0.00	1.0000	10.7301	8.76909	4.15687

[a]NTP (1992).
[b]Values <0.1 fail to meet conventional goodness-of-fit criteria
[c]Power restricted to ≥ 1
[d]Best-fitting model(s)
[e]Slope restricted to ≥ 1
[f]Betas restricted to ≥ 0
[g]Model output presented for the lowest degree polynomial with adequate fit
NA: model did not generate output values

Table A-4. Goodness-of-Fit Statistics and BMC_{10}s and $BMCL_{10}$s from Models of Incidence Data for Olfactory Epithelial Degeneration in Male Rats and Female Mice Exposed to Airborne Formic Acid, 6 Hours/Day, 5 Days/Week, for 13 Weeks[a]

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 *p*-Value[b]	AIC	$BMC_{10[HEC]}$ (mg/m^3)	$BMCL_{10[HEC]}$ (mg/m^3)
Male Rats						
Gamma[c]	3	3.09	0.3779	28.3447	20.1136	9.02608
Logistic[d]	**4**	**2.26**	**0.6874**	**25.4038**	**16.793**	**11.6166**
Log-Logistic[e]	4	4.25	0.3731	26.8688	14.5911	9.20839
Multistage 1-Degree[f,]	5	9.31	0.0974	33.7305	5.17381	3.22991
Multistage 4-Degree[f,]	4	1.59	0.8098	25.1352	15.6426	7.75841
Probit	4	2.38	0.6670	25.5378	15.5076	10.6514
Log-Probit[e]	4	4.33	0.3632	27.6323	13.2701	8.55509
Weibull[c]	4	2.71	0.6075	25.7215	14.74	9.11921
Female Mice						
Gamma[c]	4	0.60	0.9635	28.6694	15.245	8.39739
Logistic	4	2.16	0.7066	30.3468	18.6911	13.0173
Log-Logistic[e]	4	0.61	0.9620	28.7261	15.1298	8.28125
Multistage 1-Degree[f,]	5	2.95	0.7079	30.5939	8.49579	4.81388
Probit	4	1.63	0.8031	29.7379	17.5767	12.1626
Log-Probit[e]	4	0.40	0.9828	28.4233	14.8802	8.54703
Weibull[c]	4	0.77	0.9423	28.9215	15.3894	8.13333

[a]NTP (1992).
[b]Values <0.1 fail to meet conventional goodness-of-fit criteria
[c]Power restricted to ≥ 1
[d]Best-fitting model(s)
[e]Slope restricted to ≥ 1
[f]Betas restricted to ≥ 0