Formic acid

(CAS No: 64-18-6)

Health-based Reassessment of Administrative Occupational Exposure Limits

Committee on Updating of Occupational Exposure Limits,
a committee of the Health Council of the Netherlands

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1 Introduction

The present document contains the assessment of the health hazard of formic acid by the Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands. The first draft of this document was prepared by AAE Wibowo, Ph.D. (Coronel Institute, Academic Medical Centre, Amsterdam, the Netherlands).

In October 1997, literature was searched in the databases Medline, Toxline, Chemical Abstracts, and Embase (starting from 1966, 1967, 1970, and 1988, respectively), and HSELINE, CISDOC, MHIDAS, and NIOSHTIC (from 1997 backwards), and using the following key words: formic acid, hydroxycarboxylic acid, methanoic acid, and 64-18-6.

In December 1998, the President of the Health Council released a draft of the document for public review. Comments were received by the following individuals and organisations: WF ten Berge, Ph.D. (DSM N.V., Heerlen, the Netherlands), J Liesivuori, Ph.D. (University of Kuopio, Kuopio, Finland), P Wardenbach, Ph.D. (Bundesanstalt für Arbeitsschutz and Arbeitsmedizin, Dortmund, Germany), and SD Williams (BP Chemicals Ltd., Sunbury on Thames, UK). These comments were taken into account in deciding on a revised version of the document. The committee acknowledges the following experts who were consulted on the relevance of animal data: prof. Y Alarie, Ph.D. (University of Pittsburgh, Pittsburg PA, USA), T Gordon, Ph.D. (New York University Medical Center, Tuxedo NY, USA), E Oostveen, Ph.D. (Medisch Spectrum Twente, Enschede, the Netherlands), J Pauluhn, Ph.D. (Bayer AG, Wuppertal, FRG), MM Schaper, Ph.D. (U.S. Department of Labor, Arlington VA, USA). An additional literature search was performed in Medline and Toxline in November 2004.

In December 2004, the President of the Health Council released a revised draft of the document for public review. Comments were received from the following individuals and organisations: E Ball (Health and Safety Executive, London, UK) and T Scheffers (DSM-Chemelot, Geleen, the Netherlands). These comments were taken into account in deciding on the final version of the document.

2 Identity

name	: formic acid
synonyms	: hydrogen carboxylic acid; methanoic acid; formylic acid; aminic acid
molecular formula	: CH_2O_2
structural formula	: HCOOH
CAS number	: 64-18-6

3 Physical and chemical properties

molecular weight	: 46.2
boiling point	: 100.8ºC
melting point	: 8.4ºC
flash point	: 59ºC (open cup); 69ºC (closed cup)
vapour pressure	: at 20ºC: 4.2 kPa
solubility in water	: miscible
log $P_{octanol/water}$	: -0.54 (experimental); -0.46 (estimated)
conversion factors	: at 20ºC, 101.3 kPa: 1 ppm = 1.93 mg/m^3 1 mg/m^3 = 0.52 ppm

Data from Gre03, NLM04, http://www.syrres.com/esc/est_kowdemo.htm.

Formic acid is a colourless volatile fluid with a pungent, stinging odour. It is a strong acid (at 25ºC: pKa=3.75) (ACG02).

Odour thresholds of 0.05-38 (0.03-20 ppm) (Rut86) and of 95 mg/m^3 (49 ppm) (Amo83) have been listed.

4 Uses

Formic acid is used in dyeing and finishing of textiles and paper, treatment of leather, electroplating and brewing, silvering glass, and as an intermediate in the manufacture of many chemicals. Formic acid is used also in preservative solutions (ACG02, NLM04).

5 Biotransformation and kinetics

The committee did not find data on the biotransformation and kinetics following inhalation exposure to formic acid.

Formate is an endogenous, metabolic intermediate. Via the tetrahydrofolate-dependent one-carbon pathway, endogenous and exogenous formate/formic acid can be incorporated into biological macromolecules or oxidised to CO_2. It enters the pathway by combining with tetrahydrofolate (THF) to form 10-formyl-THF, a reaction catalysed by formyl-THF synthetase. 10-Formyl-THF may then be oxidised into CO_2 (and THF) by formyl-THF dehydrogenase. Some formic acid is eliminated as its sodium salt (IARC95, Kat94, Lie91, WHO89). Having higher hepatic THF levels and higher 10-formyl-THF dehydrogenase activities, rodents metabolise formic acid more rapidly than do primates in which oxidation might become saturated resulting in accumulation of formate in blood (Gre03, Lie91, Nai97). Formate oxidation rates were 300 mg/kg/h in mice, 78 mg/kg/h in rats, and 40 mg/kg/h in monkeys. Humans should oxidise formate at a rate similar to that in monkeys (Joh87, Tep91).

In rabbits intravenously injected with daily doses of buffered formic acid of 100 mg/kg bw for 5 days, sampling 1, 2, or 20 hours after the fifth dose always showed highest formic acid levels in the urine when compared to the organs. Apart from the brain, having the peak level (1.3 µmol/g) at 2 hours, levels in kidney (1.7 µmol/g), liver (1.5 µmol/g), heart (0.8 µmol/g), and blood (0.7 µmol/g) were highest 1 hour after the final injection. At 20 hours, formic acid was still present (brain: 0.7 µmol/g; kidney: 0.4 µmol/g; liver: 0.3 µmol/g; heart: 0.5 µmol/g; blood: 0.2 µmol/g). Total formic acid levels were always higher than ^{14}C-labelled levels, emanating from radiolabelled formic acid given the fifth time. The findings pointed to an accumulation of formic acid and a slower elimination from the brain (Lie87a).

The elimination of formic acid from the human body, as seen in farmers occupationally exposed to formic acid and in methanol poisoning cases, seems to be an unexpectedly slow process. The half-life of formic acid determined in methanol poisoning cases has been as long as 20 hours. The slow renal clearance of formic acid may be caused by zero-order kinetics in metabolism as well as in urinary clearance. Another explanation for the slow excretion is the continuous recycling of formic acid and protons with chloride in the kidneys (Lie86, Lie91).

Based on *in vitro*/*in situ* experiments using a perfused rat liver system and *in vivo* experiments in which rats were intravenously injected with sodium formate doses of 41-492 mg/kg bw (resulting in blood formate levels of 1-12 mmol/L), Damian and Raabe developed a quantitative, toxicokinetic model of *in vivo* formate elimination in the rat. The model consisted of a central, well-mixed compartment and a urine compartment. Other features of the model were endogenous formate production, Michaelis-Menten hepatic formate metabolism,

and renal excretion consisting primarily of glomerular filtration and saturable tubular reabsorption. The model showed that at doses that produced plasma concentrations close to the endogenous levels (i.e., ca. 1 mmol/L), formate is eliminated almost entirely by metabolism (92%). At higher dose levels of 4, 8, and 12 mmol/L, however, the proportion eliminated by urinary excretion increased to 34, 45, and 55%, respectively. Furthermore, this urinary excretion was extremely rapid with most excretion occurring within 3 hours of dosing (Dam96).

The long half-life of formic acid favours the delayed collection of urine samples in the biological monitoring of occupationally exposed workers. Liesivuori and Savolainen examined 10 workers (5 females and 5 males) in Finland, occupationally exposed to formic acid concentrations between 4.1-11.3 mg/m^3 (2.0-5.5 ppm; 8-hour TWA). The corresponding concentrations of urinary formic acid in the samples taken on Friday morning, 16 hours after the preceding work shift, were between 21.2 -118 mg/g creatinine. There was a linear correlation (r=0.88) between the formic acid concentrations in the air (in mg/m^3) and in the urine (in mg/g creatinine) sampled 16 hours after exposure (regression equation: y = 13.3 x). No correlation was found between formic acid levels in air and urine sampled immediately after the work shift (Lie87b).

In morning urine samples from non-exposed (Finnish) controls (6 females and 12 males), formic acid levels were 15 (±6.1) mg/g creatinine (Lie87b). In a Japanese study on workers occupationally exposed to methanol, arithmetic and geometric mean formic acid concentrations in urine of non-exposed controls amounted to 17.4 (±12.1) and 14.6 (±1.8) mg/g creatinine, respectively, in men (n=79) and to 28.8 (±11.3) and 26.5 (±1.5) mg/g creatinine, respectively in women (n=70) (Yas92). In a German study, the median formic acid level in the urine of 70 non-exposed persons was 14.1 mg/g creatinine (range: 1.2-278.7 mg/g creatinine). There were statistically significant differences in formic acid levels between pregnant and non-pregnant women and between children and adults. The 95th percentile in adults was 23 mg/g creatinine. In the course of the day, urinary formic acid levels may vary considerably as was seen in some persons upon analysis of urine samples collected at 3-hour intervals. This variation was attributed to the intake of large amounts of formic acid with food. Formic acid levels in morning urine sampled on 3 consecutive days differed at most by a factor of almost 3 (Sch94). In another German study, the median formic acid concentration in the urine in non-exposed adults (n=94; age: 20-80 years) was 12 mg/L (mean: 21 mg/L; range: 1-190 mg/L; 95th percentile: 60

mg/L). Smoking and dietary habits had no influence on formic acid excretion in urine, but age was positively correlated with increased concentrations (Hei92).

6 Effects and mechanism of action

Human data

Being a strong acid, the committee is of the opinion that formic acid can have irritating to corrosive effects on the respiratory tract, eyes, and skin following inhalation or dermal exposure. However, the committee found hardly any human data on irritation. Referring to a study published in 1936, von Oettingen reported that contact of formic acid with human skin caused moderate pungent pain, some erythema, and hyperaemia, and, later, cooked appearance and parchment-like necrosis with a slow tendency to heal (Oet59).

Following oral accidental or intentional exposure, formic acid caused severe local corrosion of the gastrointestinal tract accompanied by oesophageal stricture, stomach perforation, and haemorrhage. Further, nausea, vomiting, difficulties in swallowing, unconsciousness, metabolic acidosis, haemolysis, coagulation disorders, liver function disorders, reduced blood pressure, acute renal failure, and inflammation of the lungs were reported. Death, from gastrointestinal tract perforation or acute renal failure, occurred as well (BUA95). Reviewing data from the beginning of the 20th century, von Oettingen stated that no effects were seen in human subjects given 500 mg formic acid as lemonade for 4 weeks or intravenous injections of 20 mL of a 20% sodium formate solution (duration not presented). Administration of doses of formate of 2000-3000 mg, several times a day, were stated to cause vertigo, nausea, vomiting, albuminuria, haematuria, tenesmus, dyspnoea, and lowering of body temperature (Oet59).

Liesivuori et al. performed a cross-sectional study on 12 male farmers in Finland (mean age: 38±14 years) who were exposed to formic acid for several days during silage making, with formic acid levels amounting to 7.3 mg/m^3 (3.8 ppm; 8-hour time-weighted average) on the day of the study. They had worked in their current occupation for an average of 17 years. The excretion of formate was linearly related to exposure, 15 and 30 hours after the exposure. No changes were detected in the urinary pH of the exposed subjects, whereas urinary ammonia and calcium levels were increased being statistically significant at 30 hours after exposure (104 and 370 mmol/mol creatinine, respectively, vs. 26 and 227 mmol/mol creatinine, respectively, in 8 controls) (Lie92). However, the

committee judges the concentrations of ammonia and calcium in the urine of the exposed group to be within the normal range.

As appears from the Documentation of Threshold Limit Values published by ACGIH in 1971, Katz and Guest stated that workers in a textile plant exposed to formic acid concentrations of about 27 mg/m^3 (15 ppm) complained of nausea (Kat94). However, since this information is not included in recent versions of the ACGIH documentation (ACG91, ACG02), the committee doubts the reliability of this finding.

Fritschi and Siemiatycki carried out a case-control study addressing tumours at 19 different sites, including lymphoma and myeloma, in order to generate hypotheses about the occupational causes of these 2 cancers. Out of the 3730 patients interviewed (i.e., 82% of the eligible cancer patients), 215 had non-Hodgkin's lymphoma, 2 of them having had 'substantial' and 2 others 'non-substantial' exposure to formic acid (Fri96). Because of the small number of persons with exposure to formic acid and the lack of adequate information on exposure, the committee does not draw conclusions with respect to potential carcinogenic effects of formic acid in humans from this study.

Animal data

Irritation and sensitisation

According to OECD guidelines for the testing of chemicals*, substances with pH$\leq$2 or $\geq$11.5 (and high buffering capacity, if relevant) do not need to be tested for their skin- and eye-irritating potential but are assumed to be corrosive.

Referring to a study published in 1883, von Oettingen reported that application to the shaved skin of rabbits had resulted in the destruction of the cutis and in corrosion (Oet59). Referring to a data sheet of a chemical company produced in 1968, NIOSH stated that 610 mg applied to the skin of rabbits resulted in mild irritation in an open irritation test (NIO04). Sekizawa et al. tested, among other things, formic acid to evaluate a stepwise screening test for skin and eye irritation suitable for chemicals which are not required to be examined for their exact potential irritancy levels according to OECD guidelines (see above). A solution of 10% had a pH of <2.0. The minimum concentration

* OECD guideline for testing of chemicals No. 404. Acute dermal irritation/corrosion (adopted: 24th April 2002); OECD guideline for testing of chemicals No. 405. Acute eye irritation/corrosion (adopted: 24th April 2002).

which induced moderate to severe effects after unoccluded application of 1 mL/kg bw to the clipped skin of rats and mice was 10-12% (Sek94).

In a study published in 1910, application of pure liquid formic acid to the cornea of rabbits was found to cause immediate local opacity. Although this began to clear in 5 days, hypopyon, posterior subcapsular lens opacity, absence of portions of corneal endothelium, infiltration and growth of new blood vessels at the limbus, and infiltrated and hyperaemic iris were seen. Application of a 10% solution for 5 minutes caused similar effects but hypopyon was not observed (Gra86). Referring to a data sheet of a chemical company produced in 1968, NIOSH stated that instillation of 122 mg of formic acid into the eyes of rabbits had caused severe irritation (NIO04). In evaluating their screening test (see above), Sekizawa et al. found solutions of 5-6% to be the minimum concentrations inducing moderate to severe irritation after instillation of 0.01 mL into the eyes of rats and mice (Sek94).

Acute toxicity

Data on the acute lethal toxicity of formic acid are summarised in Table 1.

Table 1 Acute lethal toxicity data on formic acid in experimental animals.

route	species	LC_{50}/LD_{50}	reference
inhalation	rat	7400 mg/m^3 (4 hours)	BUA95
	rat	15,000 mg/m^3 (15 minutes)	NIO04
	mouse	6200 mg/m^3 (15 minutes)	NIO04
oral	rat	1100 mg/kg bw	NIO04
	rat	1830 mg/kg bw	Tra74
	mouse	700 mg/kg bw	NIO04
	mouse	1100 mg/kg bw	Mal69
intraperitoneal	mouse	940 mg/kg bw	Tra74
intravenous	mouse	145 mg/kg bw	Mal69

Amdur exposed groups of 7 to 16 guinea pigs for 1 hour to formic acid concentrations of 0.34, 1.0, 2.8, 6.6, 13.5, and 42.5 ppm (0.7, 2, 5, 13, 26, and 82 mg/m^3). The formic acid vapour was generated by passing air over constant-boiling formic acid in a flask, while air samples for analysis were collected in demineralised water. Respiratory measurements were determined every 5 minutes during a 1/2-hour pre-exposure and the 1-hour exposure period. Thus, each animal served as its own control. The guinea pigs responded with statistically significant, dose-dependent increases in lung resistance by 29, 44, 66, 82, 93, and 142% at 0.34, 1, 2,8, 6.6, 13.5, and 42.5 ppm, respectively.

Within one hour after exposure, lung resistance values returned to levels that were not significantly different from control values or that were within the range of reference values, except for the animals exposed 42.5 ppm. There were statistically significant decreases in lung compliance by 19, 22, 21, 24, 33, and 35%, respectively, but the values remained within the range of reference values. Respiration rate and minute volume were significantly reduced in the highest exposure group only (Amd58, Amd59, Amd60).

In his review, von Oettingen presented data from studies performed around 1900. Oral administration of doses of 4000 mg/kg to dogs and slightly larger than 4000 mg/kg bw to rabbits caused repeated vomiting in dogs and clonic convulsions, progressive dyspnoea, and death (due to respiratory paralysis) in dogs and rabbits. Intravenous injection of doses of 460-1250 g/kg bw into rabbits induced distinct depression of the nervous system while convulsions were reported at larger (not specified) doses. Formic acid affected the cardiovascular system (dose, species not specified). It also caused kidney injury, the rabbit being the most susceptible species (no doses given) (Oet59).

Methanol toxicity is associated with accumulation of formate. Martin-Amat et al. reported that intravenous infusion of monkeys with formate (formate buffer for the purpose of maintaining pH in the normal range) showed results similar to those described for methanol poisoning: optic disk oedema with normal vascular bed, and intracellular oedema with intra-axonal swelling. The rate of infusion (3.1 meq/kg bw/h) was calculated to produce concentrations of formate similar to those seen in methanol-intoxicated monkeys in which ocular toxicity was produced (Mar78). Eells et al. treated rats with nitrous oxide to reduce THF production to allow formate accumulation following methanol administration. Nitrous oxide-treated rats with blood formate concentrations rising from 0.8 to 7 mmol/L within 12 hours of methanol intraperitoneal injection and then linearly incr easing to 15 mmol/L over the next 48 hours, developed metabolic acidosis, retinal dysfunction, and retinal histological changes. In animals with formate blood levels increasing from 0.5 to 4 mmol/L within 12 hours after methanol administration and then plateaued at 4-6 mmol/L during the next 48 hours, there was evidence of retinal changes in the absence of metabolic acidosis and retinal histopathology (Eel96).

Repeated-dose toxicity

Because the central nervous system is especially vulnerable to hypoxia that might be caused by the inhibition of cytochrome oxidase by the formate anion,

Zitting and Savolainen examined the neurochemical effects in male Wistar rats (n=5/group) exposed to formic acid vapour concentrations of 39 mg/m^3 (20 ppm), 6 hours/day, for 3 or 8 days. Animals were conspicuously inactive during exposure, but did not show clinical signs of toxicity at the time of sacrifice. Cerebral glutathione levels were increased in rats sacrificed after 3 days, but similar to control values in rats exposed for 8 days. Lysosomal acid proteinase activities were similar to those of controls after 3 days and increased after 8 days. Cerebral RNA and superoxide dismutase activity were not affected. Biochemical effects observed in the liver included decreased glutathione levels and increased ethoxycoumarin deethylase activity both after 8 days while there were no changes in the other parameters (cytochrome P450, cytochrome c oxidase, p-nitrophenol glucuronide transferase, superoxide dismutase) determined. In the kidney, decreases in glutathione levels and cytochrome P450 activities were seen at both time points and in ethoxycoumarin deethylase activity after 3 days (Zit80). In a subsequent experiment, these authors investigated the effects on glial cells (which might also be vulnerable to hypoxia) in rats (male; Wistar; n=5/group) exposed to 39 mg/m^3, 6 hours/day, for 2 or 3 weeks. Determination of lysosomal acid proteinase, glutathione peroxidase, 2',3'-cyclic nucleotide 3'-phosphohydrolase, and succinate dehydrogenase activities in glial cell fractions, isolated from the cerebral hemispheres and containing astro- and oligodendroglial cells (ratio: ca. 5:2), showed an increase in the acid proteinase activity after 2 weeks and decreases in peroxidase activity after 2 weeks and in the phosphohydrolase and dehydrogenase activities after 2 and 3 weeks (Sav80). According to Savolainen and Zitting, these biochemical changes indicated hypoxia in the cerebellum, associated with increased lipid peroxidation and labilisation of the lyosomal complex, which might lead to demyelation (as seen in methanol-induce optic nerve degeneration), and in the kidney. The liver was less sensitive to hypoxic episodes (Sav80, Zit80).

In rabbits, sacrificed 1, 2, or 20 hours after the final of 5 intravenous injections of buffered sodium formate of 100 mg/kg bw, histological changes, indicative of hypoxia, were observed in the brain, heart, liver, and kidneys (Lie87a).

The National Toxicology Program (NTP) performed 2- and 13-week inhalation toxicity studies on formic acid vapour using male and female F344/N rats and $B6C3F_1$ mice. In the 2-week study, groups of 5 animals/species/sex were exposed to formic acid concentrations of 0, 31, 62.5, 125, 250, or 500 ppm (0, 60, 120, 241, 482, or 965 mg/m^3), 6 hours/day, 5 days/week. In rats, clinical signs, including nasal discharge, increased preening, hypoactivity, and laboured

breathing were observed in animals exposed to 250 and 500 ppm. Corneal cloudiness was seen in the 500-ppm group. In the 500-ppm group, 4/10 rats died. Final body weights were significantly lower in 250- and 500-ppm males (by 8 and 26%, respectively) and in 500-ppm females (by 26%) when compared to controls. Haematology and urinalysis evaluation did not show remarkable treatment-related effects. At post-mortem examinations, decreased absolute and relative thymus weights and increased relative kidney and heart (females only) weights were seen in the animals exposed to 500 ppm. There were gross lesions in the animals of the 500-ppm group including dried exudates around the external (anterior) nares in 3 males and 3 females. Although corneal cloudiness was observed clinically in the animals of the 500-ppm group during the course of the study, corneal opacity, which was characterised microscopically by a very minimal inflammatory cell infiltrate, was identified in only one male animal at the time of necropsy. Microscopic examination showed lesions in the upper respiratory tract at concentrations of 62.5 ppm and higher. The lesions increased in incidence and severity with increasing concentrations and ranged from squamous metaplasia of the nasal respiratory epithelium at 62.5 ppm to squamous metaplasia, inflammation, and necrosis of the respiratory epithelium, necrosis of the olfactory epithelium, and squamous metaplasia and inflammation of the larynx at 500 ppm (see Table 2).

In mice, there were clinical signs similar to those seen rats at 250 and 500 ppm and corneal opacity at 500 ppm. All animals exposed to 500 ppm died during the first exposure week while one 250-ppm female was killed moribund on day 4. Final body weights of the animals of the 250-ppm group were significantly decreased (by 16-19%) when compared to controls. Organ weight changes included small increases (by ca. 10%) in relative kidney weights in males exposed to 62.5 ppm and higher and in females exposed to 500 ppm and decreased absolute and relative thymus weights and increased relative lung weights in animals exposed to 250 ppm. There were no gross lesions in the animals sacrificed at the end of the study. In the treatment-related deaths, dried exudates around the nares and distension of the gastrointestinal tract with air, attributed to the swelling and occlusion of nasal passages and subsequent swallowing of air, were observed. Microscopic examination showed lesions (squamous metaplasia, necrosis, degeneration, inflammation) of the nose at concentrations of 62.5 ppm and higher and of the nose, larynx, and pharynx at 500 ppm (see Table 3). (Tho92).

Table 2 Summary of incidences and severity of histological upper respiratory tract lesions in F344/N rats following 2-week inhalation exposure to formic acid (from Tho92).

		0	31[a]	62.5	125	250	500
nose:							
respiratory epithelium							
- squamous metaplasia	males	0	0	4 (1.3)[b]	5 (1.8)	5 (2.8)	5 (2.6)
	females	0	0	3 (1.6)	5 (2.6)	5 (3.0)	5 (3.0)
- inflammation	males	0	0	0	3 (1.0)	5 (2.4)	5 (3.0)
	females	0	0	0	4 (1.3)	5 (2.0)	5 (3.0)
- necrosis	males	0	0	0	0	5 (2.0)	5 (2.6)
	females	0	0	0	0	3 (1.6)	5 (3.0)
olfactory epithelium							
- necrosis	males	0	0	0	1 (1.0)	2 (2.5)	5 (2.6)
	females	0	0	0	1 (1.0)	4 (1.5)	5 (3.0)
larynx:							
- squamous metaplasia	males	0	0	0	0	0	1 (1.0)
	females	0	0	0	0	0	1 (1.0)
- inflammation	males	0	0	0	0	0	2 (1.5)
	females	0	0	0	0	1 (1.0)	1 (2.0)

[a] Concentrations in ppm.
[b] Incidence and, between brackets, severity score, based on a scale of 1 to 4: 1=minimal, 2=mild, 3=moderate, 4=marked. Scores are averages based on the number of animals with lesions from groups of 5.

In the 13-week studies, groups of 10 animals/species/sex were exposed to formic acid concentrations of 0, 8, 16, 32, 64 or 128 ppm (0, 15, 31, 62, 123, or 247 mg/m^3), 6 hours/day, 5 days/week. All rats survived exposure and no clinical signs or effects were observed. Body weights of male animals were generally higher (by 5-8% in animals exposed to 8-64 ppm) those of females generally similar or lower (by 5% at 128 ppm) when compared with controls. Haematology and serum biochemistry evaluation at interim and terminal time points showed minimal to mild changes that were generally considered to be consistent with haemoconcentration. Post-mortem observations included increased relative liver weights in males by 8, 9, and 7% (in all cases $p \leq 0.01$ from control group by Williams' test or Dunnett's test) at 32, 64, and 128 ppm, respectively. Decreases in lung weights were seen in all male and female groups as well but were not considered to be exposure related since weights in controls were increased because of inflammation. Gross autopsy findings were essentially negative. Microscopic findings were limited to the nose and consisted of respiratory epithelial squamous metaplasia and of olfactory epithelial degeneration of minimal to mild severity in 128-ppm males and females and of olfactory

epithelial degeneration of minimal severity in one male exposed to 32 ppm and in one male exposed to 64 ppm (see Table 4).

Table 3 Summary of incidences and severity of histological upper respiratory tract lesions in B6C3F$_1$ following 2-week inhalation exposure to formic acid (from Tho92).

		0	31[a]	62.5	125	250	500
nose:							
respiratory epithelium							
- squamous metaplasia	males	0	0	0	3 (1.3)[b]	4 (1.3)	1 (1.0)
	females	0	0	2 (1.0)	3 (1.3)	4 (1.0)	0
- inflammation	males	0	0	0	2 (1.0)	4 (1.2)	5 (1.4)
	females	0	0	0	2 (1.5)	5 (1.4)	5 (1.8)
- necrosis	males	0	0	0	0	0	4 (3.5)
	females	0	0	0	0	2 (1.5)	5 (3.6)
olfactory epithelium							
- degeneration	males	0	0	0	0	3 (1.3)	1 (2.0)
	females	0	0	0	0	2 (2.0)	0
- necrosis	males	0	0	0	0	0	3 (2.0)
	females	0	0	0	0	1 (1.0)	5 (1.8)
larynx:							
- squamous metaplasia	males	0	0	0	0	0	5 (2.8)
	females	0	0	0	0	0	1 (2.0)
- inflammation	males	0	0	0	0	0	3 (1.0)
	females	0	0	0	0	0	3 (1.0)
- necrosis	males	0	0	0	0	0	0
	females	0	0	0	0	0	5 (2.2)
pharynx:							
- necrosis	males	0	0	0	0	0	3 (2.0)
	females	0	0	0	0	0	2 (1.0)

[a] Concentrations in ppm.

[b] Incidence and, between brackets, severity score, based on a scale of 1 to 4: 1=minimal, 2=mild, 3=moderate, 4=marked. Scores are averages based on the number of animals with lesions from groups of 5.

In mice, one male and one female animal of the 128-ppm group died before the end of the study. Exposure did not induce clinical signs of toxicity. Final body weights of males of the 128-ppm group (by 16%) and of females of the 64- and 128-ppm group (by 6 and 20%, respectively) were significantly lower than those of controls. Post-mortem examinations showed increased relative weights of the kidney in males exposed to 128 ppm (by 16%; $p \leq 0.01$) and in females exposed to 32, 64, and 128 ppm (by 11, 11, 33%, respectively; $p \leq 0.05$, ≤ 0.01, and ≤ 0.01, respectively), of the liver in males exposed to 32, 64, and 128 ppm (by 8, 10, and 14%, respectively; $p \leq 0.01$) and in females exposed to 128 ppm (by 11%; $p \leq 0.01$), and of the lungs in females exposed to 64 and 128 ppm (by 12 and 30%,

respectively; p≤0.05 and ≤0.01, respectively). No gross lesions were observed. Upon microscopic examination, there was minimal olfactory epithelial degeneration in 2 male mice exposed to 128 ppm and in 2 and 5 female mice exposed to 64 and 128 ppm, respectively (Tho92).

Table 4 Summary of incidences and severity of nasal lesions in F344/N rats and B6C3F$_1$ mice following 13-week inhalation exposure to formic acid (from Tho92).

		0	8[a]	16	32	64	128
rats							
respiratory epithelium							
- squamous metaplasia	males	0	0	0	0	0	9 (1.0)[b]
	females	0	0	0	0	0	6 (1.4)
olfactory epithelium							
- degeneration	males	0	0	0	1 (1.0)	1 (1.0)	9 (1.2)
	females	0	0	0	0	0	5 (1.0)
mice							
olfactory epithelium							
- degeneration	males	0	0	0	0	0	2 (1.0)
	females	0	0	0	0	2 (1.0)	5 (1.0)

[a] Concentrations in ppm.
[b] Incidence and, between brackets, severity score, based on a scale of 1 to 4: 1=minimal, 2=mild, 3=moderate, 4=marked. Scores are averages based on the number of animals with lesions from groups of 10.

From the results of the 2- and 13-week inhalation studies in rats and mice, the committee concludes that 31 mg/m^3 (16 ppm) is the overall NOAEL for systemic and local effects based on minor effects on relative liver weights (male rats and mice) and kidney weights (female mice) and the minimal nasal olfactory epithelium degeneration in male rats at the next higher level of 62 mg/m^3 (32 ppm).

Following oral (drinking water) administration of doses of formic acid of 8-360 mg/kg bw/day, for 2 to 27 weeks, to rats (n=3-6/group; no data on strain and sex), no signs of toxicity or adverse effects on body weight were observed at doses up to 160 mg/kg bw for up to 15 weeks. In 3 rats given 160 mg/kg bw for 17 weeks followed by 360 mg/kg bw for 9 weeks, there were marked decreases in body weight and food consumption (but not in water intake) (Sol21).

Malorny performed 3 long-term experiments with formats administered in the drinking water. In the first experiment, he started with 8 male and 24 female Wistar rats that were given calcium formate at a concentration of 0.2% resulting in daily doses of 150-200 mg/kg bw, throughout life span. The experiment was continued with their progenies. After more than 3 years and 5 generations, no

deaths or toxic symptoms were observed. In the second experiment, animals were given 0.4% calcium formate. No deaths or toxic signs were seen in 2 generation of animals over a 2-year period. Macroscopic and microscopic examination of more than 250 rats from 3 generations given 200 mg/kg bw/day did not show increased tumour incidences or other remarkable substance-related findings. In the third experiment, sodium formate was administered at a concentration of 1%, resulting in daily doses of ca. 730 mg/kg bw. Again, no mortality or toxic effects were induced (Mal69).

Carcinogenicity

Frei and Stephens studied the co-carcinogenicity and cell proliferation-stimulating activity of formic acid in male Swiss mice (n=10/group) by application of the test substance to both sides of the ears. Initiation was performed by applying a 1.5% solution of 7,12-dimethylbenz[a]anthracene (DMBA) to the ears once and was followed one week later by twice weekly paintings with a 8% formic acid solution, for 2, 5, 10, 20, and 50 days. At the end of each painting period, 10 animals were sacrificed and examined for the number of epithelial cells (hyperplasia), the thickness of the epidermis, and the presence of cellular inflammatory exudates. Formic acid treatment did not affect any of the end points examined at any of the time points when compared with controls (Fre68).

Mutagenicity and genotoxicity

- *In vitro* tests:
  - gene mutation assays. Formic acid was negative when tested in *S. typhimurium* strains TA97, TA98, TA100, and TA1535 in the absence and presence of 2 concentrations of S9 mix from induced rat and hamster livers (concentration range tested: 10-3333 µg/plate) (Tho92, Zei92). Toxicity but no mutagenicity was reported when formic acid was tested in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 with and without adding a metabolic activating system (no more data presented) (Slo82).
    Formic acid caused an increase in reverse mutation rate (18.1-44.0 mutants per 10^8 bacteria vs. 1.7-15.3/10^8 bacteria in the control group) when tested without metabolic activation in *E. coli* strain B/Sd-4 at a concentration range of 0.0050 to 0.0075%. Survival rates decreased with decreasing number of bacteria; mutation rates decreased with increasing survival rates (Dem51).

Formic acid induced statistically significant increases in the frequency of sex-linker lethal mutations in *D. melanogaster* following exposure of males to a vapour concentration of 0.1% (1000 ppm) or feeding larvae 0.1 % formic acid (1.31 and 1.11% vs. a spontaneous rate of 0.15%). When the pH of the feeding medium was stabilised to 7.5, formic acid (0.1%) did not induce a significant increase in mutation frequency (0.38% vs. 0.15%) (Stu69).

- cytogenicity assays. Formic acid caused a small (ca. 1.5 times the control value) but statistically significant increase in the frequency of sister chromatid exchanges (SCEs) in human lymphocytes when tested without metabolic activation at a concentration of 10 mM, while the number of SCEs were similar to control values at the other concentrations tested (range: 0.6-5 mM). Immediately after treatment with 10 mM, the pH of the culture medium was lowered to 6.53 (vs. 7.06 and 7.57 at 5mM and in control cultures, respectively). Since propionic and 2-ethylhexanoic acid produced small (ca. 1.3-1.5 times control values), but statistically significant increases at concentrations that only slightly affected the pH of the medium (by maximum 0.2 pH units), Sipi et al. concluded that the weak induction of SCEs might be related to altered culture conditions but could not be explained by lowered pH alone (Sip92). Formic acid did not increase the frequency of SCEs in Chinese hamster V79 cells when tested with and without an induced rat liver-derived metabolic activation system at concentrations between 0.4 and 2.0 mM (Bas85).
  Formic acid induced chromosomal aberrations (especially chromatid breaks and exchanges) in Chinese hamster ovary (K1) cells but only at the highest non-toxic dose tested. At 12 and 10 mM without and with S9, respectively, when the initial pH of the (F12) medium was 6.1 (pH after 6 hours treatment: 6.2-6.3), the percentage of aberrant cells (including gaps) was 15.9 and 20.5%, respectively. No clastogenic activity was observed when the pH was adjusted to 6.4 or 7.2. In cells grown in the medium containing twice the concentration of sodium carbonate usually employed as a buffer, 10% of the cells had chromosomal aberrations (including gaps) when tested without S9 at a concentration of 27.5 mM of formic acid at an initial pH of 5.7 (pH after 24 h: 6.7), while results were negative at concentrations up to 25 mM (initial pH: 5.8-6.1; pH after 24 h: 7.1-7.3). Using HEPES as a buffer, no effects were seen at doses of 10 or 20 mM (initial pH: 7.6 and 7.1, respectively; after 24 h: 6.9 and 6.8, respectively), while 12% aberrant cells (including gaps) were observed at 25 mM (initial pH: 6.7; after 24 h: 6.4). Morita et al. concluded that formic acid itself was

not clastogenic but that exposure to acidic solutions of pH 6.0 or below for a short time of exposure to weakly acidic solutions of 6.4-6.7 for a longer time might induce chromosomal aberrations (Mor90).

- *In vivo* tests:
  The committee did not find data from *in vivo* genotoxicity tests on formic acid.
- Other tests:
  Formic acid did not induce cell transformation when tested in the absence and presence of a tumour promoter, 12-*O*-tetradecanoyl phorbol-13-acetate (TPA), in C3H/10T1/2 Cl 8 mouse embryo cells at concentrations of 100, 500, and 1000 µg/mL (Rag81).
  Formic acid, tested at concentrations up to 300 µg/mL, did not inhibit intercellular communication in Chinese hamster V79 lung fibroblasts (Mal85).

Reproduction toxicity

In the 13-week inhalation study performed by the NTP (see 'Repeated-dose toxicity'), no relevant effects were found on sperm motility, sperm concentration, or on testis or epididymis weights in male rats and mice or on the oestrus cycle of female rats and mice (n=10/sex/group) exposed to formic acid concentrations of 14, 58, or 230 mg/m^3 (8, 32, or 128 ppm), when compared with controls (Tho92).

Malorny (see 'Repeated-dose toxicity') did not find evidence of effects on fertility, pregnancy outcome, and fetal or offspring development in Wistar rats. The study started with 8 males and 24 females that received calcium formate in the drinking water at concentrations of 0.2% (150-200 mg/kg bw/day) throughout life span. The experiment was continued with the progenies and lasted for more than 3 years encompassing 5 generations. In a follow-up study, concentrations of 0.4% were given and no effects were reported for 2 generations of animals over a period of 2 years (Mal69).

Dorman et al. administered single oral (gavage) doses of sodium formate of 750 mg/kg bw to CD-1 mice on gestational day 8. This dose resulted in maternal plasma and decidual formate levels similar to those seen following 6-hour exposures to methanol vapour concentrations of 15,000 ppm, an exposure level inducing exencephaly in dams exposed on gestational day 8. Sodium formate treatment did not affect the neural tube closure, head or body lengths, or body weights of fetuses (Dor95a, Dor95b).

In *in vitro* experiments, using rat or mouse embryo cultures, incubation with formic acid or formate reduced concentration dependently embryo growth and development, resulting in increased incidences of dead (formic acid only) and abnormal embryos at the higher levels. The no-effect concentrations were ca. 4 and 6 mmol/L, respectively, while significant effects were noted at formic acid and formate levels of ca. 18 mmol/L. Low(ering) pH increased the severity of the effects (And93, And95, Bro95). Injection of doses of sodium formate of 5, 10, or 20 mg into chicken eggs did not affect embryo development (Mal69).

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for formic acid in the Netherlands is 9 mg/m^3 (5 ppm), 8-hour TWA.

Existing occupational exposure limits for formic acid in some European countries and in the USA are summarised in the annex.

8 Assessment of health hazard

The committee did not find data on the biotransformation and kinetics following inhalation exposure to formic acid.

Formic acid is an endogenous, metabolic intermediate. Via the tetrahydrofolate-dependent one-carbon pathway, endogenous and exogenous formic acid can be incorporated into biological macromolecules or oxidised to CO_2. Tetrahydrofolate (THF) and formyl-THF synthetase and dehydrogenase play a role in these processes. Having higher hepatic THF levels and higher 10-formyl-THF dehydrogenase activities, rodents metabolise formic acid more rapidly than do primates in which oxidation might become saturated resulting in accumulation of formate in blood. Formate oxidation rates were 300 mg/kg/h in mice, 78 mg/kg/h in rats, and 40 mg/kg/h in monkeys. Humans should oxidise formate at a rate similar to that in monkeys. Determination of formic acid concentrations in next morning urine may offer a possibility for biological monitoring of occupationally exposed workers. Background levels up to 190 mg/L or 280 mg/g creatinine have been reported.

Being a strong acid, the committee is of the opinion that formic acid can have irritating to corrosive effects on the respiratory tract and eyes following inhalation exposure and on the skin following dermal contact. The committee did not find data on effects in workers occupationally exposed to formic acid. Following oral exposure, formic acid caused severe local corrosion of the

gastrointestinal tract accompanied by oesophageal stricture, stomach perforation, and haemorrhage. Further, systemic effects such as nausea, vomiting, unconsciousness, metabolic acidosis, haemolysis, coagulation disorders, liver function disorders, reduced blood pressure, acute renal failure, inflammation of the lungs, and death, from gastrointestinal tract perforation or acute renal failure, occurred.

The minimum concentrations inducing moderate to severe irritation to the eyes of rabbits and skin of rats and mice were 5-6 and 10-12%, respectively.

The 4-hour LC_{50} was 7400 mg/m^3 (3850 ppm) in rats; the 15-minute LC_{50} values were 15,000 and 6200 mg/m^3 (7800 and 3225 ppm) in rats and mice, respectively. Oral LD_{50} values ranged from 700-100 mg/kg bw in mice to 1100-1830 mg/kg bw in rats. In guinea pigs, exposed to concentrations of 0.7-82 mg/m^3 (0.34-42.5 ppm) for 1 hour, dose-dependent significant increases in lung resistance were observed, that, except for animals exposed to 42.5 ppm, returned to control or reference values within one hour post-exposure.

In rats, exposed to 39 mg/m^3 (20 ppm), 6 hours/day, for 3 or 8 days or 2 or 3 weeks, biochemical changes indicative of hypoxia were seen in brain and kidneys and to a lesser extent in the liver. However, no macroscopic or microscopic changes were seen in brain, kidneys, and livers of rats and mice exposed up to 965 mg/m^3 (500 ppm) for 2 weeks or up to 247 mg/m^3 (128 ppm) for 13 weeks. These 2- and 13-week NTP studies in rats and mice (Tho92) produced a NOAEL of 31 mg/m^3 (16 ppm) based on minor effects (increased relative liver and kidney weights and minimal degeneration of the nasal olfactory epithelium) found in rats and/or mice exposed to 62 mg/m^3 (32 ppm) formic acid.

Gene mutation assays performed in bacteria and fruit flies and cytogenicity assays in mammalian cell systems produced both negative and positive results. However, in most positive cases, genotoxic responses were eliminated when the acidic pH of the test solution or nutrient medium was neutralised or when the buffering capacity of the solutions was increased. The committee did not find data from *in vivo* genotoxicity tests. From the data available, the committee concludes that formic acid is not a genotoxic compound.

Long-term oral (drinking water) administration of amounts of formic acid of 150-200 mg/kg bw/day to several generations of rats did not cause increased tumour incidences. Formic acid did not act as a promoter in a skin-painting study in mice. Formic acid did not induce cell transformation in mouse embryo cells or inhibit intercellular communication in Chinese hamster lung cells, tests thought to be indicative of a carcinogenic potential.

No relevant effects were found on sperm motility, sperm concentration, or on testis or epididymis weights in male rats and mice or on the oestrus cycle of

female rats and mice exposed to formic acid concentrations up to 230 mg/m^3 (128 ppm) for 13 weeks. No evidence of effects on fertility, pregnancy outcome, and fetal or offspring development was seen in Wistar rats that received oral (drinking water) concentrations of calcium formate of 0.2% (150-200 mg/kg bw/day), for 5 generations over more than 3 years or of 4% for 2 generations over 2 years.

The committee selected the Amdur studies in guinea pigs (Amd58, Amd59, Amd60) and the 2- and 3-week NTP studies in rats and mice (Tho92) as the key studies for deriving a health-based recommended occupational exposure limit (HBROEL). The committee considers the studies by Amdur scientifically sound. The guinea pig's response to known bronchoconstricting agents mimics that of humans, and, therefore, the guinea pig is widely accepted as the preferred animal model to study airway and lung responses to smooth muscle-bronchoconstricting pharmaceuticals. In humans, an increase in airway resistance of 50% is interpreted as unambiguous bronchoconstriction. From the results of the Amdur studies, the committee infers that, in guinea pigs, a 50% increase in airway resistance would occur at an exposure concentration of formic acid between 2 and 5 mg/m^3 (1 and 2.8 ppm). Thus, in order to avoid the risk of bronchoconstriction in workers, a health-based occupational exposure limit should not exceed 5 mg/m^3. Further, the NTP inhalation toxicity studies showed a NOAEL of 31 mg/m^3 (16 ppm) in rats and mice for local irritating and systemic effects. For the extrapolation to an HBROEL, the committee is of the opinion that an overall assessment factor of 6 is warranted. This factor covers the following aspects: inter- and intraspecies variation, differences between experimental conditions and the exposure pattern of the worker, and the type, low incidence, and slightness of the critical effects at 62 mg/m^3. Applying this factor of 6 and the preferred value approach would lead to a health-based occupational exposure limit of 5 mg/m^3. The guinea pig data indicate that this level would avoid the risk of bronchoconstriction in workers. Since bronchoconstriction may occur almost immediately on exposure to irritants such as formic acid, this HBROEL should be a 15-minute time-weighted average value.

The committee expects that the amount of formic acid absorbed when exposed to this level during a working day will not cause the accumulation of formate or a decrease in blood pH (see Gre03).

The committee recommends a health-based occupational exposure limit for formic acid of 5 mg/m^3 (2.5 ppm), as a 15-minute time-weighted average.

References

ACG91 American Conference of Governmental Industrial Hygienists (ACGIH). Formic acid. In: Documentation of the Threshold limit Values and Biological Exposure Indices. 6th ed. Cincinnati OH, USA: ACGIH®, 1991: 692-3.

ACG02 American Conference of Governmental Industrial Hygienists (ACGIH). Formic acid. In: Documentation of the TLVs® and BEIs® with other worldwide occupational exposure values - CD-ROM - 2002. Cincinnati OH, USA: ACGIH®, 2002.

ACG04 American Conference of Governmental Industrial Hygienists (ACGIH). Guide to occupational exposure values - 2004. Cincinnati OH, USA: ACGIH®, 2004: 69.

ACG05 American Conference of Governmental Industrial Hygienists (ACGIH). 2005 TLVs® and BEIs® based on the documentation of the Threshold Limit Values for chemical substances and physical agents & Biological Exposure Indices. Cincinnati OH, USA: ACGIH®, 2005: 31.

Amd58 Amdur MO, Mead J. Mechanics of respiration in unanesthetized guinea pigs. Am J Physiol 1958; 192: 364-8.

Amd59 Amdur MO. The physiological response of guinea pigs to atmospheric pollutants. Int J Air Pollut 1959; 1: 170-83.

Amd60 Amdur MO. The response of guinea pigs to inhalation of formaldehyde and formic acid alone and with a sodium chloride aerosols. Int J Air Pollut 1960; 3: 201-20.

Amo83 Amoore JE, Hautala E. Odor as an aid to chemical safety: odour thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. J Appl Toxicol 1983; 3: 272-90.

And93 Andrews JE, Ebron-McCoy M, Kavlock RJ, et al. Lowering pH increases embryonic sensitivity to formate in whole embryo culture. Toxicol in Vitro 1993; 7: 757-62.

And95 Andrews JE, Ebron-McCoy M, Kavlock RJ, et al. Developmental toxicity of formate and formic acid in whole embryo culture:a comparative study with mouse and rat embryos. Teratology 1995; 51: 243-51.

Arb02 Arbejdstilsynet. Grænseværdier for stoffer og materialer. Copenhagen, Denmark: Arbejdstilsynet, 2002: 32 (At-vejledning C.0.1).

Bas85 Basler A, von der Hude W, Scheutwinkel-Reich M. Formaldehyde-induced sister chromatid exchanges in vitro and the influence of the exogenous metabolizing system S9 mix and primary rat hepatocytes. Arch Toxicol 1985; 58: 10-3.

Bro95 Brown-Woodman PDC, Huq F, Hayes L, et al. In vitro assessment of the effect of methanol and metabolite, formic acid, on embryonic development of the rat. Teratology 1995; 52: 233-43.

BUA95 GDCh-Advisory Committee on Existing Chemicals of Environmental Relevance (BUA). Formic acid, formats (No. 81; August 1991). Diethylene glycol bis-(chloroformate). Stuttgart, FRG: S Hirzel Wissenschaftliche Verlagsgesellschaft, 1995; BUA Reports 81 and 82.

Dam96 Damian P, Raabe OG. Toxicokinetic modeling of dose-dependent formate elimination in rats: in vivo - in vitro correlations using the perfused rat liver. Toxicol Appl Pharmacol 1996; 139: 22-32.

Dem51 Demerec M, Bertani G, Flint J. A survey of chemicals for mutagenic activity on E. coli. Am Nat 1951; 85: 119-36.

Dor95a Dorman DC, Struve MF, Laperle KMD, et al. The role of formate in methanol-induced exencephaly in CD-1 mice. Teratology 1995; 51: 183-4.

Dor95b Dorman DC, Bolon B, Struve MF, et al. The role of formate in methanol-induced exencephaly in CD-1 mice. Teratology 1995; 52: 30-40.

DFG05 Deutsche Forschungsgemeinschaft (DFG): Commisson for the Investigation of Health Hazards of Chemical Compounds in the Work Area. List of MAK and BAT values 2005. Maximum concentrations and biological tolerance values at the workplace. Weinheim, FRG: Wiley-VCH Verlag & Co. KGaA, 2005: 66 (rep no 41).

EC05 European Commission: Directorate General of Employment, Social Affairs and Equal Opportunities. Indicative occupational exposure limit values. http://europe.eu.int/comm/employment_social/health_safety/docs/oels_en.pdf.

Eel96 Eells JT, Salzman MM, Lewandowski MF, et al. Formate-induced alterations in retinal function in methanol-intoxicated rats. Toxicol Appl Pharmacol 1996; 140: 58-69.

Fre68 Frei JV, Stephens P. The correlation of promotion of tumour growth and of induction of hyperplasia in epidermal two-stage carcinogenesis. Br J Cancer 1968; 22: 83-92.

Fri96 Fritschi L, Siemiatycki J. Lymphoma, myeloma and occupation: results of a case-control study. Int J Cancer 1996; 67: 498-503.

Gra86 Grant WM, ed. In: Toxicology of the eye. 3rd ed. Springfield IL, USA: Charles C Thomas Publisher, 1986: 446.

Gre03 Greim H, ed. Formic acid. In: Occupational toxicants. Critical data evaluation for MAK values and classification of carcinogens. Weinheim, FRG: Wiley-VCH Verlag GmbH, 2003: 169-80 (Vol 19).

Hei92 Heinzow B, Ellrott T. Ameisensäure im Urin - ein sinnvoller Parameter der umweltmedizinischen Diagnostic? Zentralbl Hyg Umweltmed 1992; 192: 455-61.

HSE02 Health and Safety Executive (HSE). EH40/2002. Occupational Exposure Limits 2002. Sudbury (Suffolk), England: HSE Books, 2002: 13.

IARC95 International Agency for Research on Cancer (IARC). Formaldehyde. In: Wood dust and formaldehyde. Lyon, France: IARC, 1995: 217-362 (IARC monographs on the evaluation of carcinogenic risks to humans; Vol 62).

Joh87 Johlin FC, Fortman CS, Nghiem DD, et al. Studies of the role of folic acid and folate-dependent enzymes in human methanol poisoning. Mol Pharmacol 1987; 31: 557-61.

Kat94 Katz GV, Guest D. Formic acid. In: Clayton GD, Clayton FE, eds. Toxicology. 4th ed. New York, USA: John Wiley & Sons, Inc, 1994: 3572 (Patty's Industrial Hygiene and Toxicology; Vol II, Part E).

Lie86 Liesivuori J. Slow urinary elimination of formic acid in occupationally exposed farmers. Ann Occup Hyg 1986; 30: 329-33.

Lie87a Liesivuori J, Kosma VM, Naukkarinen A, et al. Kinetics and toxic effects of repeated intravenous dosage of formic acid in rabbits. Br J Exp Pathol 1987; 68: 853-61.

Lie87b Liesivuori J, Savolainen H. Urinary formic acid as an indicator of occupational exposure to formic acid and methanol. Am Ind Hyg Assoc J 1987; 48: 32-4.

Lie91 Liesivuori J, Savolainen H. Methanol and formic acid toxicity: biochemical mechanisms. Pharmacol Toxicol 1991; 69: 157-63.

Lie92 Liesivuori J, Laitinen J, Savolainen H. Kinetics and renal effects of formic acid in occupationally exposed farmers. Arch Toxicol 1992; 66: 522-4.

Mal69 Malorny G. Die akute und chronische Toxizität der Ameisensäure und ihrer Formiate. Z Ernahrungswiss 1969; 9: 332-9.

Mal85 Malcolm AR, Mills LJ, Trosko JE. Effects of ethanol, phenol, formaldehyde, and selected metabolites on metabolic cooperation between Chinese hamster V79 lung fibroblasts. Carcinogenesis 1985; 8: 305-18.

Mar78 Martin-Amat G, McMartin KE, Hayreh SS, et al. Methanol poisoning: ocular toxicity produced by formate. Toxicol Appl Pharmacol 1978; 45: 201-8.

Mor90 Morita T, Tekeda K, Okumura K. Evaluation of clastogenicity of formic acid, acetic acid and lactic acid on cultured mammalian cells. Mutat Res 1990; 240: 195-202.

Nai97 Nair B. Final report on the safety assessment of formic acid. Int J Toxicol 1997; 16: 221-34.

NIO04 US National Institute for Occupational Safety and Health (NIOSH), ed. Formic acid. In: The Registry of Toxic Effects of Chemical Substances (last update formic acid file: October 2002); http://www.cdc.gov/niosh/rtecs/lq4ac4a0.html.

NLM04 US National Library of Medicine (NLM), ed. Formic acid. In: The Hazardous Substances Data Bank (HSDB) (last revision date formic acid file: February 2004; last review date: November 1994); http://toxnet.nlm.nih.gov.

Oet59 von Oettingen WF. The aliphatic acids and their esters - toxicity and potential dangers. AMA Arch Ind Health 1959; 20: 517-31.

Rag81 Ragan DL, Boreiko CJ. Initiation of C3H/10T1/2 cell transformation by formaldehyde. Cancer Lett 1981; 13: 325-31.

Rut86 Ruth JH. Odor thresholds and irritation levels of several chemical substances: a review. Am Ind Hyg Assoc J 1986; 47: A142-51.

Sav80 Savolainen H, Zitting A. Glial cell effects of subacute formic acid vapour exposure. Acta Pharmacol Toxicol 1980; 47: 239-40.

Sch94 Schmid K, Schaller KH, Angerer J, et al. Investigations on the importance of the formic acid excretion in urine from an environmental and occupational medical point of view. Zentralbl Hyg Umweltmed 1994; 196: 139-52.

Sek94 Sekizawa J, Yasuhara K, Suyama Y, et al. A simple method for screening assessment of skin and eye irritation. J Toxicol Sci 1994; 19: 25-35.

Sip92 Sipi P, Jarventaus H, Norppa H, et al. Sister-chromatid exchanges induced by vinyl esters and respective carboxylic acids in cultured human lymphocytes. Mutat Res 1992; 279: 75-82.

Slo82 Sloop FV Jr, Baker FT. Screening selected chemical food additives for mutagenicity. Abstr Ann Meet Am Soc Microbiol 1982; 82: 124.

Sol21 Sollmann T. Studies of chronic intoxication of albino rats. III. acetic and formic acids. J Pharmacol Exp Ther 1921; 16: 463-74 (cited in Tra74).

Stu96 Stumm-Tegethoff BFA. Formaldehyde-iduced mutations in Drosophila melanogaster in dependence of the presence of acids. Theor Appl Genet 1969; 39: 330-4.

Swe00 Swedish National Board of Occupational Safety and Health. Occupational exposure limit values and measures against air contaminants. Solna, Sweden: National Board of Occupational Safety and Health, 2000: 46 (Ordinance AFS 2000:3).

SZW05 Ministerie van Sociale Zaken en Werkgelegenheid (SZW). Nationale MAC-lijst 2005. The Hague, the Netherlands: Sdu Uitgevers, 2005: 35.

Tep91 Tephly TR. The toxicity of methanol. Life Sci 1991; 48: 1031-41.

Tho92 Thompson M. Technical report on studies of formic acid (CAS No: 64-18-6) administered by inhalation to F344/N rats and B6C3F1 mice. Research Triangle Park NC, USA: National Toxicology Program, 1992; Toxicity Rep Series No 19.

Tra74 Tracor-Jitco, Inc. Scientific literature reviews on generally recognized as safe (GRAS) food ingredients-formic acid and derivatives, Rockville MD, USA: Tracor-Jitco, Inc, 1974 (available from the National Technical Information Service, Springfield VA, USA; order no PB-228558).

TRG04 TRGS 900. Technische Regeln für Gefahrstoffe. Grenzwerte in der Luft am Arbeitsplatz. BArbBl 2004; (7/8).

WHO89 World Health Organization (WHO): International Programme on Chemical Safety (IPCS). Formaldehyde. Geneva, Switzerland: WHO, 1989; Environmental Health Criteria 89.

Yas92 Yasugi T, Kawai T, Mizunuma K, et al. Formic acid excretion in comparison with methanol excretion in urine of workers occupationally exposed to methanol. Int Arch Occup Environ Health 1992; 64: 329-37.

Zei92 Zeiger E, Anderson B, Haworth S, et al. Salmonella mutagenicity tests: V. Results from the testing of 311 chemicals. Environ Mol Mutagen 1992; 19 (suppl 2): 2-141.

Zit80 Zitting A, Savolainen H. Biochemical effects of subacute formic acid vapor exposure. Res Commun Chem Pathol Pharmacol 1980; 27: 157-62.

Annex

Occupational exposure limits for formic acid in various countries.

country - organisation	occupational exposure limit		time-weighted average	type of exposure limit	note[a]	reference[b]
	ppm	mg/m^3				
the Netherlands						
- Ministry of Social Affairs and Employment	5	9	8 h	administrative		SZW05
Germany						
- AGS	5	9.5	8 h			TRG04
	5	9.5	15 min			
- DFG MAK-Kommission	5	9.5	8 h			DFG05
	10	19	15 min[c]		[d]	
Great Britain						
- HSE	5	9.6	8 h	OES		HSE02
Sweden	3	5	8 h			Swe00
	5	9	15 min			
Denmark	5	9	8 h			Arb02
USA						
- ACGIH	5	-	8 h	TLV		ACG05
	10	-	15 min	STEL		
- OSHA	5	9	8 h	PEL		ACG04
- NIOSH	5	9	10 h	REL		ACG04
European Union						
- SCOEL	5	9	8 h	IOELV		EC05

[a] S = skin notation; which means that skin absorption may contribute considerably to body burden; sens = substance can cause sensitisation.

[b] Reference to the most recent official publication of occupational exposure limits.

[c] Maximum number per shift: 4, with a minimum interval between peaks of 1 hour.

[d] Classified in pregnancy risk group C, i.e., there is no reason to fear a risk of damage to the embryo or fetus when MAK and BAT values are observed.