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FOREWORD **INTRODUCTION**

FORMALDEHYDE

CAS N°: 50-00-0

SIDS Initial Assessment Report

For

SIAM 14

Paris, France, March 2002

1. Chemical Name:	**Formaldehyde**
2. CAS Number:	**50-00-0**
3. Sponsor Country:	Germany
4. Shared Partnership with:	
5. Roles/Responsibilities of the Partners:	
• Name of industry sponsor /consortium	BMU (Bundesministerium für Umwelt, Naturschutz und Reaktorsicherheit) Contact person: Prof. Dr. Ulrich Schlottmann Postfach 12 06 29 D- 53048 Bonn- Bad Godesberg
• Process used	See next page
6. Sponsorship History	The peer review of BUA in the ecotoxicology section was mainly based on the IPCS Environment Health Criteria 89 (1989)
• How was the chemical or category brought into the OECD HPV Chemicals Programme ?	
7. Review Process Prior to the SIAM:	
8. Quality check process:	
9. Date of Submission:	01. February 2002
10. Date of last Update:	Last literature search: Toxicology: 01.08.2001; Ecotoxicology: 13.06.2001
11. Comments:	

OECD/ICCA - The BUA* Peer Review Process

Qualified BUA personnel (toxicologists, ecotoxicologists) perform a quality control on the full SIDS dossier submitted by industry. This quality control process follows internal BUA guidelines/instructions for the OECD/ICCA peer review process and includes:

- a full (or update) literature search to verify completeness of data provided by industry in the IUCLID/HEDSET

- Review of data and assessment of the quality of data

- Review of data evaluation

- Check of adequacy of selection process for key studies for OECD endpoints, and, where relevant, for non-OECD endpoints by checking original reports/publications

- Review of key study description according robust summaries requirements; completeness and correctness is checked against original reports/publications
  (if original reports are missing: reliability (4) = not assignable)

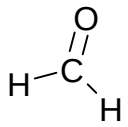
- Review of validity of structure-activity relationships

- Review of full SIDS dossier (including SIAR, SIAP and proposal for conclusion and recommendation for further work)

In case of data gaps, review of testing plan or rationale for not testing.

* BUA (GDCh-Beratergremium für Altstoffe): Advisory Committee on Existing Chemicals of the Association of German Chemists (GDCh)

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	50-00-0
Chemical Name	Formaldehyde
Structural Formula	

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Formaldehyde had acute effects in mammals: LD_{50} (rat, oral) 600 – 800 mg/kg b.w., LC_{50} (rat, inhalation, 4 h) 578 mg/m^3 (480 ppm). Inhalation of high concentrations (> 120 mg/m^3) of formaldehyde caused hypersalivation, acute dyspnea, vomiting, muscular spasms, convulsions and finally deaths. Histopathology examination showed respiratory tract irritation, bronchioalveolar constriction and lung oedema. Formaldehyde was irritating to the eyes, and aqueous solutions of formaldehyde (0.1% to 20%) were irritating to the skin of rabbits. Formaldehyde was sensitising in the guinea pig maximisation test and the local lymph node assay with mice. On the other hand, specially designed studies (IgE tests, cytokine secretion profiles of lymph node cells) did not reveal evidence of respiratory sensitisation in mice.

In humans, transient and reversible sensory irritation of the eyes and respiratory tract has been observed in clinical studies and epidemiological surveys. Odour threshold for most people ranges between 0.5 and 1 ppm. In general, eye irritation, the most sensitive endpoint, is associated with airborne concentrations beginning in the range of 0.3 to 0.5 ppm. Eye irritation does not become significant until about 1 ppm, and rapidly subsides. Moderate to severe eye, nose and throat irritation occurs at 2 to 3 ppm. Sensory irritation has also been reported at lower exposure levels, but is then difficult to distinguish from background. Most studies show no effect on lung function in either asthmatics or non-asthmatics. Formaldehyde causes skin irritation and has corrosive properties when ingested. In some individuals, contact dermatitis may occur at challenge concentrations as low as 30 ppm.

Formaldehyde is a highly reactive gas that is absorbed quickly at the point of contact and is also produced by endogenous metabolism. It is rapidly metabolised, such that exposure to high concentrations (up to 15 ppm in rats) does not result in increased blood concentrations. Repeated formaldehyde exposure caused toxic effects only in the tissues of direct contact after inhalation, oral or dermal exposure characterised by local cytotoxic destruction and subsequent repair of the damage. The typical locations of lesions in experimental animals were the nose after inhalation, the stomach after oral administration and the skin after dermal application. The nature of the lesions depended on the inherent abilities of the tissues involved to respond to the noxious event and on the local concentration of the substance. Atrophy and necrosis as well as hyper- and metaplasia of epithelia may occur. The most sensitive No Observed Adverse Effect Levels (NOAELs) for morphological lesions were between 1 and 2 ppm for inhalation exposure and about 260 mg/l in drinking water.

Formaldehyde is weakly genotoxic and was able to induce gene mutations and chromosomal aberrations in mammalian cells. DNA-protein crosslinks are a sensitive measure of DNA modification by formaldehyde. However, the genotoxic effects were limited to those cells, which are in direct contact with formaldehyde, and no

effects could be observed in distant-site tissues. In conclusion, formaldehyde is a direct acting locally effective mutagen.

Chronic inhalation of concentrations of 10 ppm and higher led to clear increases in nasal tumour incidence in rats. Most of the nasal tumours were squamous cell carcinomas. Marked non-neoplastic pathological lesions of the nasal epithelium accompanied them. No increased incidence of tumours was found in other organs after inhalation, and administration routes other than inhalation did not result in local or systemic tumour formation. The damage of nasal tissue played a crucial role in the tumour induction process, since nasal cancer was only found at concentrations inducing epithelial degeneration and increased cell proliferation. Thus the stimulation of cell proliferation seems to be an important prerequisite for tumour development. Although formaldehyde exhibits some genotoxic activity, the correlation between cytotoxicity, cell proliferation and the induction of nasal cancer in rats provides a convincing scientific basis for aetiology of the carcinogenic response to be cytotoxicity driven. In contrast to that, no significant numbers of tumours were seen in mice and Syrian hamsters following chronic exposure to concentrations up to 14.3 or 30 ppm, respectively. These clear species differences appeared to be related, in part, to the local dosimetry and disposition of formaldehyde in nasal tissues. Species differences in nasal anatomy and respiratory physiology may have a profound effect on susceptibility to formaldehyde-induced nasal tumours.

In epidemiological studies in occupationally exposed human populations, there is limited evidence of a causal association between formaldehyde exposure and nasal tumours. Taking into account the extensive information on its mode of action, formaldehyde is not likely to be a potent carcinogen to humans under low exposure conditions.

There are no indications of a specific toxicity of formaldehyde to foetal development and no effects on reproductive organs were observed after chronic oral administration of formaldehyde to male and female rats. Amounts of formaldehyde which produce marked toxic effects at the portal of entry, do not lead to an appreciable systemic dose and thus do not produce systemic toxicity. This is consistent with formaldehyde's high reactivity with many cellular nucleophiles and its rapid metabolic degradation.

Environment

Formaldehyde is a colourless gas with pungent odour, soluble in water forming methylene glycol and low molecular mass poly(oxymethylene)glycols HO(CH2O)nH (n = 1-8). It has a measured vapour pressure of 5185 hPa at 25°C.

The favourite target compartment for formaldehyde is water as indicated by Mackay Level I calculation (water: 99% equilibrium distribution). In air, formaldehyde is expected to be indirectly photodegraded, with a half life of 1.71 d. The substance is readily biodegradable. Hydrolysis is not expected under environmental conditions. However in water formaldehyde undergoes essentially complete hydration to yield the gem-diol, methylene glycol. The log P_{OW} was measured to 0.35 at 20 °C. Hence bioaccumulation is unlikely to occur.

The lowest valid effect value of 5.8 mg/l was found for *Daphnia pulex* (48h-EC_{50}). For fish the lowest effect value of 6.7 mg/l (96h-LC_{50}) was found for *Morone saxatilis* (marine). For freshwater fish the lowest effect value (96h-LC50 = 24.8 mg/l) was found for *Ictalorus melas*. For the green alga *Scenedesmus subspicatus* a 24h-EC50 of 14.7 mg/l and a 24h-EC10 of 3.6 mg/l is available for the endpoint oxygen production and consumption. Applying an assessment factor of 1000 according to EU Risk Assessment procedure to the lowest valid effect value, a $PNEC_{aqua}$ of 5.8 µg/l can be derived.

Exposure

Formaldehyde is ubiquitously present in the environment as a result of natural processes and from man-made sources. The major source of atmospheric formaldehyde is the photochemical oxidation and incomplete combustion of hydrocarbons. The global production of formaldehyde in 1999 is estimated to be 5 – 6 million tons. The substance is mainly used as an intermediate in the chemical industry for the production of condensed resins for the wood, paper and textile processing industries and in the synthesis of methylene dianiline (MDA), diphenylmethane diisocyanate (MDI), hexamethylenetetraamine (HTMA), trimethylol propane, neopentylglycol, pentaerythritol and acetylenic agents. Aqueous solutions of formaldehyde are employed as germicides, bactericides and fungicides. The use of formaldehyde as biocide and in other applications is estimated to be 1.5 % of the total production, i.e. 75 000 to 90 000 t/a related to the worldwide production amount. Formaldehyde is used as a preservative in a large number of consumer products, such cosmetics and household cleaning agents. Tobacco smoke as well as urea-formaldehyde foam insulation and formaldehyde-containing disinfectants are all important sources of formaldehyde exposure. Releases into the environment are likely to occur during production and processing as intermediate as well as from use of products containing the substance. For almost all sites there is no information available about releases into the waste water from production and processing. In Canada, about 1424 t were released into the environment from

industrial sites in 1997, from which about 20 t/a were releases to surface waters by 4 sites. The US TRI gives industrial releases of formaldehyde for 1999 with about 6,000 t/a to air and about 175 t/a to surface waters. From the direct use of the substance as e.g. biocide it can be assumed that a very high amount is released into the environment. With an amount of 75 000 to 90 000 t/a worldwide this is a significant pollution source. It can be estimated that formaldehyde contained in consumer products, like cleaning agents is released completely into the wastewater. In addition, reported use of formaldehyde in fish farming and in animal husbandry may lead to a significant environmental exposure.

NATURE OF FURTHER WORK RECOMMENDED

Environment: The substance is a candidate for further work. No information is available about releases into surface water from production and processing sites. In addition, it can be assumed that from the use of 1.5 % of the worldwide production volume (5 to 6 Mio t/a) as biocide and in other applications i.e. 75 000 – 90 000 t/a a high amount of formaldehyde is released into the environment (e.g. from fish and livestock farming). Product register information shows that fomaldehyde is contained in a large number of consumer products, like cleaning agents, detergents, soaps etc. For these applications it can be estimated that the whole amount is released into the waste water. Due to the low PNECaqua of 5.8 µg/l a risk to the aquatic environment cannot be excluded. Therefore, an exposure assessment is recommended.

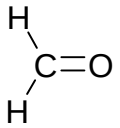
Human Health: No recommendation for further work, because all SIDS endpoints are adequately covered and because exposure is controlled in occupational settings.

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 50-00-0
Name: Formaldehyde
Molecular Formula: CH_2O
Structural Formula:



Molecular Weight:
Synonyms:

Formaldehyde solution
Formaldehyde, gas
Formalin
Formalith
Formol
Formic aldehyde
Methaldehyde
Morbicid
Oxomethane
Paraform
Methanal
Methylene oxide
Oxymethylene

1.2 Purity/Impurities/Additives

Substance type: organic
Physical status: gaseous
Purity: 100 % w/w

The sales product in aqueous solution contains in general 35 – 55 % formaldehyde. The 49 - 49.3 % sales solution of BASF product of formaldehyde contains the following impurities:
Methanol: 0.5 – 2 % w/w
Formic acid: about 0.3 % w/w
Iron: < 0.0001 - % w/w

1.3 Physico-Chemical properties

Formaldehyde is a colourless gas with pungent odour (Römpp, 1990). The theoretical solubility of formaldehyde in water is 95% (w/w) at 120°C. However, at room temperature, pure aqueous solutions contain formaldehyde in the form of methylene glycol $HOCH_2OH$ and its oligomers. Aqueous solutions containing more than 30% (w/w) formaldehyde becomes cloudy at room

temperature due to formation of larger poly(oxymethylene)glycols (Ullmann´s Encyclopedia of Industrial Chemistry, 1985 and 2000). The calculated vapour pressure at 25°C is 5176 hPa (BASF, 1998) that is in good agreement with a measured value of 5185 hPa quoted in the literature (Boublík, 1984). The partition coefficient log P_{OW} is measured to 0.35 at 25°C (Sangster, 1989). The density of liquid formaldehyde is 0.8153 g/cm³ at –20°C (BG Chemie, 1991). Melting point and boiling point of the substance are –92 °C and –19.2°C respectively (BG Chemie, 1991).

2 GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes and Use Pattern

Formaldehyde is ubiquitously present in the environment as a result of natural processes and from man-made sources. The major source of atmospheric formaldehyde is the photochemical oxidation and incomplete combustion of hydrocarbons (i.e. methane or other gases, wood, coal, oil, tobacco and gasoline) (Ullmann´s Encyclopedia of Industrial Chemistry, 1985). Formaldehyde is technically produced as aqueous solution (50-55% w/w) by oxidative dehydrogenation of methanol with air (BASF-SRI Consulting, Jan. 2000). The global production of formaldehyde in 1999 is estimated to be 5 – 6 million (metric) tons (Asia: 1–1.5 million tons, North America: 1-1.5 million tons, Western Europe: 2-2.5 million tons). Formaldehyde is mainly used as an intermediate in the chemical industry for the production of condensed resins for the wood, paper and textile processing industries (approx. 40% urea-formaldehyde resins, 10% phenol-formaldehyde resins, 10% polyacetal resins and 5% melamin-formaldehyde resins). Formaldehyde is also used in the synthesis of methylene dianiline (MDA), diphenylmethane diisocyanate (MDI), hexamethylenetetraamine (HTMA), trimethylol propane and neopentylglycol (in total approx. 25%), pentaerythritol (5%) and acetylenic agents (5%) (BASF-SRI Consulting, Jan. 2000).

Aqueous solutions of formaldehyde are employed as germicides, bactericides and fungicides. The concentration of the substance as diluted disinfectant and sterilising agent is less than 0.5 % (0.9 % in exceptional cases). The use of formaldehyde as biocide and in other applications is estimated to be 1.5 % of the total production, a relatively small amount compared with its use in the manufacture of synthetic resins and chemical compound (WHO IPCS, 1989). However, related to the total worldwide production amount of 5 to 6 million tons, a total volume of 75 000 to 90 000 t/a is used in this area.

According to Swiss, Danish and Swedish Products Registers formaldehyde is contained in a large number of products, part of them is available for consumers (Swiss Products Register, 2001; Danish Product Register 2002, Swedish Products Register, 2000). In the Swiss product register there are more than 4000 products that contain formaldehyde. Product types are e.g. paints and lacquers (concentrations up to 10 %), adhesives (concentrations 0.1 to 10 %), cleaning agents (concentrations 0.1 to 50 %), biocides (concentrations 0.1 to 100 %), disinfectants (concentrations 0.1 to 100 %). More than 1000 products are for consumer use. In the Swedish product register there are almost 1400 products, among them almost 200 for consumer use, that contain formaldehyde. The Danish product register mentions 2289 products that contain formaldehyde. In addition, formaldehyde is used in fish farming, to treat sheep footroot, as a fumigant for animal husbandry and as an insecticide /preservative in museums and buildings of historic interest.

Releases into the environment are likely to occur during production and processing as intermediate as well as from use of products containing the substance. During production and internal processing at BASF AG, Ludwigshafen (Germany), approx. 21 tons formaldehyde were emitted into the air in 2000. No information on the emission into wastewater or surface water are available for this site. At the production site of Methanova (two factories), Mainz-Mombach (Germany), less than 5 tons are emitted per year during production and processing to para-formaldeyde. No emission of formaldehyde into wastewater treatment plant occurs during production and processing (Methanova, 2001). In Canada, about 1424 t formaldehyde were released into the environment from industrial sites in 1997, from which about 20 t/a were released to surface waters by 4 sites (Environment Canada, 2000). The US TRI gives industrial releases of formaldehyde for 1999 with about 6,000 t/a to air and about 175 t/a to surface waters. No further information is available about industrial environmental releases. From the direct use of the substance as e.g. biocide it can be assumed that a very high amount is released into the environment. With an amount of 75 000 to

90 000 t/a worldwide this is a significant pollution source. It can be estimated that formaldehyde contained in consumer products, like cleaning agents is released completely into the wastewater. In addition, reported use of formaldehyde in fish farming and animal husbandry may lead to significant environmental exposure.

2.2 Environmental Exposure and Fate

Transport and distribution modelling using Mackay Level I (BASF, 1995) indicates water to be the main target compartment for formaldehyde (99%) (input values see IUCLID). In the atmosphere, formaldehyde is expected to be indirectly photodegraded by reaction with OH-radicals, with a half life of 1.71 d (Atkinson, R., 1992). Direct photolysis is also a relevant removal process for formaldehyde in air. A half-life of 4.1 hours was measured (Gardner *et al*, 1984). Under OECD 301 D test (closed bottle test) conditions, formaldehyde is readily biodegradable (90% after 28 days; Gerike, 1990). Hydrolysis is not expected under environmental conditions. Formaldehyde undergoes, however, essentially complete hydration to yield the gem-diol, methylene glycol (Betterton, 1992).

The experimental value for the Henry constant of 0.034 Pa m³ mol^{-1} at 25 °C (Betterton, 1988) indicates that volatilization from an aquatic environment is not expected under normal environmental conditions. The measured log P_{OW} of 0.35 at 20°C (Sangster, 1989) indicates a low potential for bioaccumulation. This is confirmed by negative results of bioaccumulation studies with shrimps and fishes (Hose, 1980; Sills, 1979).

2.3 Human Exposure

Outdoor

Air concentrations of formaldehyde near the ground in coastal, mountain or oceanic areas in different parts of the world were in good agreement and ranged from 0.05 to 14.7 µg/m³ (WHO IPCS, 1989). Measurements conducted in Germany and considered to be representative for the air in the rural areas of Central Europe ranged from 0.1 to 4.5 µg/m³, with a mean value of about 1.5 µg/m³. Measurements in a highly industrialised area with also heavy traffic conducted in Germany (1979 –1984) gave annual mean values of 7 – 12 µg/m³ (WHO IPCS, 1989). Additional measurements conducted in recent years in different locations indicate mean outdoor concentrations ranging from 2.5 µg/m³ to 15.7 µg/m³ (Jurvelin, 2001).

Indoor

Indoor air levels (non workplace), measured in various countries, ranged between <10 µg/m³ and a maximum of 5260 µg/m³. The highest levels were measured in trailers in Germany (WHO IPCS, 1989). The concentrations are mainly dependent on the age of the building, building materials, type of construction and ventilation (WHO IPCS, 1989). In more recent monitoring campaigns conducted in various countries (1992 –1998), mean indoor concentrations of formaldehyde in a range between 20.2 µg/m³ (greater Boston) and 68.5 µg/m³ (New Jersey) have been measured (Jurvelin, 2001).

2.3.1 Occupational Exposure

Occupational exposure to formaldehyde may occur during manufacture and processing and during use of formaldehyde containing products, mainly via the dermal and inhalation routes. Exposure measurements at workplace have been performed at different production sites in the Sponsor Country (BASF AG, ISP GmbH, Methanova).

Site 1 (1998 –2000; 8 h TWA, personal sampling; BASF AG):

- Production (30 measurements): 0.32 mg/m³ (90-percentile)
- Processing (268 measurements): 0.19 mg/m³ (90-percentile)

Site 2 (1991 –1998; 8 h TWA, personal sampling; ISP GmbH):

- Production and processing (117 measurements): <0.02 – 0.37 mg/m³

Site 3 (Methanova):

- Production: 0.01– 0.08 mg/m³
- Processing: 0.02 – 0.25 mg/m³

Workplace measurements conducted in Helsinki, Finland indicated a mean exposure level of 15.05 µg/m³ (Jurvelin, 2001)

2.3.2 Consumer Exposure

There is some natural formaldehyde in raw food and contamination may occur through fumigation, the use of formaldehyde as a preservative and through cooking. The daily formaldehyde intake from food may range between 1.5 and 14 mg. Tobacco smoke as well as urea-formaldehyde foam insulation and formaldehyde-containing disinfectants are all important sources of formaldehyde exposure. Smoking 20 cigarettes per day corresponds to an intake of 1 mg/day via inhalation.

Formaldehyde is used as a preservative in consumer products, such as cosmetics and household cleaning agents. The general public may also be exposed during release from some building materials such as pressed wood products. The estimates for the systemic absorption of formaldehyde through the entire epidermal layer and across the circulatory layer are negligible. The levels of exposure to formaldehyde of housewives were determined in 1985 (measured by personal air sampling apparatus). The individual exposures varied between 0.011 and 0.311 mg/m^3 (0.009 to 0.259 ppm) equivalent to a daily dose of 0.13 to 3.7 mg. The usual exposure was between 0.018 and 0.030 mg/m^3. These measurements included the indoor and outdoor background levels as well as the usual exposure by consumer products (WHO IPCS, 1989).

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

Formaldehyde is a normal metabolite in mammalian systems. It can be generated by the metabolism of certain xenobiotics or endogenous compounds, such as amino acids. It can be introduced directly into cells and tissues by inhalation or oral routes (Sipes and Gandolfi, 1986; Bosron and Li, 1980; Ziegler, 1980). In rodents, which are obligate nose-breathers, airborne formaldehyde is absorbed in the upper airways, while in humans this occurs primarily in the nasal passages and oral cavity but also in the trachea and proximal bronchi. Because it is rapidly metabolised, formaldehyde concentrations in the blood of rats, monkeys, and humans were not increased by exposure to high airborne concentrations (up to 15, 6 and 2 ppm respectively) (Heck *et al.*, 1985; Casanova *et al.*, 1988). At the site of contact, formaldehyde may produce DPCs (DNA Protein Crosslinks). Under conditions when there was measurable binding to macromolecules in the nasal epithelium (inhalation of up to 15 ppm) in rats, formaldehyde did not cause DPC formation in bone marrow cells (Casanova and Heck, 1987). This further indicates the systemic absence of reactive formaldehyde.

The biological fate of inhaled formaldehyde was studied in Fischer 344 rats exposed to either 0.63 or 13.1 ppm of [^{14}C]-formaldehyde for 6 h (Heck *et al.*, 1983). About 40% of the inhaled ^{14}C was exhaled in the expired air as [^{14}C]O_2 during the 70 h post-exposure period, 17% was excreted in the urine, 5% was eliminated in the faeces, and 35-39% remained in the tissues and carcass, presumably as products of metabolic incorporation. Analysis of the residual radioactivity in the blood following inhalation of [^{14}C]-formaldehyde showed that the profiles of total ^{14}C in plasma and erythrocytes were virtually identical to those following *i.v.* injection of [^{14}C]formate, suggesting that formaldehyde is rapidly oxidised to formate and incorporated into biological macromolecules (Heck *et al.*, 1983). The tissue distribution of ^{14}C in the rat is widespread throughout the organism and has been investigated using whole-body autoradiography (Chang *et al.*, 1983).

Glutathione (GSH) is required for the oxidation of formaldehyde to formate catalysed by formaldehyde dehydrogenase (FDH). If GSH tissue levels were depleted, one would expect an increase to occur in the amount of reactive formaldehyde bound to other molecules. When nasal GSH was depleted with phorone (Casanova and Heck, 1987) or acrolein (Lam *et al.*, 1985), an increase was indeed observed in the amount of covalently bound formaldehyde in rat nasal mucosal DNA. Metabolism of reactive formaldehyde occurs by a variety of pathways: Formaldehyde can enter into the one-carbon pool via a direct reaction with tetrahydrofolate (Kallen and Jencks, 1966). Formaldehyde can be oxidised to formic acid by the peroxisomal enzyme, catalase. This reaction probably represents only a minor pathway for formaldehyde metabolism, due to the rate limiting generation of hydrogen peroxide (Waydhas *et al*., 1978).

A substantial portion of the formaldehyde is probably bound to GSH (see above). *S*-hydroxymethylglutathione is oxidised by formaldehyde dehydrogenase (EC 1.2.1.1, a class III alcohol dehydrogenase) (Uotila and Koivusalo, 1974a). The resulting thiol ester is rapidly hydrolysed to free formate by another cytosolic enzyme, S-formylglutathione hydrolase, which regenerates GSH (Uotila and Koivusalo, 1974b). Cytosolic formaldehyde dehydrogenase was present in all animal tissues tested (Uotila and Koivusalo, 1983). In particular, it was detected in the respiratory and olfactory nasal mucosa of rats (Casanova-Schmitz *et al.*, 1984; Keller *et al.*, 1990). In addition, there are mitochondrial and microsomal aldehyde dehydrogenases.

The highly non-linear dose response relation of DPC formation (surrogate for tissue dose) in the nasal tissue of rats and monkeys, with a steep increase in DPC concentration measured at exposure

concentrations above concentrations of about 3 ppm indicates saturation of detoxification pathways in the nasal epithelial cells (Casanova *et al.* 1991). This coincides with the increase of damaging effects to these cells by non-specific reaction of "free" formaldehyde with vulnerable cellular constituents.

Conclusion

Conclusion: Formaldehyde is produced endogenously during the metabolism of amino acids and xenobiotics. In rodents, absorption of inhaled formaldehyde occurs primarily in the nasal passages, while in humans this occurs also in the oral cavity, the trachea and bronchus. At the site of first contact, formaldehyde produces DNA protein crosslinks (DPC). It is also rapidly metabolised to formate by a number of enzymatic reactions. Detoxification by formaldehyde dehydrogenase occurs subsequent to formation of a formaldehyde-glutathione conjugate. Formaldehyde and formate are incorporated into the one-carbon pathway. Much is eliminated in the expired air shortly after exposure. The other major route of elimination is excretion of formate in the urine.

3.1.2 Acute Toxicity

Studies in Animals

Table 3.1-2 Acute toxicity of formaldehyde

Species	Route		Reference
Rat	Oral	LD_{50} 600 – 700 mg/kg body weight	Tsuchiya K. *et al.* ,1975
Rat	Oral	LD_{50} 800 mg/kg body weight	Smyth *et al*., 1941
Rabbit	Dermal	LD_{50} 270 mg/kg body weight	WHO IPCS 1989 [1]
Rat	4 h inhalation	LC_{50} 578 mg/m^3 (480 ppm)	Nagorny *et al*., 1979
Rat	30 min inhalation	LC_{50} 984 mg/m^3 (816 ppm)	Skog, 1950

[1]No further details were available. Secondary literature; reliability was not assignable

The acute oral toxicity was examined in Wistar rats treated by gavage with 2 or 4 % formaldehyde solutions (formaldehyde with or without methanol stabilisation). No relevant differences in toxicity were observed. Lethality occurred mainly during the first day after administration. Signs of toxicity were not reported (Tsuchiya *et al*., 1975, Smyth *et al*., 1941).

After acute inhalation, irritation of the eyes, nose and throat are observed. Exposure to high concentrations (> 120 mg/m^3) of formaldehyde vapour caused hypersalivation, acute dyspnea, vomiting, muscular spasms, convulsions and finally deaths. Histopathology examination revealed respiratory tract irritation, bronchioalveolar constriction and lung oedema (Skog,1950; WHO IPCS, 1989). Effects found microscopically in rats following exposure to formaldehyde (10 ppm) for 4 hours included ciliar lesions, cellular swelling and secretion of mucus of goblet cells. The severity of the lesions were reported to be dependent upon localisation and cell type (Bhalla *et al*., 1991)

Studies in Humans

In humans, serious ulceration and damage of the gastrointestinal tract have been found after ingestion of formaldehyde (45 ml of a 37 % v/v solution) (Kochar *et al*., 1986), or a gulp of a 40 % v/v solution (Ferrandiere *et al*., 1998). No reports on deaths following acute inhalation exposure were located (WHO IPCS, 1989)

Conclusion

Evaluation: The major acute effects are a result of the irritating properties of formaldehyde. After acute inhalation, irritation of the eyes, nose, throat, and lungs, as well as cellular changes, such as ciliar lesions and cellular swelling in the upper respiratory tract have been observed. A 4-hour LC_{50} value of 480 ppm has been determined for rats. The oral LD_{50} was 600-800 mg/kg b.w. in rats. In humans, no reports of deaths following acute inhalation exposure to formaldehyde were located. Serious ulceration of the gastrointestinal tract has been observed in humans after ingestion of formaldehyde.

3.1.3 Irritation

Skin Irritation

Studies in Animals

Aqueous solutions of formaldehyde (0.1% to 20%) were irritating to the skin of rabbits (no details available; WHO IPCS 1989).

Eye Irritation

Studies in Animals

Formaldehyde was irritating to the eyes of rabbits. 0.005 ml of a 5% and a 15% aqueous solution was applied to the eyes of rabbits. The scores were read 18 - 20 hours post application. The irritation score was 8 (on a scale of 0 -10). No further details were given (Carpenter and Smyth, 1946).

Studies in Humans

Studies in the literature have reported a variety of responses induced by exposure to gaseous formaldehyde, generally beginning in the range of 0.3 to 0.5 ppm for eye irritation, the most sensitive endpoint (Andersen and Molhave, 1983, Bender *et al*., 1983, Day *et al*., 1984, Witek *et al*., 1986, 1987, Sauder *et al*., 1986, Schachter *et al*., 1986, Green *et al*., 1987, 1989, Kulle *et al*., 1987, 1993, Pazdrak *et al*., 1993, Petterson and Rehn, 1977, Alexandersson and Hedenstierna, 1988, Paustenbach *et al*., 1997). However, the severity of response at these levels is generally mild, and only a small portion of the population may respond. It is difficult to differentiate reported irritation in exposed persons from background, especially at levels below 1 ppm, as a 20 to 30% response rate is common in controls (Sauder *et al*., 1987, Schachter *et al*., 1987, Witek *et al*., 1987, Harving *et al*., 1990). At levels from 0.3 to 1.0 ppm, response rates in different studies are quite variable. Eye irritation does not become significant until about 1 ppm, and based on most studies, rapidly subsides (Kulle *et al*., 1987; Paustenbach *et al*., 1997). Moderate to severe eye, nose and throat irritation does not occur until 2 to 3 ppm (Sauder *et al*., 1986, Green *et al*., 1987). Eye irritation occurs at concentrations, when usually effects on mucociliary clearance or histopathological changes of the nasal mucosa were not observed (Andersen and Molhave, 1983).

Chamber studies provide the highest quality data for determining the presence of eye, nose, or throat irritation at a known level of formaldehyde. In the Kulle study, nearly half of the subject population reported eye irritation at levels of 2 ppm formaldehyde, whereas only 16 percent reported irritation at 1 ppm. No one experienced eye irritation at 0.5 ppm (Kulle *et al*., 1987). In Sauder, two-thirds of the participants reported eye irritation at 3 ppm (Sauder *et al*., 1986), and in Witek's paper, 70 percent of the volunteers clearly demonstrated eye irritation at 2 ppm (Witek *et al*., 1987).

Studies of sensory irritation from a manufacturing setting may provide useful boundaries, but are generally confounded by the presence of many other airborne agents. In studies involving small numbers of workers exposed to formaldehyde in the production of fiberglass, chemicals, and furniture and wood products using formaldehyde resins, there was a higher prevalence of symptoms, primarily of eye and respiratory tract irritation, compared to controls. However, a dose-response relationship was not established (Alexandersson and Hedenstierna, 1988, 1989, Holmstroem and Wilhelmsson, 1988, Holmstroem *et al*., 1991, Malaka and Kodama, 1990). In a study of molded products and particleboard workers, 4% of subjects reported throat irritation and 24% reported eye irritation at 0.4 ppm to 1 ppm formaldehyde levels (Horvath *et al*., 1988).

Aqueous solutions of formaldehyde cause skin irritation in humans (Maibach, 1983). Serious ulcerations of the gastrointestinal tract have been found after oral ingestion (Kochar *et al*., 1986 ; cf. section on acute toxicity).

Values for odour threshold spread over a wide range (0.05 to 1 ppm) (Leonardos *et al*., 1969, Petterson and Rehn, 1977). The odour threshold of formaldehyde for most people is in the 0.5 to 1.0 ppm range (Kulle *et al*., 1993, Andersen and Molhave, 1983).

Conclusion

Formaldehyde is known to be a primary skin and eye irritant in animals. This is based more on anecdotal evidence than robust animal studies. Formaldehyde causes skin irritation in humans. Transient and reversible sensory irritation of the eyes and respiratory tract has been observed in clinical studies and epidemiological surveys. Airborne concentrations associated with sensory irritation are above 0.3 to 0.5 ppm, eye irritation being the most sensitive endpoint. Moderate eye, nose and throat irritation occurs at 2 to 3 ppm

3.1.4 Sensitisation

Studies in Animals

Skin

Formaldehyde was tested and found to be a skin sensitiser in numerous tests. The induction with a 5% aqueous solution and challenge with 2 and 4% aqueous solutions, for instance, gave a positive result in a guinea pig maximisation test, performed according to OECD Guideline No. 406 (Hoechst AG, 1994). The same result was found with 5, 10 and 25% solutions in acetone/olive oil in a local lymph node assay with mice (Kimber *et al.*, 1991).

Respiratory Tract

In a specially designed study (immuno globulin E test) the dermal application of 10, 25 and 50% formalin solutions in DMF did not result in an elevation of serum IgE and thus did not reveal evidence of respiratory sensitisation in mice (Hilton *et al.*, 1996). This result was verified by the specific cytokine expression patterns in lymph node cell cultures of mice dermally sensitised with 50% formaldehyde solution (Dearman *et al.* 1999). Both studies do not indicate a potential for respiratory sensitisation. Yet, they do not allow for a definite prediction of respiratory sensitisation in humans.

Studies in Humans

Allergic Reactions in Humans

Systemic (e.g., anaphylaxis) or localised (e.g., contact dermatitis) allergic reactions have been associated with formaldehyde exposure (Cronin, 1991, Liden *et al*., 1993, Lindskov, 1982, Andersen and Maibach, 1984, Trattner *et al*., 1998, Ebner and Kraft, 1991).

Skin

The thresholds for elicitation of allergic contact dermatitis in sensitised subjects range from 30 ppm (w/w), aqueous solution, for patch testing to 60 ppm (w/w) for products containing formaldehyde. A threshold for induction has not been clearly established, but it is estimated to be less than 5 % aqueous solution (ACGIH, 1991).

Respiratory Tract

Formaldehyde induced asthma has been studied and findings from detailed clinical evaluations of suspected subjects suggest that it is rare, if it exists at all (Frigas *et al*., 1984, Nordman *et al*., 1985, Grammer *et al*., 1993).

Effects on Pulmonary Function in Humans

No significant pulmonary function decrements have been observed in adults with or without asthma after three hours of exposure to 0.5 to 3 ppm (3.6 mg/m^3) formaldehyde (Kulle *et al.*, 1987, Sauder *et al*., 1986, 1987). Other studies show no pulmonary effects in adults at the same levels of formaldehyde but for differing periods of time (Schachter *et al*., 1986, 1987, Green *et al*., 1987, 1989, Witek *et al*., 1987, Harving *et al*., 1990). Although asthmatics are considered to be more sensitive to irritants, studies show they are not particularly sensitive to formaldehyde (Green *et al*., 1987, Sauder *et al*., 1986, 1987, Witek *et al*., 1987).

A slight degree of reversible airway obstruction might appear at levels approaching 2 ppm in both asthmatics and non-asthmatics. Levels of 1 or 2 ppm formaldehyde induced pulmonary function changes in a small group of individuals characterised as formaldehyde-sensitive (less than 1 to 5 percent of the total population tested) (Nordman *et al*., 1985).

Studies involving large numbers of occupationally exposed populations (84 to 254) in the wood products, funeral services, and resin manufacturing industries, show no evidence of diminished lung function after exposure to mean formaldehyde concentrations of up to 2 ppm (Nunn *et al*., 1990, Holness and Nethercott, 1989). Smaller studies of chemical, furniture, and plywood workers exposed to mean concentrations of 0.3 ppm formaldehyde or greater showed small and transient effects on lung function that were reversible after relatively short periods without exposure (Alexandersson and Hedenstierna, 1989).

An increase in chronic respiratory symptoms (cough and phlegm, wheeze, attacks of breathlessness) and changes in pulmonary function, measured as peak expiratory flow rate, was reported in children aged 5-15 in homes with formaldehyde levels of 60 to 140 ppb in their homes with co-exposure to environmental tobacco smoke. Adult smokers also showed the same effect, but to a lesser degree (Krzyzanowski *et al.*, 1990).

Conclusion

Formaldehyde is a skin sensitiser in animals. Yet, there is no indication of respiratory sensitisation in a specially designed animal study. Most epidemiological studies show no effect on lung function in either asthmatics or non-asthmatics. No clear evidence of formaldehyde-induced asthma attributable to immunologic mechanisms has been identified. In some individuals contact dermatitis may occur.

3.1.5 Repeated Dose Toxicity

Studies in Animals

Inhalation

The most extensive database is available for inhalation exposure in rats. Table 3.5-1 demonstrates NOAECs and LOAECs for nasal pathology derived from inhalation studies with rats depending on duration of the studies:

Table 3.1.5-1 Studies with Repeated Inhalative Exposure of Rats

Duration	NOAEC [ppm]	LOAEC [ppm]	References
4 to 6 weeks	2	6.2	Monticello 1990 Monticello *et al.*, 1991
3 months	1 – 2	4	Woutersen *et al.*, 1987 Wilmer *et al.* 1989
longer than 12 months	1 – 2	2 - 6	Monticello, 1990 Kerns *et al.*, 1983

The ranges of the values are caused by the different concentrations selected in the various studies.

High concentrations of formaldehyde (10 - 20 ppm) cause marked hyperplasia and squamous metaplasia of the nasal respiratory epithelium. The lesions are primarily located in the anterior part of the nose and spread with increasing exposure time and concentrations to more distal locations in the nasal cavity (Monticello, 1990; Kerns *et al.*, 1983). The lesions developing in the nasal cavity at high concentrations increase in severity with prolonged exposure and, depending on severity, are not fully reversible even after considerable post exposure observation periods (Monticello, 1990).

No histopathological changes were found in the lungs or in other organs in various chronic studies (Kerns *et al.*, 1983). This is explained by the quantitative deposition of formaldehyde in the upper respiratory tract following an anterior-posterior gradient. Detailed dosimetry information is presented via CIIT (1999). From Table 3.5-1 it can be seen that concentrations of 1 - 2 ppm (1 – 2.5 mg/m^3) do not cause histopathologically detectable nasal damage, independent of exposure duration. The concentration-time-response pattern for non-neoplastic nasal lesions induced by inhalation of formaldehyde in the rat is characterised by three concentration categories:

1. a no adverse effect concentration range of 1 - 2 ppm (1 – 2.5 mg/m^3) which is independent from exposure duration (NOAEC)

2. a low effect concentration range 2 to 6 ppm (2.5 - 7 mg/m^3) which is also independent from exposure duration (LOAEC)

3. a marked effect concentration range > 6 ppm (7 mg/m^3) in which the expansion and severity of effects varies with duration of exposure.

The findings described above and studies with various exposure regimes leading to comparable cumulative doses (c x t products) using different concentrations (Rusch *et al.* 1983; Wilmer *et al.*,1987 and 1989), lead to the conclusion that below concentrations of 10 ppm (12 mg/m^3) epithelial damage in the nasal cavity of rats is concentration-dependent but not cumulative dose-dependent. The increasing severity of damage in higher concentrations is a function of the concentration. Another way of expressing this result is that formaldehyde toxicity is independent of

the total dose (c x t) but that it depends on the dose rate [(c x t)/t = c] or concentration. This can be explained by saturation of detoxification pathways for formaldehyde at high concentrations. Strong non-linearity in the induction of cell proliferation, DNA-protein-crosslinks, cytotoxic effects and carcinogenicity are observed (CIIT 1999). The observed non-linearity is likely attributable to a large extent to mechanisms present in biological systems to deal with low levels of formaldehyde.

Inhalative Exposure of Other Species

Qualitatively the same findings as described for rats were found in inhalation studies of various durations in mice, hamsters, guinea pigs and monkeys. Table 3.5-2 gives an overview on NOAECs and LOAECs for mice and monkeys. Mice and hamsters show somewhat higher NOAECs than rats, guinea pigs and monkeys. At least in mice, this may be attributed to the change in respiration pattern due to sensory irritation.

Concerning systemic toxicity, the studies cited in Table 3.5-2 do not report evidence of substance-related lesions outside of the upper respiratory tract.

Table 3.1.5-2 Studies with Repeated Inhalative Exposure of Mice and Monkeys

Species	NOAEC [ppm]	LOAEC [ppm]	References
Mouse			
3 months	2	4.1	Maronpot *et al.*, 1986
24 months	2	5.6	Kerns *et al.*, 1983
Monkey	1	3 - 6	Rusch *et al.*, 1983
1.5 to 6 months			Monticello *et al.*, 1989

The ranges of the values are caused by the different concentrations selected in the various studies.

Dermal

Repeated exposure studies in mice were performed using dermal application, mostly in the context of skin initiation / promotion (Krivanek *et al.*, 1983; Iversen, 1986). None of these studies showed evidence of substance-specific systemic toxicity. In the study of Krivanek *et al.* a formaldehyde solution in acetone/water 50:50 was tested on 30 mice. Initially 50 µl of a 10% solution (5 mg/animal = 125 mg/kg b.w.) was applied and then 100 µl of a solution containing 0.1, 0.5, or 1% (2.5, 12.5, or 25 mg/kg b.w., respectively) was applied 3 times a week for 26 weeks. After termination of exposure, the mice were post-observed for additional 26 weeks. Local irritation to mouse skin was minimal at formaldehyde concentrations of 0.5 to 1% (Krivanek *et al.*, 1983).

skin irritation NOAEC (mouse, dermal, 26 weeks) 0.1%
skin irritation LOAEC (mouse, dermal, 26 weeks) 0.5%
systemic effect NOAEC (mouse, dermal, 26 weeks) $\geq$ 1% (highest concentration tested)

Oral

A drinking water study with a duration of 2 years using dosages of up to 82 mg/kg b.w./day (males) and 109 mg/kg b.w./day (females) was performed in rats (Til *et al.*, 1989). The doses correspond to calculated formaldehyde concentrations in the drinking water of 20, 260 and 1900 mg/l. Liquid consumption was considerably decreased (40%) in the high dose group in both genders. The rats in the mid-dose group consumed less liquid than the controls did, but the differences were generally not significant.

A decreased food consumption, reduced body weight development and some unspecific findings in clinical pathology, which could be similarly produced by water restriction, occurred at the high concentration. At this concentration lesions were found in the forestomach and in the glandular stomach. Hyperkeratosis, hyperplasia and ulceration of the forestomach epithelium, as well as focal atrophic gastritis, glandular hyperplasia erosions/ulcerations and submucosal inflammatory infiltration in the glandular stomach were diagnosed. This finding is in line with the irritant properties of formaldehyde at its portal of entry. No signs of specific systemic toxicity were reported in this study. The NOAEL was 260 mg/l corresponding to 15 and 21 mg/kg b.w. for male and female rats, respectively. Virtually the same results were found in a 28 days drinking water study reported by the same authors (Til *et al.*, 1988 and 1989) and in another 2 years drinking water study with rats by Tobe *et al.*, 1989. In the study of Tobe *et al.* an even higher dose of 5000 mg/l (300 mg/kg b.w./day) was tested. At this high dose a poor general state, reduction of body weight gain and both food and water consumption (ca. 50%), increased mortality (ca. 50% after 12 months) and lesions of the stomach (ulcers and hyperplasia, most pronounced after 12 months) were observed. In a 28 days gavage study with rats decreased body weight gain and increased haematocrit were observed in the high dose group (80 mg/kg b.w./day). Haematocrit was also increased in the mid-dose group (40 mg/kg b.w./day). Other effects reported at 40 and 20 mg/kg b.w./day are interpreted as secondary effects to primary irritation since they are either of doubtful biological significance (i.e. a reduced antibody response without changes in IgM or IgG levels and a slightly reduced phagocytic activity) or without a dose response (i.e. a slight increase in lymph node weights) (Vargova *et al.*, 1993).

Studies in Humans

Because a variety of substances and conditions can cause histological changes in the nasal mucosa, the weight of scientific evidence does not support an association between formaldehyde exposure alone and histopathological changes in human nasal mucosa (Berke, 1987, Holmstroem *et al.*, 1989, Edling *et al.*, 1988, Ballarin *et al.*, 1992). Although several studies have found changes, these cannot be associated with formaldehyde exposure alone and are confounded by other air contaminants. Boysen *et al.* (1990) found no significant histopathology differences in nasal mucosa of 37 workers and 37 controls exposed to 0.5 ppm to over 2 ppm of formaldehyde.

Neurobehavioral Effects

Neurobehavioral effects from mixed exposures to formaldehyde and solvents have been implicated for histology technicians from survey studies (Kilburn *et al.*, 1989, Kilburn and Warshaw,1992, Kilburn, 1994). The contribution by formaldehyde in these findings is complicated by co-exposure to the solvents xylene, toluene and chloroform, which are known to produce neurotoxic effects. These studies are not convincing in identifying formaldehyde as a neurotoxic chemical in humans.

Conclusion

Formaldehyde causes toxic effects only in the tissues of direct contact after inhalation, oral or dermal exposure characterised by local cytotoxic destruction. Toxic effects in the target tissues are dependent upon concentration rather than cumulative dose, and are highly non-linear. The typical locations of lesions in experimental animals are the nose after inhalation, the stomach after oral administration and the skin after dermal application. The nature of the lesions depends on the inherent abilities of the tissues involved to respond to the noxious event and on the local concentration of the substance. Atrophy and necrosis as well as hyper- and metaplasia of epithelia may occur.

The most sensitive No Observed Adverse Effect Concentrations (NOAECs) for morphological lesions are between 1 and 2 ppm for inhalation exposure and the NOAEC was 260 mg/l (corresponding to 15 and 21 mg/kg b.w. for male and female rats) in drinking water in rats. In

dermal studies no systemic toxicity was found for concentrations up to 1% (highest tested concentration level) and the NOAEC for local irritation in mice was 0.1%.

General signs of toxicity occur if the exposure conditions (e.g. concentrations in air or drinking water) lead to an extent of local lesions, which subsequently impair the general health of the exposed animals. This applies for the hepatotoxic effects after *in vivo* exposure reviewed extensively by Beall and Ulsamer 1984. A number of findings indicate, that there is no distant-site toxicity of formaldehyde:

1. Distant site toxicity associated with formaldehyde exposure has not been observed in at least four inhalation bioassays of formaldehyde (Kerns *et al.*, 1983; Sellakumar *et al.*, 1985; Woutersen *et al.*, 1987; Appelman *et al.*, 1988; Monticello, 1990)

2. Formaldehyde concentrations in the blood of rats, monkeys, and humans were not increased by inhalation exposure (Heck *et al.*, 1985; Casanova *et al.*, 1988)

3. Chromosomal aberrations in peripheral lymphocytes of rats were not induced by exposure to a high airborne concentration of formaldehyde (15 ppm; 6 h/day, 5 days) (Kligerman *et al.*, 1984), although chromosomal aberrations can be induced by formaldehyde *in vitro* (WHO IARC, 1995, and chapter 3.1.6 of this report)

4. Chronic administration to rats of very high doses of formaldehyde in the drinking water did not induce hepatotoxicity or cancer (Til *et al.*, 1989)

5. Inhalation of formaldehyde did not cause DNA-protein cross-link formation in the rat bone marrow even under conditions of GSH depletion (Casanova-Schmitz e*t al.*, 1984; Casanova and Heck, 1987). The localization of formaldehyde toxicity in the upper respiratory tract of rats and the absence of distant site toxicity are consistent with the high reactivity and rapid metabolism of inhaled formaldehyde.

In summary, there is no evidence of genuine systemic toxicity or of a systemic target organ. The high reactivity and the fast metabolic degradation of formaldehyde in biological environments prevent its systemic availability via physiological exposure routes.

3.1.6 Mutagenicity

Studies in Animals

In vitro Studies

Formaldehyde is weakly mutagenic in a variety of *in vitro* assays. It induced gene mutations in bacteria (e.g. Ames test by Marnett, 1985) in the absence (and also, generally weaker in the presence) of external metabolic activation (S9-mix). Formaldehyde was also positive in mutation assays with mammalian cells. The mutational profile varies among cell types. However, in many cases the effects were caused by deletions; furthermore point mutations were observed (human and mouse lymphoblast assays by Liber *et al.*, 1989 and by Blackburn *et al.*, 1991). The induction of chromosomal aberrations by formaldehyde was demonstrated (e.g. cytogenetic assays in mammalian cells by Galloway *et al.*, 1986).

Moreover single-strand breaks and DNA-protein crosslinks (DPC) were formed in various mammalian cells, including rat tracheal epithelial cells and human bronchial epithelial cells (e.g. alkaline elution assays by Cosma, 1988a,b).

A recent test demonstrated that chromosomal aberrations, sister chromatid exchanges (SCE) and DPC - but not HPRT gene mutations - in V79 Chinese hamster cells occur within the same concentration range of formaldehyde and are parallel to the cytotoxic effect (Merk and Speit, 1998).

A comprehensive summary of *in vitro* genotoxicity tests is provided by WHO IARC 1995.

In vivo Studies

No convincing evidence of genotoxic effects were detected in tissues other than those of the portal of entry: Chromosomal aberrations in peripheral lymphocytes of rats were not induced in the majority of studies with inhalation of up to 15 ppm (6 h/day, 5 days) (e.g. Kligerman *et al.*, 1984). In another study the inhalation of up to 15 ppm (6 h/day, 5 days/week for up to 8 weeks) caused chromosomal aberrations in pulmonary macrophages (which is considered doubtful due to dosimetric and cell kinetic considerations), but not in bone marrow cells (Dallas *et al.*, 1992). A significant increase in the proportion of bone marrow cells with chromosomal aberrations in rats exposed to 0.4 and 1.25 ppm (0.0005 and 0.0015 mg/l) formaldehyde were described in a poorly documented study by Kitaeva *et al.* 1990. However the outcome of this study is not consistent with the results of all available valid and reliable studies and hence its relevance is doubtful.

A single oral gavage of 200 mg/kg b.w. formaldehyde to rats caused chromosomal aberrations in cells of the gastro-intestinal epithelium; the genotoxic effect correlated with severe local irritations (micronucleus assay by Migliore *et al.*, 1989).

Formaldehyde formed DPC at the sites of first contact. DPC were found in the nasal mucosa of rats (Casanova *et al.*, 1989), but there was no indication of an accumulation of DPC in high-tumour sites of the noses. DPC were similar after acute and subchronic exposures, suggesting that rat nasal DPC are rapidly removed (Casanova *et al.*, 1994).

Formaldehyde inhalation by rhesus monkeys caused DPC in the mucosa of the middle turbinate at 0.7 ppm (ca. 0.0009 mg/l) and above; lower DPC concentrations were observed in the larynx, trachea, carina and in the proximal portions of the major bronchi and no DPC were found in the maxillary sinuses and lung parenchyma. The concentration-effect relationship of DPC-formation in the respiratory tract is non-linear with a steep increase above concentrations of about 4 ppm (Casanova *et al.*, 1991).

There are five dominant-lethal tests available (four in mice and one in rats). Tamada *et al.* 1978 performed a test with oral application of 70 mg/kg b.w. to mice with no effects. Likewise two tests with *i.p.* administration of up to 40 mg/kg b.w. to mice exhibited no effects (Eppstein et al., 1968 and 1972). Whereas two others with *i.p.* administration of 50 mg/kg b.w. and 0.6 mg/kg b.w. to mice and rats, respectively, exhibited an effect (Fontignie-Houbrechts, 1981, Odeigah, 1997). However, none of these tests is considered valuable for evaluating toxicity *in vivo* because they are either invalid or treatment was not performed via a relevant route of exposure.

Studies in Humans

Results of human cytogenetic population monitoring studies are somewhat equivocal, as noted in WHO IARC (1995). An increased incidence of micronucleated buccal or nasal mucosal cells was observed in occupationally exposed subjects (Ballarin *et al.*, 1992, Suruda *et al.*, 1993, Titenko-Holland *et al.*, 1996, He *et al.*, 1998). Chromosomal aberrations and sister chromatid exchanges (SCE) in peripheral lymphocytes of exposed persons were seen in some studies (Bauchinger and Schmid, 1985, Yager *et al.*, 1986) but not in others (Fleig *et al.*, 1982, Thomson *et al.*, 1984, Ying *et al.*, 1999). Interpretation of these results is difficult because of the small number of subjects, co-exposure to wood dust, and lack of details in the reports. At best a weak positive response is indicated, at the site of initial contact.

Conclusion

In vitro, formaldehyde is able to induce gene mutations and chromosomal aberrations in mammalian cells without (and also in presence of) external metabolic activation. DNA-protein crosslinks are a sensitive measure of DNA interaction by formaldehyde.

In vivo, the overall evidence of available studies supports the conclusion that the genotoxic effects after exposure via relevant routes are limited to those cells which are in direct contact with formaldehyde and no effects are observed in distant-site tissues. This is consistent with formaldehyde's high reactivity with many cellular nucleophiles and its rapid metabolic degradation.

Cytogenetic population monitoring studies are somewhat equivocal and the interpretation is difficult. At best a weak positive response is indicated, at the site of initial contact.

In conclusion, formaldehyde is a locally effective mutagen exhibiting only weak effects.

3.1.7 Carcinogenicity

Inhalation

Markedly increased numbers of neoplastic lesions of the nose were found in rats (Kerns *et al.*, 1983; Monticello *et al.*, 1992, 1996) after chronic inhalation exposure to formaldehyde vapour at concentrations of approx. 10 ppm (12 mg/m^3) or above. Squamous cell carcinoma (SCC) was the predominant lesion. An increase in the numbers of polyploid adenomas and papillomas of the nasal epithelium were also observed in some studies (Kerns *et al.*, 1983; Monticello *et al.*, 1996). These benign tumours occurred at or above concentrations of 10 ppm (12 mg/m^3) (Monticello *et al.*, 1996) or without clear concentration response relation (Kerns *et al.*, 1983).

The incidence of squamous cell carcinomas shows a very steep concentration-effect curve (see Table 3.1-7), strongly suggesting a non-linear dose-response relationship for tumourigenic activity.

Woutersen *et al.* (1989) found an increase in the incidence of nasal tumours in rats after controlled damage to the nasal mucosa by electrocoagulation followed by exposure to 10 ppm (12 mg/m^3) formaldehyde for 28 months (squamous cell carcinomas in 15/58 = 26%).

Mice were markedly less susceptible to inhalation of formaldehyde with a statistically non-significant increase in nasal carcinoma reported in approx. 1% of the animals exposed to 14.3 ppm (17 mg/m^3) (Kerns *et al.*, 1983).

No tumourigenic response was produced in Syrian hamsters after long term inhalation of formaldehyde up to 30 ppm (36 mg/m^3) (Dalbey, 1982).

Table 3.1-7 Incidence of squamous cell carcinoma in rats

Concentration [ppm]	Incidence [number]	Incidence [%]
0[1,2,3]	0/232 0/90 0/198 0/32 (27 at risk)	0
0.3[3]	0/32 (27 at risk)	0
0.7[2]	0/90	0
2.0[1,2]	0/236 0/96	0
2.2 [3]	0/32 (27 at risk)	0
5.6 [1]	2/225	1
6.0 [2]	1/90	1
9.9 [2]	20/90	22
14.3 [1]	103/232	44
14.9 [3]	14/32 (27 at risk)	43(52)
15 [2]	69/147	47

1 Kerns *et al.*, 1983; *2* Monticello *et al.*, 1996; *3* Tobe *et al.*, 1985; Kamata *et al.* 1997

Dermal

Intermittent dermal treatment of mice with formaldehyde (up to 10%) for application periods up to 26 weeks followed by different observation times did not lead to skin tumour development in the presence of skin irritation (Krivanek *et al.*, 1983).

Dermal initiation/promotion studies in mice using dimethylbenz[*a*]anthracene (DMBA) as initiator and 48 week promotion (about 4% formaldehyde in acetone, Spangler and Ward, 1983) or 60 week promotion (up to 1% formaldehyde in acetone/water, Iversen 1986) resulted in the evidence of a weak promoting potential.

Oral

A chronic drinking water study with doses up to 82 mg/kg b.w. (males) and 109 mg/kg b.w. (females) was performed in rats (Til *et al.*, 1989). The doses correspond to calculated formaldehyde concentrations in the drinking water of 20, 260 and 1900 mg/l. At the high dose some impairment of general health and non-neoplastic kidney lesions were found. The kidney lesions were mainly ascribed to the dehydration of the animals due to the impalatability of the drinking water preparation. In another 2 years drinking water study with rats by Tobe *et al.*, 1989, non-neoplastic stomach lesions were found at levels of 1000 mg/l (approx. 50 mg/kg b.w.). The stomach lesions were ascribed to the irritant properties of the formaldehyde solutions. The studies did not find any increase of local or systemic tumour incidence.

Soffritti *et al.*, 1989, reported leukaemia and gastro-intestinal tumours after chronic drinking of water with up to 2500 mg/l. The study was challenged by Feron *et al.* 1990, due to several methodological deficiencies, i.e. because the leukaemia incidence was not significantly different from methanol controls and was within the range of historical controls, because there was a lack of dose response relation for gastro-intestinal tumors, because there was a heterogeneity of tumour

types in both leukaemias and gastrointestinal tumours, and because non-neoplastic lesions were not reported. Moreover, the results were clearly disproved by the studies of Til *et al.*, 1989 and Tobe *et al.*, 1989.

Takahashi *et al.*, 1986 performed an initiation/promotion study in rats with MNNG (Methyl-*N*-nitrosoguanidin) as initiator and formaldehyde as promotor. They found a tumour promoting activity in the gastric mucosa in rats initiated with carcinogenic MNNG by treatment with drinking water with 5000 mg/l formaldehyde for 32 weeks accompanied by non-neoplastic epithelial lesions.

Other Studies Related to Carcinogenicity

Initiation and/or promotion models using mouse skin and rat stomach (*cf.*above) indicated a weak promoting potential.

Studies in Humans

Non-respiratory Tract Cancers in Humans

Possible associations between formaldehyde and cancers of various organs have been examined in epidemiology studies in occupationally exposed populations. In most epidemiology studies, the potential association between exposure to formaldehyde and cancer of the respiratory tract has been examined. In some studies increased risks of various non-respiratory tract cancers (e.g. multiple myeloma, non-Hodgkin´s-lymphoma (NHL), melanoma, brain, connective tissue, pancreatic, leukemic, lymphoid and haematopoietic, colon) have been observed, but without any consistent pattern and without evidence of a causal relationship with formaldehyde exposure. Since kinetic studies (*cf.*3.1.1) indicate that most inhaled formaldehyde is deposited within the upper respiratory tract, available evidence for tumours at sites other than the respiratory tract does not fulfil criteria of causality (e.g. consistency, biological plausibility).

Nasal and Nasopharyngeal Cancers in Humans

There is no convincing evidence of increased risks of nasopharyngeal cancer in cohort studies of populations of professionals or industrial workers exposed to formaldehyde, since the total number of cases of this rare cancer is small.

In cohort studies with anatomists or mortuary workers (Hayes *et al*., 1990) and industrial workers (Hansen and Olsen, 1995), no increased risk of nasopharyngeal cancer was found. In a cohort of 11000 garment workers, the number of deaths was too small to evaluate (Stayner *et al*., 1988). In a cohort of 14000 in six chemical plants in the UK, only one nasal cancer was observed versus 1.7 expected (Gardner *et al*., 1993). A cohort study of 26000 workers at ten plants in the USA showed an increased risk for nasopharyngeal cancer (Blair *et al*., 1986). However, subsequent analyses revealed that exposure to particulates was present in five of seven deaths, a cluster of four of the seven deaths occurred in one particular plant, employment was less than 1 year in three of the seven cases, and the four deaths at one particular plant occurred equally in short- and long-term workers (Blair *et al*., 1987, Collins *et al*., 1987, Marsh *et al*., 1996).

In case-control studies, while sometimes no increase was observed, overall, significantly increased risks of nasopharyngeal cancer were observed among workers with 10-25 years of exposure or in the highest exposure category in three out of four investigations (Vaughan *et al*., 1986, Roush *et al*., 1987, West *et al*., 1993, Olsen and Asnaes, 1986).

Risk for nasal squamous cell carcinomas was increased in two studies (Olsen and Asnaes, 1986, Hayes *et al*. 1990) and not increased in a third one (Luce *et al*., 1993). Although there were limitations to most of these studies as described in detail in the WHO IARC, 1995 evaluation, WHO IARC concluded that based upon the lack of consistency between cohort and case-control studies, the epidemiology studies were suggestive, but inconclusive with regard to a causal role of

occupational exposure to formaldehyde in squamous cell carcinoma of nasal cavities and paranasal sinuses. In an updated meta-analysis of these formaldehyde and upper respiratory tract cancer studies, the data do not support a causal relationship between formaldehyde exposure and nasopharyngeal cancer (Collins *et al*., 1997).

Other Respiratory Tract Cancers in Humans

There is no convincing evidence for a causal association between formaldehyde and lung cancer in case-control and cohort studies. In most case-control studies, there have been no increases in lung cancer. (Bond *et al*., 1986, Brownson *et al*., 1993, Andjelkovich *et al*., 1994, Gerin *et al*., 1989).

In cohort studies of professional and industrial workers no significant excesses of the cancers of the trachea, bronchus or lung (Hayes *et al*., 1990, Andjelkovich *et al*., 1995), the buccal cavity or pharynx (Matanoski, 1989, Hayes *et al*., 1990, Andjelkovich *et al*., 1995), the lung (Stroup *et al*., 1986, Bertazzi, 1989, Hansen and Olsen, 1995) or the respiratory system (Matanoski, 1989) were observed. In a cohort of 11000 garment workers, there was no increase in cancers of the trachea, bronchus or lung, buccal cavity or pharynx (Stayner *et al*., 1988). In a cohort of 14000 of six chemical plants in the UK there was a non-significant excess of lung cancers in workers. Standardized mortality ratio (SMR) for lung cancer was significantly increased in a highly exposed subgroup of one plant. However there was no relationship with years of employment or cumulative exposure. There was no excess of buccal cavity or pharynx cancer (Gardner *et al*., 1993). There was a slight (1.3 fold) but statistically significant excess of deaths due to lung cancer among a subcohort with ≥20 years since first exposure out of an industrial cohort of 26000 workers at ten plants in the USA. (Blair *et al*., 1986). However, follow-up studies to that work have shown no convincing evidence of an exposure-response relationship (Blair *et al*., 1990, Marsh *et al*., 1992, Blair *et al*., 1994, Callas *et al*., 1996).

No significant association between squamous cell carcinoma of the oral cavity, pharynx, larynx, and oesophagus and formaldehyde exposure was seen in a community-based case-control study (Gustavsson *et al*., 1998).

<u>Conclusion</u>

Formaldehyde has been tested in chronic animal studies and a number of other experimental models to assess its carcinogenic potential in different species. Inhalation of concentrations of 10 ppm (12 mg/m^3) or above leads to clear increases in nasal tumour incidence in rats. Marked non-neoplastic pathological lesions of the nasal cavity were present at tumourigenic concentrations (*cf*.3.1.5). In contrast, no significant numbers of tumours were seen in mice and Syrian hamsters following chronic exposure to concentrations up to 14.3 or 30 ppm (17 - 36 mg/m^3), respectively.

These clear species differences appear to be related, in part, to the local dosimetry and disposition of formaldehyde in nasal tissues. For example, mice possess the capacity to minimise inhalation of irritating substances more efficiently than rats through a reflex depression of respiratory rate.

The majority of the tumours in rats were localised on the lateral surface of the anterior portion of the nasoturbinate and adjacent lateral wall, as well as the mid ventral nasal septum. This pattern and site specificity of the response is believed to be attributable to the structure of the nasal cavity of rats, which controls intranasal airflow and the deposition of formaldehyde in the upper respiratory tract (Monticello *et al.*, 1996). Hence, species differences in nasal anatomy and respiratory physiology may have a profound effect on susceptibility to formaldehyde-induced nasal tumours (CIIT, 1999).

Squamous metaplasia of respiratory epithelium, which normally is present at the major tumour locations, may play a significant role for tumour formation.

No increased incidence of tumours was found in other organs after inhalation, and administration routes other than inhalation did not result in local or systemic tumour formation.

Studies to elucidate the tumourigenic mechanism of action of formaldehyde indicate that its promoting activity is a major factor in tumour development. This is in line with the finding that stimulation of cell proliferation seems to be an absolute prerequisite for tumour development (Monticello *et al*., 1992; Monticello *et al.*, 1996).

Tissue damage was shown to play a crucial role in the tumour induction process, since nasal cancer was only found at concentrations inducing epithelial degeneration and cell proliferation, with the cancer incidence further enhanced by artificial damage to nasal mucosa (Woutersen *et al.*, 1989).

The dose response relations of DPC formation (surrogate for tissue dose and saturation of detoxification pathways; Casanova *et al.* (1989, 1994)), cell proliferation (marker of tissue damage; Monticello *et al*. 1996) and incidence of nasal tumours (see Table 3.8-1) show a steep increase at exposure levels (hockey stick behaviour) beyond about 3 ppm (see Fig. 1).

In epidemiological studies in occupationally exposed populations, there is limited evidence of a causal relationship between formaldehyde exposure and nasal tumours. Taking into account the extensive information on its mode of action, formaldehyde is not likely to be carcinogenic to humans under exposure conditions that do not cause cytotoxic effects and hence formaldehyde is not likely to be a potent carcinogen to humans under low exposure conditions.

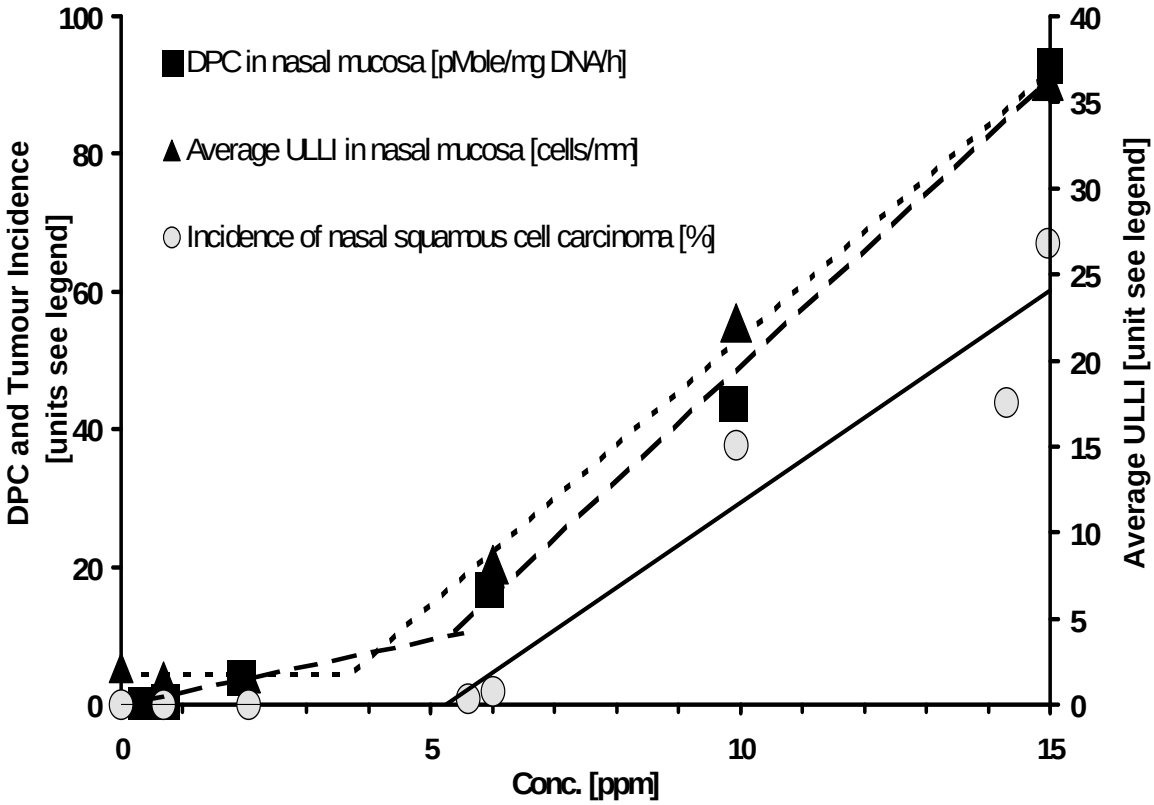


Fig. 1: Concentration-response curves of DNA Protein Crosslink (DPC) formation rate [pMole/mg DNA/h], cell proliferation [labeled cells/ mm (unit length labeling index, ULLI)] and incidence of nasal squamous carcinoma. The data points were gathered from Casanova *et al.* (1989, 1994) and Monticello *et al.* 1996. The lines are derived by linear regression using data points, which obviously fit the lines.
The figure shows that in the range of concentrations between 3 and 6 ppm a steep increase of all three effects occurs. Additionally it becomes obvious that the increase of DPC formation and cell proliferation run parallel and start at lower concentrations than increase in tumor formation. This behavior suggests that DPC and increase in cell proliferation rate are interrelated and that increased cell proliferation is a prerequisite for tumor development.

3.1.8 Toxicity for Reproduction

Studies in Animals

Effects on Fertility

No studies devoted solely to reproductive effects using formaldehyde were performed.

Doses that induced stomach lesions in the chronic drinking water study (*cf.*3.1.5, Til *et al.*, 1989) with rats (approx. 82 and 109 mg/kg b.w./day for male and female rats, respectively, did not reveal adverse effects on reproductive organs. In this study, ovaries and testes of a subset of animals (at least 10 animals per dose and gender) were weighed in weeks 53, 79 and 105. Histological examinations of ovaries, mammary glands, uteri and testes, prostate glands, epididymides were performed on all animals of control and high-dose groups. Additionally, mammary glands, ovaries and testes of three animals of low- and mid-dose groups were examined in week 105.

Furthermore, there are studies on the effect of formaldehyde on sperm morphology after oral gavage (Ward *et al.*, 1984) and *i.p.* administration (Odeigah 1997; Yi *et al.*, 2000). There was no

significant effect after oral gavage but there emerged some effects in the *i.p.* studies. Effects on testicular morphology and sperm parameters after i.p. administration of 5 to 15 mg/kg formaldehyde solutions for 30 consecutive days were reported by Chowdhury *et al.* 1992 and Majumder *et al.* 1995. The i.p. administration was accompanied by considerable non dose dependent impairment of body weight development, which was probably due to marked peritoneal irritation. The presentation of results prevents the utility of the data for final evaluation. Yet, the significance of effects after *i.p.* administration is doubtful.

Additionally, multi-generation studies with hexamethylenetetramine, which is an *in vivo* formaldehyde liberator, did not give convincing evidence of reproductive disturbance up to concentrations of 2% in the drinking water in rats. The actual concentration and kinetics of released formaldehyde is not known. However, formaldehyde concentrations in the gonades are probably higher after hexamethylenetetramine exposure than the concentrations achieved by formaldehyde exposure via physiological routes (which are expected to be virtually zero) (Della Porta, 1970).

Developmental Toxicity

An inhalation prenatal toxicity study using up to date methodology (Martin, 1990) showed the absence of teratogenicity after inhalation of 2, 5, or 10 ppm (2.4, 6, 12 mg/m^3) of formaldehyde during gestation days 6 - 15 in the rat. Two control groups were included in this study, one was handled in an identical manner to the formaldehyde treated groups except that it was treated with air, and the other was maintained in the animal room throughout the study without treatment. In the group exposed to 10 ppm formaldehyde, a significant decrease in maternal food consumption and body weight gain was observed; pregnancy parameters were unaffected. In the other groups no evidence of maternal toxicity was found. The overall incidences of litters and foetuses with major malformations, minor external and visceral anomalies and minor skeletal anomalies were similar. At the 10 and 5 ppm levels, an apparently significant dose-related decrease in ossification was detected in the bones of the pelvic girdle. However, this alteration was only significant when compared with air-controls, but not when compared with room-controls. According to the authors, this finding was associated with slightly larger litter sizes being accompanied by slightly decreased foetal weights in the 10 and 5 ppm groups. The authors also state that, neither this finding nor other parameters assessed demonstrated any adverse effect on the conceptus due to formaldehyde exposure under the conditions used in this study. Therefore the NOAECs are: NOAEC (maternal) 5 ppm (6 mg/m^3), NOAEC (foetal) 10 ppm (12 mg/m^3). These results are confirmed by a teratogenicity study by Saillenfait *et al.*, 1989 using even higher formaldehyde concentrations (up to 40 ppm, 50 mg/m^3). At 20 ppm (25 mg/m^3) and above a slight decrease of the foetal weights was observed. These concentrations cause severe irritations of the upper respiratory tract.

Administration of up to 9.4 mg/kg b.w./day formaldehyde in feed to dogs on days 4 through 56 of their pregnancy did not result in prenatal toxicity (Hurni and Ohder 1973).

Studies in Humans

No increased risk of spontaneous abortion was seen after maternal or paternal exposure to formaldehyde based upon survey questionnaire results (Hemminki *et al*., 1985, Taskinen *et al*., 1994, 1999, Lindbohm *et al*., 1991). In one study of cosmetologists who used formaldehyde based disinfectant products as well as other chemicals a slight excess of spontaneous abortions is reported, but that finding could not be linked to any chemical exposure (John *et al*., 1994). Formaldehyde exposure levels were not reported in these studies. Low birth weight was not statistically significant associated with formaldehyde exposure in a population-based epidemiological study (Grazuleviciene *et al*., 1998). No effects on sperm morphology were seen inexposed individuals exposed to formalin from a hospital autopsy service (Ward *et al*., 1984). A comprehensive review of the reproductive and developmental effects is given by Collins *et al.*, 2001.

Conclusion

There are no indications of a specific toxicity of formaldehyde to foetal development and no effects on reproductive organs were observed by chronic oral administration of formaldehyde to male and female rats. Amounts of formaldehyde, which produce marked toxic effects at the portal of entry do not lead to an appreciable systemic dose and thus do not produce systemic toxicity (*cf.*3.1.5). Formaldehyde readily undergoes spontaneous reactions with cellular nucleophiles and is rapidly metabolised by various enzymes (*cf.*3.1.1).

There is no significant evidence, that formaldehyde causes spontaneous abortions or has an effect on sperm morphology in humans.

In WHO IARC (1995) it is concluded that "whether administered by inhalation, ingestion or the skin to various species, formaldehyde did not exert adverse effects on reproductive parameters or foetal development" (WHO IARC, 1995).

3.2 Initial Assessment for Human Health

Formaldehyde had acute effects in mammals: LD_{50} (rat, oral) 600 – 800 mg/kg b.w.,LC_{50} (rat, inhalation, 4 h) 578 mg/m^3 (480 ppm). Inhalation of high concentrations (> 120 mg/m^3) of formaldehyde caused hypersalivation, acute dyspnoea, vomiting, muscular spasms, convulsions and finally deaths. Histopathology examination showed respiratory tract irritation, bronchioalveolar constriction and lung oedema. Formaldehyde was irritating to the eyes, and aqueous solutions of formaldehyde (0.1% to 20%) were irritating to the skin of rabbits. Formaldehyde was sensitising in the guinea pig maximisation test and the local lymph node assay with mice. On the other hand, specially designed studies (IgE tests, cytokine secretion profiles of lymph node cells) did not reveal evidence of a potential for respiratory sensitisation in mice.

In humans, transient and reversible sensory irritation of the eyes and respiratory tract has been observed in clinical studies and epidemiological surveys. Odour threshold for most people ranges between 0.5 and 1 ppm. In general, eye irritation, the most sensitive endpoint, is associated with airborne concentrations beginning in the range of 0.3 to 0.5 ppm. Eye irritation does not become significant until about 1 ppm, and rapidly subsides. Moderate to severe eye, nose and throat irritation occurs at 2 to 3 ppm. Sensory irritation has also been reported at lower levels, but is then difficult to distinguish from background. Most studies show no effect on lung function in either asthmatics or non-asthmatics. Formaldehyde causes skin irritation and has corrosive properties when ingested. In some sensitised individuals, contact dermatitis may occur at challenge concentrations as low as 30 ppm.

Formaldehyde as a gas is highly reactive and is absorbed quickly at the point of contact. It is rapidly metabolised and is also produced by endogenous metabolism. Exposure to high concentrations (up to 15 ppm in rats) does not result in increased blood concentrations. Repeated formaldehyde exposure caused toxic effects only in the tissues of direct contact after inhalation, oral or dermal exposure characterised by local cytotoxic destruction and subsequent repair of the damage. The typical locations of lesions in experimental animals were the nose after inhalation, the stomach after oral administration and the skin after dermal application. The nature of the lesions depended on the inherent abilities of the tissues involved to respond to the noxious event and on the local concentration of the substance. Atrophy and necrosis as well as hyper- and metaplasia of epithelia may occur. The most sensitive No Observed Adverse Effect Levels (NOAELs) for morphological lesions in repeated dose studies were between 1 and 2 ppm for inhalation exposure, about 0.1% after dermal exposure and about 260 mg/l in drinking water.

Formaldehyde is weakly genotoxic and was able to induce gene mutations and chromosomal aberrations in mammalian cells. However, the genotoxic effects were limited to those cells, which

are in direct contact with formaldehyde, and no effects could be observed in distant-site tissues. DNA-protein crosslinks are a sensitive measure of DNA modification by formaldehyde. In conclusion, formaldehyde is a directly acting locally effective mutagen.

Chronic inhalation of concentrations of 10 ppm and higher led to clear increases in nasal tumour incidence in rats. Most of the nasal tumours were squamous cell carcinomas. Marked non-neoplastic pathological lesions of the nasal epithelium accompanied them. No increased incidence of tumours was found in other organs after inhalation, and administration routes other than inhalation did not result in local or systemic tumour formation. The damage of nasal tissue played a crucial role in the tumour induction process, since nasal cancer was only found at concentrations inducing epithelial degeneration and increased cell proliferation. Thus the stimulation of cell proliferation seems to be an important prerequisite for tumour development. Although formaldehyde exhibits some genotoxic activity, the correlation between cytotoxicity, cell proliferation and the induction of nasal cancer in rats provides a convincing scientific basis for aetiology of the carcinogenic response to be cytotoxicity driven.

In contrast to that, no significant numbers of tumours were seen in mice and Syrian hamsters following chronic exposure to concentrations of up to 14.3 or 30 ppm, respectively. These clear species differences appeared to be related, in part, to the local dosimetry and disposition of formaldehyde in nasal tissues. Species differences in nasal anatomy and respiratory physiology may have a profound effect on susceptibility to formaldehyde-induced nasal tumours.

In epidemiological studies in occupationally exposed human populations, there is limited evidence of a causal association between formaldehyde exposure and nasal tumours. Taking into account the extensive information on its mode of action, formaldehyde is not likely to be a potent carcinogen to humans under low exposure conditions.

There are no indications of a specific toxicity of formaldehyde to foetal development and no effects on reproductive organs were observed after chronic oral administration of formaldehyde to male and female rats. Amounts of formaldehyde, which produce marked toxic effects at the portal of entry, do not lead to an appreciable systemic dose and thus do not produce systemic toxicity. This is consistent with formaldehyde’s high reactivity with many cellular nucleophiles and its rapid metabolic degradation.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

In the following section a selection of results from acute aquatic toxicity tests relevant to risk assessment is summarised:

Acute Toxicity Test Results

Fish

The acute toxicity of formaldehyde to fishes ranges from LC50(96 h) = 6.7 - 1020 mg/l (result of a literature search). The marine fish *Morone saxatilis* was the most sensitive species. In a static test conducted with an aqueous solution of formaldehyde (37% by weight), a LC50(96 h)= 6.7 mg/l was obtained. This value is related to pure formaldehyde (Wellborn 1969). For freshwater fish the lowest effect value of 24.8 mg/l (96h-LC50) was found for *Ictalurus melas* in a flow-through system (Bills et al. 1977).

Invertebrates

Tests conducted with aquatic invertebrates ranged from LC50(24 h) = 0.46 – 1800 mg/l. The salt water organism *Cypridopsis sp*. turned to be the most sensitive species with a LC50(24 h) of 0.46 mg/l (Bills et al. 1977). However, as this low effect value could not be reproduced by other authors in both short- and long-term tests with Cypridopsis vidua, this value is not used for the further effect assessment (Hohreiter and Rigg, 2001). The next lowest effect value of 5.8 mg/l (48h-EC50) was found for Daphnia pulex (Tisler, Zagorc-Koncan, 1996).

Acute toxicity of formaldehyde to *Daphnia magna* was tested using an aqueous solution of formaldehyde (35% solution). EC50(24 h) resulted to be 14.7 and 18.2 mg/l of pure substance (Bringmann and Kuehn 1982 and 1977a). An EC50(48 h) = 29 mg/l for *Daphnia magna* was also measured in a test performed following the OECD guidelines (Janssen and Persoone 1993).

Algae

Toxicity of formaldehyde to *Scenedesmus quadricauda* was investigated in a static cell multiplication inhibition test using an aqueous solution of formaldehyde (35% solution). The toxic threshold (192 h) was 0.88 mg/L referred to the pure substance (Bringmann 1978). The toxic threshold is defined in this investigation as the concentration of the test substance causing 3% inhibition of cell multiplication compared to untreated controls. As there is no information whether the algae were in the exponential growth phase during the whole study, this test is not used for the effect assessment.

Another test with the green algae *Scenedesmus quadricauda* gives a 24h-EC50 of 14.7 mg/l and a 24h-EC10 of 3.6 mg/l for the endpoint oxygen production and consumption (Tisler, Zagorc-Koncan, 1997). Although this result is also not from a standardized algae test, it can be used for the further assessment.

Conclusions on Aquatic effects

Distribution modelling estimates water to be the main target compartment for formaldehyde. The most sensitive organism in an valid acute aquatic toxicity test was *Daphnia pulex* with an EC50 (48 h) of 5.8 mg/l. For the derivation of the PNECaqua an assessment factor of 1000 is applied on this value resulting in a $PNEC_{aqua}$ of 5.8 µg/l.

Toxicity to Microorganisms

In a cell multiplication inhibition test with *Pseudomonas putida*, a 16h-EC3 of 14 mg/l was found (Bringmann and Kühn, 1977b). For the protozoan species *Chilomonas paramaecium* and *Uronema parduzci*, toxic threshold values of 4.5 mg/l after 48 h and 6.5 mg/l after 20 h were determined (Bringmann et al. 1980; Bringmann and Kühn 1980). In an activated sludge respiration inhibition test a 3h-EC50 of 20.4 mg/l was found (Klecka, Landi 1985).

4.2 Terrestrial Effects

Nematodes in peat were killed by application of formalin (37 % formaldehyde solution) at 179 ml/m³ (Lockhart 1972).

Pollen grains of *Lilium longiflorum* which had been sown in a straight line on a culture medium were exposed separately to various concentrations of injurious gases. A 5 h exposure to formaldehyde at 0.44 mg/m³ (0.37 ppm) resulted in a significant reduction in pollen-tube length, whereas a 1 or 2 h exposure was innocuous. When the formaldehyde concentration was increased to 2.88 mg/m³ (2.4 ppm), a 1 h exposure caused a decrease in tube length (Masaru et al. 1976).

These data cannot be used for the determination of a PNECsoil.

4.3 Initial Assessment for the Environment

The global production of formaldehyde in 1999 is estimated to be 5 – 6 million (metric) tons (Asia: 1–1.5 million tons, North America: 1-1.5 million tons, Western Europe: 2-2.5 million tons). Formaldehyde is mainly used as an intermediate in the chemical industry for the production of condensed resins for the wood, paper and textile processing industries (approx. 40 % urea-formaldehyde resins, 10 % phenol-formaldehyde resins, 10 % polyacetal resins and 5 % melamin-formaldehyde resins).

Formaldehyde is also used in the synthesis of methylene dianiline (MDA), diphenylmethane diisocyanate (MDI), hexamethylenetetraamine (HTMA), trimethylol propane and neopentylglycol (in total approx. 25 %), pentaerythritol (5 %) and acetylenic agents (5 %) (BASF-SRI Consulting, Jan. 2000).

Aqueous solutions of formaldehyde are employed as germicides, bactericides and fungicides. The concentration of the substance as diluted disinfectant and sterilising agent is less than 0.5 % (0.9 % in exceptional cases).

The use of formaldehyde as biocide and in other applications is estimated to be 1.5 % of the total production, a relatively small amount compared with its use in the manufacture of synthetic resins and chemical compound (WHO IPCS, 1989). However, related to the total worldwide production amount of 5 to 6 million tons, a total volume of 75 000 to 90 000 t/a is used in this area.

According to Swiss, Danish and Swedish Products Registers formaldehyde is contained in a large number of products, part of them is available for consumers.

Releases into the environment are likely to occur during production and processing as intermediate as well as from use of products containing the substance.

For almost all sites there is no information available about releases into the waste water from production and processing. From the direct use of the substance as e.g. biocide it can be assumed that a very high amount is released into the environment. With an amount of 75 000 to 90 000 t/a worldwide this is a significant pollution source. It can be estimated that formaldehyde contained in consumer products, like cleaning agents is released completely into the wastewater. In addition,

reported use of formaldehyde in fish farming and animal husbandry may lead to a significant environmental exposure.

The favourite target compartment for formaldehyde is water as indicated by Mackay Level I calculation (water: 99 % equilibrium distribution). In air, formaldehyde is expected to be indirectly photodegraded, with a half life of 1.71 d. Direct photolysis is also a relevant removal process. The substance is readily biodegradable. Hydrolysis is not expected under environmental conditions. However in water formaldehyde undergoes essentially complete hydration to yield the gem-diol, methylene glycol. The log P_{OW} was measured to 0.35 at 20 °C. Hence bioaccumulation is unlikely to occur.

In an acute aquatic toxicity test, the most sensitive organism was *Daphnia pulex.* With an EC_{50}(48 h) of 5.8 mg/l. Applying an assessment factor of 1000 according to EU Risk Assessment procedure, a $PNEC_{aqua}$ of 5.8 µg/l can be derived.

5 RECOMMENDATIONS

Environment: The substance is a candidate for further work. No information is available about releases into surface water from production and processing sites. In addition, it can be assumed that from the use of 1.5 % of the worldwide production volume (5 to 6 Mio t/a) as biocide and in other applications i.e. 75 000 – 90 000 t/a a high amount of formaldehyde is released into the environment (e.g. from fish and livestock farming). Product register information shows that formaldehyde is contained in a large number of consumer products, like cleaning agents, detergents, soaps etc. For these applications it can be estimated that the whole amount is released into the waste water. Due to the low PNECaqua of 5.8 µg/l a risk to the aquatic environment cannot be excluded. Therefore, an exposure assessment is recommended.

Human Health: No further work is recommended, because all SIDS endpoints are adequately covered and because exposure is controlled in occupational settings.

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I U C L I D D a t a S e t

Existing Chemical	ID: 50-00-0
CAS No.	50-00-0
EINECS Name	formaldehyde
EC No.	200-001-8
TSCA Name	Formaldehyde
Molecular Formula	CH2O
Producer Related Part	
Company:	BASF AG
Creation date:	01-JUL-1998
Substance Related Part	
Company:	BASF AG
Creation date:	01-JUL-1998
Memo:	OECD HPV Chemicals Programme, SIDS Dossier approved at SIAM 14 (26-28 March 2002)
Printing date:	02-SEP-2003
Revision date:	
Date of last Update:	25-JUN-2003
Number of Pages:	411
Chapter (profile):	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile):	Reliability: without reliability, 1, 2, 3, 4
Flags (profile):	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 Applicant and Company Information

Type: lead organisation
Name: BASF AG
Contact Person: Product Safety Date:
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Homepage: www.basf.com

Flag: Critical study for SIDS endpoint
07-AUG-2002

Type: cooperating company
Name: Atofina SA
Country: France

Flag: Critical study for SIDS endpoint
07-AUG-2002

Type: cooperating company
Name: Borden Chemicals, Inc.
Country: United States

Flag: Critical study for SIDS endpoint
07-AUG-2002

Type: cooperating company
Name: Caldic Chemie BV
Country: Netherlands

Flag: Critical study for SIDS endpoint
07-AUG-2002

Type: cooperating company
Name: Casco Products AB
Country: Sweden

Flag: Critical study for SIDS endpoint
07-AUG-2002

Type: cooperating company
Name: Celanese Ltd.
Country: United States

Flag: Critical study for SIDS endpoint
07-AUG-2002

Type: cooperating company
Name: Cytec Industries, Inc.
Country: United States

Flag: Critical study for SIDS endpoint
07-AUG-2002

Type: cooperating company
Name: Daicel Chemical Industries, LTD.
Country: Japan

Flag: Critical study for SIDS endpoint
07-AUG-2002

Type: cooperating company
Name: DuPont
Country: United States

Flag: Critical study for SIDS endpoint
07-AUG-2002

Type: cooperating company
Name: Dynea Corporation
Country: United States

Flag: Critical study for SIDS endpoint
07-AUG-2002

Type: cooperating company
Name: Dynea Resins BV
Country: Netherlands

Flag: Critical study for SIDS endpoint
07-AUG-2002

Type: cooperating company
Name: Georgia-Pacific Corporation
Country: United States

Flag: Critical study for SIDS endpoint
07-AUG-2002

Type: cooperating company
Name: ISP Marl GmbH
Country: Germany

Flag: Critical study for SIDS endpoint
07-AUG-2002

Type: cooperating company
Name: Methanova GmbH
Country: Germany

Flag: Critical study for SIDS endpoint
07-AUG-2002

Type: cooperating company
Name: Mitsubishi Gas Chemical Company, Inc.
Country: Japan

Flag: Critical study for SIDS endpoint
07-AUG-2002

Type: cooperating company
Name: Mitsui Chemicals, Inc.
Country: Japan

Flag: Critical study for SIDS endpoint
07-AUG-2002

Type: cooperating company
Name: Perstorp AB
Country: Sweden

Flag: Critical study for SIDS endpoint
07-AUG-2002

Type: cooperating company
Name: Solutia Inc.
Country: United States

Flag: Critical study for SIDS endpoint
07-AUG-2002

Type: cooperating company
Name: Sumitomo Seika Chemicals Co., Ltd.
Country: Japan

Flag: Critical study for SIDS endpoint
07-AUG-2002

1.0.2 Location of Production Site, Importer or Formulator

1.0.3 Identity of Recipients

1.0.4 Details on Category/Template

1.1.0 Substance Identification

IUPAC Name: Formaldehyde
Mol. Formula: CH2O
Mol. Weight: 30.03 g/mol

Flag: non confidential, Critical study for SIDS endpoint

21-JAN-2003

1.1.1 General Substance Information

Purity type: other: pure
Substance type: organic
Physical status: gaseous
Purity: 100 - % w/w
Colour: colourless
Odour: pungent

Flag: non confidential, Critical study for SIDS endpoint
23-DEC-2002 (132)

Purity type: other: sales products in aqueous solution
Substance type: organic
Physical status: liquid
Colour: colourless
Odour: pungent

Remark: The sales products in aqueous solution contains in general 35-55% formaldehyde.
Flag: non confidential, Critical study for SIDS endpoint
23-DEC-2002 (42) (132)

1.1.2 Spectra

1.2 Synonyms and Tradenames

Formaldehyd

Flag: non confidential, Critical study for SIDS endpoint
02-DEC-1992

Formaldehyde (8CI, 9CI)

Flag: non confidential, Critical study for SIDS endpoint
02-DEC-1992

Formaldehyde solution

Flag: non confidential, Critical study for SIDS endpoint
02-DEC-1992

Formaldehyde, gas

Flag: non confidential, Critical study for SIDS endpoint
02-DEC-1992

Formalin

Flag: non confidential, Critical study for SIDS endpoint
02-DEC-1992

Formalith

Flag: non confidential, Critical study for SIDS endpoint
02-DEC-1992

Formic aldehyde

Flag: non confidential, Critical study for SIDS endpoint
02-DEC-1992

Formol

Flag: non confidential, Critical study for SIDS endpoint
02-DEC-1992

Methaldehyde

Flag: non confidential, Critical study for SIDS endpoint
02-DEC-1992

Methanal

Flag: non confidential, Critical study for SIDS endpoint
02-DEC-1992

Methyl aldehyde

Flag: non confidential, Critical study for SIDS endpoint
02-DEC-1992

Methylene oxide

Flag: non confidential, Critical study for SIDS endpoint
02-DEC-1992

Morbicid

Flag: non confidential, Critical study for SIDS endpoint
02-DEC-1992

Oxomethane

Flag: non confidential, Critical study for SIDS endpoint
02-DEC-1992

Oxymethylene

Flag: non confidential, Critical study for SIDS endpoint
02-DEC-1992

Paraform

Flag: non confidential, Critical study for SIDS endpoint
02-DEC-1992

1.3 Impurities

CAS-No: 67-56-1
EC-No: 200-659-6
EINECS-Name: methanol
Mol. Formula: CH4O
Contents: .5 - 2 % w/w

Remark: INDEX-No.: 603-001-00-X
Hazard symbol(s): F,T
R-phrase(s): 11,23/24/25,39/23/24/25
The specified pollutions refer to 49 - 49.3 % sales solution of BASF product of formaldehyde
Flag: non confidential, Critical study for SIDS endpoint
23-DEC-2002 (42)

CAS-No: 64-18-6
EC-No: 200-579-1
EINECS-Name: formic acid
Mol. Formula: C H2 O2
Contents: ca. .3 - % w/w

Remark: The specified pollutions refer to 49 - 49.3 % sales solution of BASF product of formaldehyde.

Flag: non confidential, Critical study for SIDS endpoint
23-DEC-2002

CAS-No: 7439-89-6
EC-No: 231-096-4
EINECS-Name: iron
Mol. Formula: Fe
Contents: <= .0001 - % w/w

Remark: The specified pollutions refer to 49 - 49.3 % sales solution of BASF product of formaldehyde.
Flag: non confidential, Critical study for SIDS endpoint
23-DEC-2002

1.4 Additives

CAS-No: 5118-80-9
EC-No: 225-859-0
EINECS-Name: 6,6'-(m-phenylene)bis(1,3,5-triazine-2,4-diamine)
Mol. Formula: C12 H12 N10

Remark: The specified additives refers to 49 - 49.3% sales solution of BASF product of formaldehyde.

Flag: non confidential, Critical study for SIDS endpoint
23-DEC-2002

CAS-No: 7732-18-5
EC-No: 231-791-2
EINECS-Name: water
Mol. Formula: H2O
Contents: ca. 49 % w/w
Funct. of add.: Solvent

Remark: The specified additives refers to 49 - 49.3% sales solution of BASF product of formaldehyde.
Flag: non confidential, Critical study for SIDS endpoint
23-DEC-2002

1.5 Total Quantity

Remark: All production 1999-estimates (calc. 100%):

Asia: 1.0-1.5 mio t/a
North America: 1.0-1.5 mio t/a
Western Europe: 2.0-2.5 mio t/a

World: 5.0-6.0 mio t/a trend antipicated: moderately increasing
Flag: Critical study for SIDS endpoint
23-DEC-2002 (46)

1.6.1 Labelling

Labelling: as in Directive 67/548/EEC
Symbols: (T) toxic

Nota: (B) Some substances (acids, bases etc.) are placed on the market in aqueous solutions at various concentrations and therefore require different labelling since the hazards vary (in Annex 1 the highest concentration is labelled)
(D) Certain substances which are susceptible in spontaneous polymerisation or decomposition are generally placed on the market in a stabilized form. It is in this form that they are listed in Annex 1 to this Directive
Specific limits: yes
R-Phrases: (23/24/25) Toxic by inhalation, in contact with skin and if swallowed
(34) Causes burns
(43) May cause sensitization by skin contact
S-Phrases: (1/2) Keep locked up and out of reach of children
(26) In case of contact with eyes, rinse immediately with plenty of water and seek medical advice
(36/37/39) Wear suitable protective clothing, gloves and eye/face protection
(45) In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible)
(51) Use only in well-ventilated areas

Remark: R-phrase: 40 (new) Limited evidence of a carcinogenic effect.

INDEX-No.: 605-001-00-
Flag: non confidential, Critical study for SIDS endpoint
23-DEC-2002 (150)

1.6.2 Classification

Classified: as in Directive 67/548/EEC
Class of danger: carcinogenic, category 3
Specific limits: yes
Conc./Class. 1: >= 25% T; R 23/24/25-34-40-43
Conc./Class. 2: 5% <= 25% Xn; R 20/21/22-36/37/38-40-43
Conc./Class. 3: 1% <= 5% Xn; R 40-43

Remark: R-phrase: 40 (new) Limited evidence of a carcinogenic effect.

INDEX-No.: 605-001-00-
Flag: non confidential, Critical study for SIDS endpoint
23-DEC-2002 (150)

Classified: as in Directive 67/548/EEC
Class of danger: corrosive
R-Phrases: (34) Causes burns
Specific limits: yes
Conc./Class. 1: >= 25% T; R 23/24/25-34-40-43

Remark: INDEX-No. 605-001-00-5
Flag: non confidential, Critical study for SIDS endpoint
25-MAR-2002 (150)

Classified: as in Directive 67/548/EEC
Class of danger: sensitizing

R-Phrases: (43) May cause sensitization by skin contact
Specific limits: yes
Conc./Class. 1: >= 25% T; R 23/24/25-34-40-43
Conc./Class. 2: 5% <= 25% Xn; R 20/21/22-36/37/38-40-43
Conc./Class. 3: 1% <= 5% Xn; R 40-43
Conc./Class. 4: 0,2% <= 1% Xi; R 43

Remark: INDEX-No. 605-001-00-5
Flag: non confidential, Critical study for SIDS endpoint
25-MAR-2002 (150)

Classified: as in Directive 67/548/EEC
Class of danger: toxic
R-Phrases: (23/24/25) Toxic by inhalation, in contact with skin and if swallowed
Specific limits: yes
Conc./Class. 1: >= 25% T; R 23/24/25-34-40-43

Remark: INDEX-No. 605-001-00-5
Flag: non confidential, Critical study for SIDS endpoint
25-MAR-2002 (150)

1.6.3 Packaging

1.7 Use Pattern

Type: type
Category: Non dispersive use

Flag: non confidential, Critical study for SIDS endpoint
09-JAN-2003

Type: type
Category: Use in closed system

Flag: non confidential, Critical study for SIDS endpoint
30-JAN-2002

Type: industrial
Category: Chemical industry: used in synthesis

Flag: non confidential, Critical study for SIDS endpoint
09-JAN-2003

Type: industrial
Category: Textile processing industry

Flag: non confidential, Critical study for SIDS endpoint
07-MAR-1994

Type: use
Category: Adhesive, binding agents

Flag: non confidential, Critical study for SIDS endpoint
07-MAR-1994

Type: use
Category: Cleaning/washing agents and disinfectants

Flag: non confidential, Critical study for SIDS endpoint
07-MAR-1994

Type: use
Category: Impregnation agents

Flag: non confidential, Critical study for SIDS endpoint
07-MAR-1994

Type: use
Category: Intermediates

Flag: non confidential, Critical study for SIDS endpoint
07-MAR-1994

Type: use
Category: Vulcanizing agents

Flag: non confidential, Critical study for SIDS endpoint
10-SEP-2001

Type: use
Category: other

Remark: Derivative/end use: Formaldehyde is used primarily as a feedstock:

- Urea-formaldehyde (UF) resin production, accounting for approx. 40% global consumption in 1999.
- Phenol-formaldehyde (PF) resins, accounting for approx. 10% global consumption in 1999.
- Polyacetal resins, accounting for approx. 10% global consumption in 1999.
- Melamine-formaldehyde (MF) resins, accounting for approx. 5% global consumption in 1999.
- Acetylenic chemicals, accounting for approx. 5% global consumption in 1999.
- Pentaerythritol, accounting for approx. 5% global consumption in 1999.
- Other uses approx. 25%, including methylene dianiline (MDA)/diphenylmethane diisocyanate (MDI), and hexamethylenetetraamine (HTMA), trimethylol propane, neopentyl glycol and biocide use.

Flag: non confidential, Critical study for SIDS endpoint
23-DEC-2002 (46)

1.7.1 Detailed Use Pattern

1.7.2 Methods of Manufacture

Orig. of Subst.: Synthesis
Type: Production

Remark: Formaldehyde is produced by two major processes.
More than 75% of the industry uses the oxidation-dehydrogenation process, which reacts methanol with air over a silver catalyst. The reaction is exothermic and is quenched with water, to produce a 50 wt % solution of formaldehyde.
In the ferric molybdate process, methanol is oxidized in air in the presence of a mixed oxide catalyst to produce a 55 wt % solution of formaldehyde in water.
Flag: non confidential, Critical study for SIDS endpoint
23-DEC-2002 (46)

1.8 Regulatory Measures

1.8.1 Occupational Exposure Limit Values

Type of limit: MAK (DE)
Limit value: .3 ml/m3

Remark:
If mixed exposure see that there will be no irritation
carcinogenic Cat.: 4
pregnancy group: C
germ cell mutagenic Cat.: 5
skin sensitizing
top limit: short-time value category: I
exceeding factor: 2
An instantaneous value of 1 ml/m³ (1.2 mg/m³) should not be exceeded.
Flag: non confidential, Critical study for SIDS endpoint
15-MAY-2003 (452)

Type of limit: MAK (DE)
Limit value: .37 mg/m3

Remark: carcinogenic Cat.: 4
pregnancy group: C
germ cell mutagenic Cat.: 5
skin sensitizing

top limit: short-time value category: I
exceeding factor: 2
An instantaneous value of 1 ml/m³ (1.2 mg/m³) should not be exceeded.

If mixed exposure see that there will be no irritation
Flag: non confidential, Critical study for SIDS endpoint
15-MAY-2003 (452)

Type of limit: MAK (DE)

Remark: Carcinogenic, EG Category C3
Danger to reproduction, Category C
Flag: non confidential, Critical study for SIDS endpoint
24-SEP-2001 (72) (660) (661)

Type of limit: TLV (US)
Limit value: .3 other: ppm (Ceiling)

Remark: Suspected human carcinogen, A2
Flag: non confidential, Critical study for SIDS endpoint
24-SEP-2001 (3)

Type of limit: other: PEL (US)
Short term exposure
Limit value: .75 other: ppm
Schedule: 8 hour(s)

Flag: non confidential, Critical study for SIDS endpoint
24-SEP-2001 (676)

Type of limit: other: PEL (US)
Short term exposure
Limit value: 2 other: ppm
Schedule: 15 minute(s)

Remark: STEL
Flag: non confidential, Critical study for SIDS endpoint
15-JAN-2003 (676)

1.8.2 Acceptable Residues Levels

1.8.3 Water Pollution

Classified by: other: VwVwS (Germany), Annex 2
Labelled by: other: VwVwS (Germany), Annex 2
Class of danger: 2 (water polluting)

Remark: ID-number: 112
Flag: non confidential, Critical study for SIDS endpoint
16-JAN-2003 (131)

1.8.4 Major Accident Hazards

Legislation: Stoerfallverordnung (DE)
Substance listed: yes

Remark: Störfall-Stoff-No. 25
according formaldehyde >= 90% w/w
Flag: non confidential, Critical study for SIDS endpoint
24-SEP-2001 (627)

Legislation: Stoerfallverordnung (DE)
Substance listed: yes

Remark: Störfall-Stoff-No. 2
according formaldehyde >= 25% w/w
Flag: non confidential, Critical study for SIDS endpoint
24-SEP-2001 (627)

1.8.5 Air Pollution

Classified by: TA-Luft (DE)
Labelled by: TA-Luft (DE)
Number: 3.1.7 (organic substances)
Class of danger: I

Flag: non confidential, Critical study for SIDS endpoint

24-SEP-2001 (637)

1.8.6 Listings e.g. Chemical Inventories

Type: EINECS
Additional Info: EINECS No. 200-001-8

Flag: non confidential, Critical study for SIDS endpoint
23-DEC-2002 (504)

Type: ENCS
Additional Info: ENCS No. 2-482

Remark: ENCS Classification:
Low molecular chain-like organic compounds.
Flag: non confidential, Critical study for SIDS endpoint
23-DEC-2002 (504)

Type: ECL
Additional Info: ECL Serial No. KE-17074
ECL Toxic Chemical No. 97-1-345

Remark: This substance and mixtures containing more than 1% as formaldehyde.
Flag: non confidential, Critical study for SIDS endpoint
23-DEC-2002 (504)

Type: other: SWISS
Additional Info: SWISS No. G-1642

Remark: SWISS Classification:
Giftliste 1 (List of toxic substances 1), 31 May 1999
Toxic category 3: acute oral lethal dose of 50-500 mg/kg.
Inddor air concentrations in inhabited rooms should not exceed 0.1 ppm.
Flag: non confidential, Critical study for SIDS endpoint
23-DEC-2002 (504)

Type: other: ISRAEL
Additional Info: ISRAEL No. 9.1

Remark: ISRAEL Classification:
Proposed Israel Hazardous Substances List 2001.
This list has not been finalized.
Classification Regulations: This Substance is exempt from reporting under the Hazardous Substances Law of 1993 if the reportable quantity is lower than 50 kg.
Flag: non confidential, Critical study for SIDS endpoint
23-DEC-2002 (504)

Type: other: TAIWAN
Additional Info: TAIWAN No. 66-01

Remark: TAIWAN Classification:
This is a Class II and III toxic chemical. Regulated treshold quantity is 50 kg.
Minimum control level is 25 w/w%.
Flag: non confidential, Critical study for SIDS endpoint
23-DEC-2002 (504)

Type: TSCA

Flag: non confidential, Critical study for SIDS endpoint
23-DEC-2002 (504)

Type: DSL

Flag: non confidential, Critical study for SIDS endpoint
23-DEC-2002 (504)

Type: AICS

Flag: non confidential, Critical study for SIDS endpoint
23-DEC-2002 (504)

Type: PICCS

Flag: non confidential, Critical study for SIDS endpoint
23-DEC-2002 (504)

1.9.1 Degradation/Transformation Products

EINECS-Name: No decomposition if correctly stored and handled.

Remark: Refers to 49 - 49.3 % aqueous solution of formaldehyde.
Flag: non confidential, Critical study for SIDS endpoint
23-DEC-2002 (42)

1.9.2 Components

1.10 Source of Exposure

Remark: Indoor air levels (non workplace), measured in various countries, ranged between <10 µg/m³ and a maximum of 5260 µg/m³. The highest levels were measured in trailers in Germany. The concentrations are mainly dependent on the age of the building, building materials, type of construction and ventilation.
Reliability: (4) not assignable
Flag: Critical study for SIDS endpoint
13-MAY-2003 (351)

Remark: Formaldehyde is ubiquitously present in the environment as a result of natural processes and from man-made sources. The major source of atmospheric formaldehyde is the photochemical oxidation and incomplete combustion of hydrocarbons.
Flag: Critical study for SIDS endpoint
23-DEC-2002 (667)

1.11 Additional Remarks

Memo: In presence of little quantities of impurities there is danger of rapid polymerisation.

Flag: non confidential, Critical study for SIDS endpoint
23-DEC-2002 (132)

Memo: according to Swiss and Swedish Products Registers formaldehyde is contained in more than 50 products, part of them is available for consumers.

Reliability: (4) not assignable
only secondary literature (tables)
Flag: Critical study for SIDS endpoint
12-DEC-2001 (630) (634)

1.12 Last Literature Search

Chapters covered: 1
Date of Search: 21-JAN-2003

Remark: update 2003
Flag: non confidential, Critical study for SIDS endpoint
25-APR-2003

Chapters covered: 8
Date of Search: 21-JAN-2003

Remark: update 2003
Flag: non confidential, Critical study for SIDS endpoint
21-JAN-2003

Type of Search: Internal and External
Chapters covered: A45-011
Date of Search: 02-OCT-2002

Flag: non confidential, Critical study for SIDS endpoint
25-APR-2003

Type of Search: External
Chapters covered: 5
Date of Search: 25-JUL-2001

Remark: Databases: agricola, caba, cancerlit, chemlist, embal, embase, esbiobase, healsafe, jicst-eplus, lifesci, ntis toxlit via stn and csnb
Profile: special tox profile for BASF
Flag: non confidential, Critical study for SIDS endpoint
25-APR-2003

1.13 Reviews

2.1 Melting Point

Value: = -118 degree C

Reliability: (2) valid with restrictions
Declaration of a national institution
21-SEP-2001 (72)

Value: = -117 degree C

Reliability: (4) not assignable
Manufacturer / producer data without proof
17-APR-2000 (672)

Value: = -92 degree C

Reliability: (2) valid with restrictions
Handbook
Flag: Critical study for SIDS endpoint
31-MAR-2003 (647)

2.2 Boiling Point

Value: = -19.1 degree C at 1013 hPa

Reliability: (2) valid with restrictions
Handbook
19-OCT-2000 (646)

Value: = -21 degree C

Reliability: (4) not assignable
Secondary quotation
19-OCT-2000 (668)

Value: = -20 degree C

Reliability: (4) not assignable
Handbook
19-OCT-2000 (562)

Value: = -19 degree C

Reliability: (4) not assignable
Handbook
19-OCT-2000 (218)

Value: = -19.2 degree C

Reliability: (4) not assignable
Declaration of a national institution
Flag: Critical study for SIDS endpoint
21-SEP-2001 (72)

2.3 Density

Type: density

Value: = .8153 g/cm³ at -20 degree C

Reliability: (4) not assignable
Declaration of a national institution
Flag: Critical study for SIDS endpoint
21-SEP-2001 (72)

Type: density
Value: = .816 g/cm³ at -19 degree C

Reliability: (4) not assignable
Secondary quotation
17-APR-2000 (668)

Type: relative density
Value: = 1.03

Remark: relative density of vapour (air = 1.00)
Reliability: (4) not assignable
Handbook
17-APR-2000 (499)

Type: relative density
Value: = 1.04

Remark: relative density of vapour (air = 1.00)
Reliability: (2) valid with restrictions
Declaration of a national institution
21-SEP-2001 (72)

Type: relative density
Value: = 1.067

Remark: relative density of vapour (air = 1.00)
Reliability: (4) not assignable
Secondary quotation
17-APR-2000 (669)

2.3.1 Granulometry

2.4 Vapour Pressure

Value: = 4378 hPa at 20 degree C

Reliability: (4) not assignable
Manufacturer / producer data without proof
17-APR-2000 (672)

Value: = 4420 hPa at 20 degree C

Reliability: (4) not assignable
Handbook
17-APR-2000 (562)

Value: = 5176 hPa at 25 degree C

Method: other (calculated):
Year: 1998

Remark: Value calculated using data critically evaluated by the Design Institute for Physical Properties (DIPPR) and contained in
"Selected values of Properties of Chemical Compounds" Thermodynamics Rresearch Center, Texas A+M University , College Station, 1980
Spence, R, Wild, W., "The Vapor Pressure curve of Formaldehyde and Some Related Data", J. Chem. Soc., 506, 3042 (1935)

Reliability: (2) valid with restrictions
Calculated value in accordance with generally accepted methods
Flag: Critical study for SIDS endpoint
31-MAR-2003 (44)

Value: = 5185 at 25 degree C

Method: other (measured)

Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
16-JUN-2003 (88)

2.5 Partition Coefficient

log Pow: = 0

Method: other (calculated)

Reliability: (4) not assignable
Handbook
19-OCT-2000 (682)

log Pow: = .35 at 25 degree C

Method: other (measured)

Method: Shake-flask method
Remark: Recommended value
Reliability: (2) valid with restrictions
Scientifically verified data
Flag: Critical study for SIDS endpoint
31-MAR-2003 (582)

log Pow: = .35

Method: other (calculated)
Year: 1998

Method: The value was calculated according to the Atom/Fragment Contribution (AFC) method.
In this method a structure is divided into fragments (atom or larger functional groups) and coefficient values of each fragment or group are summed together to yield the log P estimate.

Reliability: (2) valid with restrictions
Calculated value in accordance with generally accepted estimation methods
Flag: Critical study for SIDS endpoint
09-AUG-2001 (402)

2.6.1 Solubility in different media

Method: other

Result: completely soluble in water
Reliability: (4) not assignable
Declaration of a national institution
21-SEP-2001 (72)
Value: = 95 other: wt% at 120 degree C

Reliability: (4) not assignable
Handbook, (secondary quotation)
Flag: Critical study for SIDS endpoint
16-JUN-2003 (668) (670)

Value: <= 55 other:wt%

Reliability: (4) not assignable
Handbook, (secondary quotation)
Flag: Critical study for SIDS endpoint
10-AUG-2001 (647)

Method: other

Result: completely soluble in water
Reliability: (4) not assignable
Declaration of a national institution
Flag: Critical study for SIDS endpoint
21-SEP-2001 (72)

2.6.2 Surface Tension

2.7 Flash Point

Value: = -53.2 degree C

Method: other: calculated value

Remark: Original data: 220 °K
Reliability: (2) valid with restrictions
Scientifically verified data
Flag: Critical study for SIDS endpoint
10-AUG-2001 (173)

2.8 Auto Flammability

Value: ca. 300 degree C

Reliability: (4) not assignable
Secondary quotation

20-OCT-2000 (669)

Value: = 424 degree C

Method: other: calculated value

Remark: Original data: 697.15 °K
Reliability: (2) valid with restrictions
Scientifically verified data
Flag: Critical study for SIDS endpoint
10-AUG-2001 (44)

Value: = 430 degree C

Remark: ignition temperature
Reliability: (4) not assignable
Declaration of a national institution
Flag: Critical study for SIDS endpoint
21-SEP-2001 (72)

2.9 Flammability

2.10 Explosive Properties

Result: not explosive

Remark: because of chemical structure
Reliability: (2) valid with restrictions
Expert judgement
Flag: Critical study for SIDS endpoint
26-SEP-2001 (43)

2.11 Oxidizing Properties

Result: no oxidizing properties

Remark: because of chemical structure
Reliability: (2) valid with restrictions
Expert judgement
Flag: Critical study for SIDS endpoint
26-SEP-2001 (43)

2.12 Dissociation Constant

2.13 Viscosity

2.14 Additional Remarks

Remark: Critical properties:
critical temperature: 402.7 K
critical pressure: 65.9 bar
critical volume: 99.5 cm3/mol (estimated)
critical compressibility factor: 0.197 (estimated)
acentric factor: 0.253

```
Reliability:      (4) not assignable
                  Secondary quotation
17-APR-2000                                                          (718)

Remark:           Explosive limits in air: 7 - 72 vol.%
Reliability:      (4) not assignable
                  Declaration of a national institution
Flag:             Critical study for SIDS endpoint
21-SEP-2001                                                           (72)

Remark:           formaldehyde is a colourless gas with pungent odour.
                  Handbook
Flag:             Critical study for SIDS endpoint
24-SEP-2001                                                          (577)

Remark:           Freezing point
Result:           -117 °C
Test substance:   other: formaldehyde 37 % uninhibited
Flag:             Critical study for SIDS endpoint
26-SEP-2001                                                          (343)
```

3.1.1 Photodegradation

```
Type:             air
INDIRECT PHOTOLYSIS
  Sensitizer:     OH
  Conc. of sens.: 500000 molecule/cm³
  Rate constant:  = .00000000000937 cm³/(molecule * sec)
  Degradation:    = 50 % after 1.7 day(s)

Method:           other (calculated)

Remark:           Recommended rate constant at 298 °K based on the statistical
                  evaluation of experimental rate constants. Assuming an
                  average OH-radical concentration of 5E5 molecules/cm³ over
                  24 hours, a half-life of 1.71 days can be calculated
Reliability:      (2)  valid with restrictions
                  Calculated value in accordance with generally accepted
                  standard methods
Flag:             Critical study for SIDS endpoint
24-SEP-2001                                                              (34)

Type:             air
Light source:     Sun light
DIRECT PHOTOLYSIS
  Halflife t1/2:  = 4.1 hour(s)

Method:           other (measured)

Method:           The quantum efficiency of the primary processes in
                  formaldehyde photolysis were determined as a function of
                  wavelength in the range from 2890 to 3380 Angstroem and at
                  25 °C. The P of CH2O was 10 torr.
Remark:           Direct photolysis with sunlight at sea-level and 40 degrees
                  latitude; First-Order Photodissociation constant amounts
                  4.7*10e-5/sec.
Reliability:      (1)  valid without restriction
                  Original Literature without fault
25-JUN-2003                                                     (244) (336)

Type:             air
Light source:     Sun light
DIRECT PHOTOLYSIS
  Halflife t1/2:  = 1 - 2 hour(s)

Method:           other (measured)

Remark:           Urban air with the effect of sunlight
Reliability:      (2)  valid with restrictions
                  Official assessment
25-JUN-2003                                                             (593)

Type:             air
INDIRECT PHOTOLYSIS
  Sensitizer:     NO3
  Rate constant:  = .000000000000000323 cm³/(molecule * sec)

Method:           other (calculated)
```

Test condition: 298 K
Reliability: (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment
31-MAR-2003 (31)

Type: air
INDIRECT PHOTOLYSIS
Sensitizer: NO3
Rate constant: = .00000000000000058 cm^3/(molecule * sec)

Method: other (calculated)

Test condition: 298 K
Reliability: (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment
31-MAR-2003 (30)

Type: air
INDIRECT PHOTOLYSIS
Sensitizer: O3
Rate constant: < 0 cm^3/(molecule * sec)

Method: other (calculated)

Test condition: 298 K
Reliability: (2) valid with restrictions
Calculated value, accepted method
24-SEP-2001 (32)

Type: air
INDIRECT PHOTOLYSIS
Sensitizer: OH
Rate constant: = .0000000000084 cm^3/(molecule * sec)

Method: other (measured)
Test substance: other TS: Formaldehyde C-13

Test condition: 299 +-2 K
Reliability: (2) valid with restrictions
Scientifically verified data
25-JUN-2003 (33)

Type: air
INDIRECT PHOTOLYSIS
Sensitizer: OH
Rate constant: = .0000000000096 cm^3/(molecule * sec)

Method: other (calculated)

Test condition: 298 K
Reliability: (2) valid with restrictions
Scientifically verified data
31-MAR-2003 (30)

Type: air
INDIRECT PHOTOLYSIS
Sensitizer: OH
Rate constant: = .00000000001 cm^3/(molecule * sec)

Method: other (measured)

Test condition: 298 K
Reliability: (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment
31-MAR-2003 (214)

Type: air
INDIRECT PHOTOLYSIS
Sensitizer: OH
Rate constant: ca. .000000000014 cm^3/(molecule * sec)

Method: other (measured)
Test substance: other TS: Formaldehyde d1

Test condition: 298 K
Reliability: (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment
31-MAR-2003 (33)

Type: air
INDIRECT PHOTOLYSIS
Sensitizer: OH

Remark: Formaldehyd is listed as hazardous air pollutant under Title III of CAAA (Clean Air Act Amendments) with an atmospheric lifetime of 30-36 hours.
Reliability: (4) not assignable
23-OCT-2000 (377)

Type: air
INDIRECT PHOTOLYSIS
Sensitizer: other: Br
Rate constant: = .000000000001 cm^3/(molecule * sec)

Test condition: 298 K
Reliability: (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment
31-MAR-2003 (30)

Type: air
INDIRECT PHOTOLYSIS
Sensitizer: other: Cl
Rate constant: = .000000000073 cm^3/(molecule * sec)

Test condition: 298 K
Reliability: (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment
31-MAR-2003 (30)

Type: air

Method: other (measured)

Remark: Direct photolysis in the air; primary process: CH2O + hv --> H + HCO; quantum yield at 25 deg C
lambda 2890-3392 Angstroem: 0.701 - 0.00 quantum yield
Reliability: (1) valid without restriction
Meets generally accepted scientific standards and is described in sufficient details
25-JUN-2003 (336)

3.1.2 Stability in Water

Method: other

Remark: A value of 2E+03 is indicated for the hydration constant, defined as Khyd = HCH(OH)2/HCHOaq
Result: Formaldehyde undergoes essentially complete hydration to yield the gem-diol, methylene glycol.
Reliability: (2) valid with restrictions
Scientifically verified data
Flag: Critical study for SIDS endpoint
31-MAR-2003 (70)

3.1.3 Stability in Soil

3.2.1 Monitoring Data (Environment)

Type of measurement: background concentration
Medium: air

Remark: Air concentrations of formaldehyde near the ground in coastal, mountain or oceanic areas ranged from 0.05 to 14.7 µg/m³. Measurements conducted in Germany, and considered to be representative for the air in the rural areas of Central Europe, ranged from 0.1 to 4.5 µg/m³, with a mean value of about 1.5 µg/m³.
Measurements in a high industrialized area with also heavy traffic conducted in Germany (1979 - 1984) gave annual mean values of 7 - 12 µg/m³.
Reliability: (4) not assignable
Secondary quotation
Flag: Critical study for SIDS endpoint
21-AUG-2001 (215)

Type of measurement: other: indoor
Medium: air

Remark: indoor air levels (non workplace), measured in various countries, most ranged from a minimum of 10 µg/m³ and a maximum of 4000 µg/m³. The concentrations are mainly dependent on the age of the building, building materials, type of construction and ventilation
15-JAN-2002 (351)

Type of measurement: other: indoor
Medium: air

Remark: indoor formaldehyde concentrations were measured in classrooms of schools (one frame construction with particleboard used extensively as panelling vs a brick building; location: Vienna, Austria; period: Dec. 92-March 93).

Indoor formaldehyde concentrations ranged from 0.023 to 0.075 ppm (28.8 - 94 µg/m3)
07-DEC-2001 (692)

Type of measurement: other: indoor
Medium: air

Remark: a survey was conducted in the umid environment of Taipei City during April and May of 1991, to investigate the indoor formaldehyde exposure. Levels of formaldeyhde: the geometric mean and geometric standard deviation were found to be 8+-4 nL/L for the bedroom, 7+-3 nL/L for the living room and 6+-3 nL/L for the kitchen. Range: approx. 1 nL/L-129 nL/L
11-DEC-2001 (362)

Type of measurement: other: indoor
Medium: air

Remark: as part of a long-term study of indoor air pollution, formaldehyde concentrations were determined in 792 apartments in Austria between 1988 and 1995. Concentrations determined indoors clearly decreased in the course of the period of investigation. Concentrations above 1.0 ppm as registered in the years 1988 and 1989 in older-style prefabricated homes have not been found in the past five years; concentrations above 0.5 ppm (627 µg/m3) have not been found in the past three years
07-DEC-2001 (399)

Type of measurement: other: indoor
Medium: air

Remark: the average concentration of formaldehyde measured in 202 households (Tucson, Arizona), was 26 ppb (32.6 µg/m3). Only in a few cases the concentration exceeded 90 ppb (112.9 µg/m3), with a maximum value of 140 ppb (175.5 µg/m3). Over 83 % of subjects lived in houses with 2-week average levels below 40 ppb (50.16 µg/m3)
11-DEC-2001 (408)

Type of measurement: other: indoor
Medium: air

Remark: an indoor air quality survey was conducted in Southern Louisiana to determine levels of airborne formaldehyde. Analyses of 419 air samples collected from 53 houses revealed levels of formaldehyde ranging from non-detectable to 6600 µg/m3. The mean was 460 µg/m3
07-DEC-2001 (420)

Type of measurement: other: indoor
Medium: air

Remark: the average concentration of formaldehyde measured in households (apartment houses that had been built 10 years before, Poland) was 25.86 +-10.98 µg/m3 (range 2.00-66.75 µg/m3)
06-DEC-2001 (531)

Type of measurement: other: indoor
Medium: air

Remark: indoor concentrations, outdoor concentrations and personal exposure was measured in a medium sized French town: indoor: 25 µg/m3 (mean value); outdoor: 2.9 µg/m3 (mean value); personal exposure: 15.2 µg/m3 (mean value)
06-DEC-2001 (263)

Type of measurement: other: indoor

Remark: formaldehyde levels were measured in 80 houses in the Latrobe Valley, Victoria, Australia, beween March 1994 and Feb. 1995. The median indoor level was 15.8 µg/m3 (12.6 ppb) with a maximun of 139 µg/m3 (111 ppb)
06-DEC-2001 (245)

Type of measurement: other: indoor
Medium: air

Remark: residential formaldehyde levels in study residences (Indiana):
- mobile homes: 0.0120 ppm (median value) (15.05 µg/m3)
- conventional (particleboard subflooring): 0.070 ppm (median value) (87.8 µg/m3)
- mobile and conventional (particle board subflooring): 0.090 ppm (median value) (112.8 µg/m3)
07-DEC-2001 (254)

Type of measurement: other: indoor, outdoor
Medium: air

Remark: 802 houses, located within about 60 miles of central Toronto, period: 1983-1985
indoor formalehyde concentrations were in the range of 0.035-0.046 ppm (43.9 - 57.7 µg/m3) and outdoor levels in the range of 0.005-0.007 ppm (6.27 - 8.78 µg/m3)
07-DEC-2001 (104)

Type of measurement: other: indoor, outdoor, workplace, personal exposure
Medium: air

Remark: personal 48 hours exposures to formaldehyde of 15 randomly selected participants were measured during the summer/autumn of 1997 in Helsinki, Finland. In addition to personal exposures, simultaneous measurements of microenvironmental concentrations were conducted at each participant´s residence (indoor and outdoor) and workplace.

Results are compared to measurements performed in Perth, Western Australia (Dingle P. et al., 1993), New Jersey (Zhang J. et al, 1994) and greater Boston, MA, area (Reiss R., 1995):

- indoor:

Helsinki Metropolitan	33 ppb (41.4 µg/m3; mean level)
Perth, Western Australia	19.7 ppb (24.7 µg/m3; mean level)
New Jersey	54.6 ppb (68.5 µg/m3; mean level)
greater Boston area	16.1 ppb (20.2 µg/m3; mean level)

- outdoor:

Helsinki Metropolitan	2.6 ppb (3.26 µg/m3; mean level)
Perth, Western Australia	2.0 ppb (2.51 µg/m3; mean level)
New Jersey	12.5 ppb (15.67 µg/m3; mean level)
greater Boston area	2.6 ppb (3.26 µg/m3; mean level)

- personal exposure:

Helsinki Metropolitan	21.4 ppb (26.8 µg/m3; mean level)
Perth, Western Australia	17.5 ppb (21.9 µg/m3; mean level)

- workplace:

Helsinki Metropolitan	12 ppb (15.05 µg/m3; mean level)

Reliability: (2) valid with restrictions
acceptable study, meets basic scientifc principles
Flag: Critical study for SIDS endpoint
11-DEC-2001 (193) (371) (559) (724)

3.2.2 Field Studies

3.3.1 Transport between Environmental Compartments

Type: volatility
Media: water - air
Method: other: measurement

Method: The Henry's law constant has been determined as a function of temperature by bubble-column and by head-space techniques
Remark: Study result: 2.97E3 M/atm (corresponds to 0.034 Pa*m³/mol)
Result: Henry Law Constant: 0.034 Pa*m3/mol
Reliability: (2) valid with restrictions
acceptable study meets basic scientific principles
Flag: Critical study for SIDS endpoint
31-MAR-2003 (71)

3.3.2 Distribution

Media: air - biota - sediment(s) - soil - water
Method: Calculation according Mackay, Level I

Remark: Input data for the calculation:
Log Pow: 0.35
Henry's law constant: 0.03 Pa/m³mol
Molecular Weight: 30 g/mol
Characteristics of the Evaluative Environment:

Compartment	Volume(m³)	Density (kg/m³)	Composition
Air	6E+09	1.2	-
Water	7E+06	1000	-
Soil	4.5E+04	1500	2% OC
Sediment	2.1E+04	1300	5% OC
Susp. Sediment	35	1500	16.7% OC
Aereosols	0.12	1500	30 µg/m³
Aquatic biota	7	1000	5% lipid

Result: Preferred aiming compartment: water (99%)
Reliability: (2) valid with restrictions
Calculation accepted (standard method)

Flag: Critical study for SIDS endpoint
17-JUN-2003 (45)

3.4 Mode of Degradation in Actual Use

3.5 Biodegradation

Type: aerobic
Inoculum: other: not pre-acclimated inoculum
Degradation: = 90 % after 28 day(s)
Result: readily biodegradable

Method: OECD Guide-line 301 D "Ready Biodegradability: Closed Bottle Test"
Year: 1990
GLP: no

Result: % THOD
Test condition: Concentration of test substance: 2-5 mg/l
Reliability: (2) valid with restrictions
Guideline study without detailed documentation
Flag: Critical study for SIDS endpoint
10-AUG-2001 (248)

Type: aerobic
Inoculum: other: activated sludge, municipal treatment plant
Degradation: = 98 - 99 %

Method: other: Adaptation in a model treatment plant
Year: 1983
GLP: no

Remark: During adaptation period 2-8 days at each concentration in the influent degradation was followed 33 days at maximum concentration (2000 mg/l influent).
Test condition: Step by step adaptation of 600 mg/l to 2000 mg/l formaldehyde
23-OCT-2000 (118)

Type: aerobic
Inoculum: other: activated sludge, adapted (photo-effluent)
Degradation: = 18 %

Method: other: 14-C Degradation with synthetic photolaboratory effluent
Year: 1976
GLP: no

Result: %THCO2
Test condition: Activated sludge from industrial treatment plant, incubation period: 5 days
Test substance: mixture of formaline, sulfite, thiosulfite
23-OCT-2000 (60)

Type: aerobic
Inoculum: activated sludge, domestic

```
Method:           other: Adaptation Test
  Year:           1984
   GLP:           no

Remark:           With adaptation and addition of glucose as cosubstrate
                  formaldehyde (1000 mg/l) is biodegradable.
Test condition:   Concentration of test substance: step by step from 100 mg/l
                  to 1000 mg/l
23-OCT-2000                                                              (59)

Type:             aerobic
Inoculum:         other: formaldehyde containing effluents of hospitals

Method:           other: ArtEV-Procedure
  Year:           1996
   GLP:           no

Result:           18.2-20.8 g/l formaldehyde were eliminated 99.99%
                  (degradation rate: 728 mg/l*d).
Reliability:      (2)  valid with restrictions
                  Study not in accordance with a defined standard method, but
                  meets generally accepted scientific principles
23-OCT-2000                                                             (594)

Type:             aerobic
Degradation:      = 97.4 % after 5 day(s)

Method:           other: BOD5 Dilution Method
  Year:           1976
   GLP:           no

23-OCT-2000                                                             (382)

Type:             aerobic
Inoculum:         activated sludge, industrial
Concentration:    284 mg/l related to Test substance
Degradation:      = 63 - 77 % after 7 day(s)
Result:           other: biodegradable

Method:           other: Respirometric Test
  Year:           1979
   GLP:           no
Test substance:   other TS: formaldehyde 35%

Result:           TOC-elimination: 63/77%; O2/C-ratio: 2.1/2.4; Concentration
                  of test substance: 284/320 mg/l
Reliability:      (2)  valid with restrictions
23-OCT-2000                                                              (41)

Type:             aerobic
Inoculum:         activated sludge, industrial
Degradation:      = 63 - 81 % after 7 day(s)

Method:           other: Respirometric Test
  Year:           1979
   GLP:           no
Test substance:   other TS: formaldehyde 35%
```

Remark: Formaldehyde is biologically degradable after adaptation:
O2/C relation: less 1
Respiration inhibition after 24 hours incubation:
EC20 = 60 mg/l; EC50 = 500 mg/l
Test condition: TOC-concentration: 60 and 120 mg/l
Reliability: (2) valid with restrictions
Study not in accordance with a defined standard method, but meets generally accepted scientific principles
23-OCT-2000 (40)

Type: aerobic
Inoculum: other: sludge, municipal
Concentration: 500 mg/l related to Test substance
Degradation: = 0 % after 1 day(s)

Method: other: Respirometric Test (Warburg)
Year: 1966
GLP: no

Result: No degradation, toxic effects.
23-OCT-2000 (247)

Type: anaerobic
Inoculum: other: acetate/propionate enriched culture, adapted
Concentration: 400 mg/l related to Test substance
Degradation: = 55 - 60 % after 40 day(s)

Method: other: Anaerobic Degradation Test
Year: 1988
GLP: no

Remark: SRT = Solid Retention Times
Result: 25% volatilization, biosorption and other physico-chemical processes (total 80% elimination)
Test condition: Continuous addition of 400 mg/l
23-OCT-2000 (74)

3.6 BOD5, COD or BOD5/COD Ratio

Method: other: Standard Dilution Method
Year: 1955
GLP: no
Year:
Method:
Result: BOD5 = 0.57 g/g (average value); THOD = 1.065 g/g
Reliability: (3) invalid
18-DEC-2000 (319)

3.7 Bioaccumulation

Species: other: marine shrimp (Penaeus stylirostris)
Exposure period: 24 hour(s)

Method: other: static exposure in 30 l glass aquaria containing sea water (4 % salinity; 22-24°C)
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: unpeeled shrimp tails were used in assays, extraction with 10% perchloric acid. Recovery 57%; estimated detection limit 0.3 ppm (mg/kg) (lowest measurement given)
Result: No extractable formaldehyde residues could be detected when analysed immediately after treatment. However during longer post-mortem storage up to 72 hours, significant amounts of extractable formaldehyde were produced biologically due to tissue decomposition.
Test condition: Concentration: 0, 18,5 and 55,5 ppm
Reliability: (2) valid with restrictions
Study well documented, meets generally accepted scientific principles, acceptable for assessment
Flag: Critical study for SIDS endpoint
20-AUG-2001 (341)

Method: other: static exposure followed by different depuration periods
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Channel catfish (Ictalurus puntatus) and largemouth bass (Micropterus salmoides) were exposed to 300 µl/l solutions of formalin (111 mg/l formaldehyde) for 3 hours. Coho salmon (Oncorhynchus kisutch) and rainbow trout (Salmo gairdneri) were exposed for 1 hour. All fish were placed in fresh water after exposure, except those taken immediately for residue analysis (extraction with 10% trichloroacetic acid). Five fish of each species were analysed 0, 1 and 24 hours after withdrawal from the chemical.
Result: No formaldehyde was detected in the muscle, liver or blood plasma (detection limit : 5 µg/g fish tissue, recovery 36-62% with fish tissue)
Test condition: Species:
Channel cat fish (Ictalurus punctatus)
Large mouth bass (Micropterus salmoides)
Coho salmon (Oncorhynchus kisutch)
Rainbow trout (Salmo gairdneri)

Exposure period: 1-3 h
Concentration: 300 µl/l solution of formalin (111 mg/l formaldehyde)
Reliability: (2) valid with restrictions
Study well documented, meets generally accepted scientific principles, acceptable for assessment
Flag: Critical study for SIDS endpoint
20-AUG-2001 (607)

3.8 Additional Remarks

Result: Water pollution factors /BOD5 (different references):
60% of THOD
0.6-1.07 std. dil. at <260 mg/l
0.728
0.33-1.06 std. dil. sewage
1.06 std. dil. sew. (99.3%)
0.64 std. dil. sew. (60%)
0.33 std. dil. sew. at 2.5-10 ppm (31%)
0.45 std. dil. sew. at 1.7-20 ppm (42%)
1.10 manom 50% sew; at 260 ppm (103%)
0.57 manom 5% sew; at 260 ppm
0 Sierp, 10% sew; at 440 ppm
1.00 Warburg, 50% sew; at 130 ppm (94%)
1.10 Warburg, 25-50% sew; 250 ppm (103%)

06-JAN-2000 (684)

Memo: BOD20: 1.228 (115%)

06-JAN-2000 (684)

Memo: Impact on biodegradation processes: inhibition of anaerobic sludge digestion at 100 mg/l, aerobic degradation at 135-175 mg/l methane fermentation can be acclimated up to 15% formaldehyde (150 g/l)

06-JAN-2000 (684)

Memo: Different strains of bacteria decomposing formaldehyde have been isolated from activated sludge, mainly belonging to Pseudomonas. Less numerous were Achromobacter, Flavobacterium, Mycobacterium and Xanthomonas.

06-JAN-2000 (265)

Memo: Pseudomonas induces at growth on C1 (not glucose or peptone) 2 soluble enzyme systems, which oxidize formaldehyde. Formaldehyde itself is no substrate.

06-JAN-2000 (413)

Memo: Formaldehyde degradation was tested in a Warburg respirometer with a pure culture of alcaligenes faecalis. Oxygen uptake stopped after brief period, the authors concluded inhibition.

06-JAN-2000 (455)

Memo: Formaldehyde-casein-oil-complex was metabolized by ruminants (sheep). 14-CO2 and 14-CH4 was released, no formaldehyde accumulation in tissues.

06-JAN-2000 (482)

Memo: Respirometric test on degradation inhibition with 10-500 mg/l formaldehyde in municipal sewage showed 55% inhibition at 500 mg/l. Primary degradation after 2.5 days totally (240 mg/l).
06-JAN-2000 (537)

Memo: Formaldehyde inhibits anaerobic degradation of contents of chemical toilets at shock-loading: 200 mg/l (200 ppm).
06-JAN-2000 (540)

AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

```
Type:              flow through
Species:           Ictalurus melas  (Fish, fresh water)
Exposure period:   24 hour(s)
Unit:              mg/l                   Analytical monitoring: no data
LC50:              = 69.2 -

Method:            other: acute toxicity test; "flow through bioassay"
   GLP:            no
Test substance:    other TS: formalin, commercial grade, 37%

Remark:            fingerling; pH 6.5, water hardness 8, water temperature 12
                   degrees Centigrade
Result:            Test result: 173 µl/l formalin (solution 37%)
Reliability:       (2)  valid with restrictions
                   Test procedure in accordance with generally accepted
                   scientific standards and described in sufficient detail
30-AUG-2001                                                                (76)

Type:              flow through
Species:           Ictalurus melas  (Fish, fresh water)
Exposure period:   96 hour(s)
Unit:              mg/l                   Analytical monitoring: no
LC50:              = 24.8 -

Method:            other: acute toxicity test; "flow through bioassay"
  Year:            1977
   GLP:            no
Test substance:    other TS: formalin, commercial grade, 37%

Remark:            fingerling; pH 6.5, water hardness 8, water temperature 12
                   degrees Centigrade
Result:            Test result: 62.1 µl/l formalin (solution 37%)
Reliability:       (2)  valid with restrictions
                   Test procedure in accordance with generally accepted
                   scientific standards and described in sufficient detail
Flag:              Critical study for SIDS endpoint
21-SEP-2001                                                                (75)

Type:              flow through
Species:           Ictalurus punctatus  (Fish, fresh water)
Exposure period:   3 hour(s)
Unit:              mg/l                   Analytical monitoring: no data
LC50:              = 198 -

Method:            other: acute toxicity test; "flow through bioassay"
   GLP:            no
Test substance:    other TS: formalin (solution 37%)

Remark:            fingerling; pH 6.5, water hardness 8, water temperature 12
                   degrees Centigrade
Result:            Test result: 495 µl/l
Reliability:       (2)  valid with restrictions
                   Test procedure in accordance with generally accepted
                   scientific standards and described in sufficient detail
```

30-AUG-2001 (76)

Type: flow through
Species: Ictalurus punctatus (Fish, fresh water)
Exposure period: 6 hour(s)
Unit: mg/l Analytical monitoring: no data
LC50: = 92.8 -

Method: other: acute toxicity test; "flow through bioassay"
GLP: no
Test substance: other TS: formalin (solution 37%)

Remark: fingerling; pH 6.5, water hardness 8, water temperature 12 degrees Centigrade
Result: Test result: 232 µl/l
Reliability: (2) valid with restrictions
Test procedure in accordance with generally accepted scientific standards and described in sufficient detail

30-AUG-2001 (76)

Type: flow through
Species: Ictalurus punctatus (Fish, fresh water)
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring: no data
LC50: = 48.8 -

Method: other: acute toxicity test; "flow through bioassay"
GLP: no
Test substance: other TS: formalin (solution 37%)

Remark: fingerling; pH 6.5, water hardness 8, water temperature 12 degrees Centigrade
Result: Test result: 122 µl/l
Reliability: (2) valid with restrictions
Test procedure in accordance with generally accepted scientific standards and described in sufficient detail

30-AUG-2001 (76)

Type: flow through
Species: Ictalurus punctatus (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no data
LC50: = 26.3 -

Method: other: acute toxicity test; "flow through bioassay"
GLP: no
Test substance: other TS: formalin (solution 37%)

Remark: fingerling; pH 6.5, water hardness 8, water temperature 12 degrees Centigrade
Result: Test result: 65.8 µl/l
Reliability: (2) valid with restrictions
Test procedure in accordance with generally accepted scientific standards and described in sufficient detail

30-AUG-2001 (76)

Type: flow through
Species: Lepomis cyanellus (Fish, fresh water)
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring: no data

```
LC50:             = 129 -

Method:           other: acute toxicity test; "flow through bioassay"
   GLP:           no
Test substance:   other TS: formalin (solution 37%)

Remark:           fingerling; pH 6.5, water hardness 8, water temperature 12
                  degrees Centigrade
Result:           Test result: 323 µl/l
Reliability:      (2)  valid with restrictions
                  Test procedure in accordance with generally accepted
                  scientific standards and described in sufficient detail
30-AUG-2001                                                              (76)

Type:             flow through
Species:          Lepomis cyanellus  (Fish, fresh water)
Exposure period:  96 hour(s)
Unit:             mg/l                   Analytical monitoring: no data
LC50:             = 69.2 -

Method:           other: acute toxicity test; "flow through bioassay"
   GLP:           no
Test substance:   other TS: formalin (solution 37%)

Remark:           fingerling; pH 6.5, water hardness 8, water temperature 12
                  degrees Centigrade
Result:           Test result: 173 µl/l
Reliability:      (2)  valid with restrictions
                  Test procedure in accordance with generally accepted
                  scientific standards and described in sufficient detail
30-AUG-2001                                                              (76)

Type:             flow through
Species:          Lepomis macrochirus  (Fish, fresh water)
Exposure period:  3 hour(s)
Unit:             mg/l                   Analytical monitoring: no data
LC50:             = 916 -

Method:           other: acute toxicity test; "flow through bioassay"
   GLP:           no
Test substance:   other TS: formalin (solution 37%)

Remark:           fingerling; pH 6.5, water hardness 8, water temperature 12
                  degrees Centigrade
Result:           Test result: 2290 µl/l
Reliability:      (2)  valid with restrictions
                  Test procedure in accordance with generally accepted
                  scientific standards and described in sufficient detail
30-AUG-2001                                                              (76)

Type:             flow through
Species:          Lepomis macrochirus  (Fish, fresh water)
Exposure period:  6 hour(s)
Unit:             mg/l                   Analytical monitoring: no data
LC50:             = 640 -

Method:           other: acute toxicity test; "flow through bioassay"
   GLP:           no
Test substance:   other TS: formalin (solution 37%)
```

Remark: fingerling; pH 6.5, water hardness 8, water temperature 12 degrees Centigrade
Result: Test result: 1600 µl/l
Reliability: (2) valid with restrictions
Test procedure in accordance with generally accepted scientific standards and described in sufficient detail
30-AUG-2001 (76)

Type: flow through
Species: Lepomis macrochirus (Fish, fresh water)
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring: no data
LC50: = 84.4 -

Method: other: acute toxicity test; "flow through bioassay"
GLP: no
Test substance: other TS: formalin (solution 37%)

Remark: fingerling; pH 6.5, water hardness 8, water temperature 12 degrees Centigrade
Result: test result: 211 µl/l
Reliability: (2) valid with restrictions
Test procedure in accordance with generally accepted scientific standards and described in sufficient detail
30-AUG-2001 (76)

Type: flow through
Species: Lepomis macrochirus (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no data
LC50: = 40 -

Method: other: acute toxicity test; "flow through bioassay"
GLP: no
Test substance: other TS: formalin (solution 37%)

Remark: fingerling; pH 6.5, water hardness 8, water temperature 12 degrees Centigrade
Result: Test result: 100 µl/l
Reliability: (2) valid with restrictions
Test procedure in accordance with generally accepted scientific standards and described in sufficient detail
30-AUG-2001 (76)

Type: flow through
Species: Micropterus dolomieui (Fish, fresh water, marine)
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring: no data
LC50: = 88.8 -

Method: other: acute toxicity test; "flow through bioassay"
GLP: no
Test substance: other TS: formalin (solution 37%)

Remark: pH 6.5, water hardness 8, water temperature 12 degrees Centigrade
Result: Test result: 222 µl/l
Reliability: (2) valid with restrictions
Test procedure in accordance with generally accepted scientific standards and described in sufficient detail

30-AUG-2001 (76)

Type: flow through
Species: Micropterus dolomieui (Fish, fresh water, marine)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no data
LC50: = 54.4 -

Method: other: acute toxicity test; "flow through bioassay"
GLP: no
Test substance: other TS: formalin (solution 37%)

Remark: fingerling; pH 6.5, water hardness 8, water temperature 12 degrees Centigrade
Result: Test result: 136 µl/l
Reliability: (2) valid with restrictions
Test procedure in accordance with generally accepted scientific standards and described in sufficient detail

30-AUG-2001 (76)

Type: flow through
Species: Micropterus salmoides (Fish, fresh water)
Exposure period: 6 hour(s)
Unit: mg/l Analytical monitoring: no data
LC50: = 412 -

Method: other: acute toxicity test; "flow through bioassay"
GLP: no
Test substance: other TS: formalin (solution 37%)

Remark: pH 6.5, water hardness 8, water temperature 12 degrees Centigrade
Result: Test result: 1030 µl/l
Reliability: (2) valid with restrictions
Test procedure in accordance with generally accepted scientific standards and described in sufficient detail

30-AUG-2001 (76)

Type: flow through
Species: Micropterus salmoides (Fish, fresh water)
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring: no data
LC50: = 113 -

Method: other: acute toxicity test; "flow through bioassay"
GLP: no
Test substance: other TS: formalin (solution 37%)

Remark: fingerling; pH 6.5, water hardness 8, water temperature 12 degrees Centigrade
Result: Test result: 283 µl/l
Reliability: (2) valid with restrictions
Test procedure in accordance with generally accepted scientific standards and described in sufficient detail

30-AUG-2001 (76)

Type: flow through
Species: Micropterus salmoides (Fish, fresh water)
Exposure period: 96 hour(s)

```
Unit:              mg/l                    Analytical monitoring: no data
LC50:              = 57.2 -

Method:            other: acute toxicity test; "flow through bioassay"
   GLP:            no
Test substance:    other TS: formalin (solution 37%)

Remark:            fingerling; pH 6.5, water hardness 8, water temperature 12
                   degrees Centigrade
Result:            Test result: 143 µl/l
Reliability:       (2)  valid with restrictions
                   Test procedure in accordance with generally accepted
                   scientific standards and described in sufficient detail
30-AUG-2001                                                              (76)

Type:              flow through
Species:           Salmo gairdneri  (Fish, estuary, fresh water)
Exposure period:   3 hour(s)
Unit:              mg/l                    Analytical monitoring: no data
LC50:              = 492 -

Method:            other: acute toxicity test; "flow through bioassay"
   GLP:            no
Test substance:    other TS: formalin (solution 37%)

Remark:            fingerling; pH 6.5, water hardness 8, water temperature 12
                   degrees Centigrade
Result:            Test result: 1230 µl/l
Reliability:       (2)  valid with restrictions
                   Test procedure in accordance with generally accepted
                   scientific standards and described in sufficient detail
30-AUG-2001                                                              (76)

Type:              flow through
Species:           Salmo gairdneri  (Fish, estuary, fresh water)
Exposure period:   6 hour(s)
Unit:              mg/l                    Analytical monitoring: no data
LC50:              = 262 -

Method:            other: acute toxicity test; "flow through bioassay"
   GLP:            no
Test substance:    other TS: formalin (solution 37%)

Remark:            fingerling; pH 6.5, water hardness 8, water temperature 12
                   degrees Centigrade
Result:            Test result: 655 µl/l
Reliability:       (2)  valid with restrictions
                   Test procedure in accordance with generally accepted
                   scientific standards and described in sufficient detail
30-AUG-2001                                                              (76)

Type:              flow through
Species:           Salmo gairdneri  (Fish, estuary, fresh water)
Exposure period:   24 hour(s)
Unit:              mg/l                    Analytical monitoring: no data
LC50:              = 120 -

Method:            other: acute toxicity test; "flow through bioassay"
   GLP:            no
```

```
Test substance:   other TS: formalin (solution 37%)

Remark:           fingerling; pH 6.5, water hardness 8, water temperature 12
                  degrees Centigrade
Result:           Test result: 300 µl/l
Reliability:      (2)  valid with restrictions
                  Test procedure in accordance with generally accepted
                  scientific standards and described in sufficient detail
30-AUG-2001                                                              (76)

Type:             flow through
Species:          Salmo gairdneri  (Fish, estuary, fresh water)
Exposure period:  96 hour(s)
Unit:             mg/l                   Analytical monitoring: no
LC50:             = 47.2 -

Method:           other: acute toxicity test; "flow through bioassay"
   GLP:           no
Test substance:   other TS: formalin (solution 37%)

Remark:           fingerling; pH 6.5, water hardness 8, water temperature 12
                  degrees centigrade
Result:           Test result: 118 µl/l
Reliability:      (2)  valid with restrictions
                  Test procedure in accordance with generally accepted
                  scientific standards and described in sufficient detail
30-AUG-2001                                                              (76)

Type:             flow through
Species:          Salmo salar  (Fish, fresh water, marine)
Exposure period:  96 hour(s)
Unit:             mg/l                   Analytical monitoring: no
LC50:             = 69.2 -

Method:           other: acute toxicity test, "flow through bioassay"
   GLP:           no
Test substance:   other TS: formalin (solution 37%)

Remark:           fingerling; pH 6.5, water hardness 8,water temperature 12
                  degrees centigrade
Result:           Test result: 173 µl/l
Reliability:      (2)  valid with restrictions
                  Test procedure in accordance with generally accepted
                  scientific standards and described in sufficient detail
30-AUG-2001                                                              (76)

Type:             flow through
Species:          Salmo salar  (Fish, fresh water, marine)
Exposure period:  3 hour(s)
Unit:             mg/l                   Analytical monitoring: no data
LC50:             = 564 -

Method:           other: acute toxicity test; "flow through bioassay"
   GLP:           no
Test substance:   other TS: formalin (solution 37%)

Remark:           fingerling; pH 6.5, water hardness 8, water temperature 12
                  degrees Centigrade
Result:           Test result: 1410 µl/l
```

```
Reliability:      (2)  valid with restrictions
                  Test procedure in accordance with generally accepted
                  scientific standards and described in sufficient detail
30-AUG-2001                                                            (76)

Type:             flow through
Species:          Salmo salar  (Fish, fresh water, marine)
Exposure period:  6 hour(s)
Unit:             mg/l                  Analytical monitoring: no data
LC50:             = 336 -

Method:           other: acute toxicity test; "flow through bioassay"
   GLP:           no
Test substance:   other TS: formalin (solution 37%)

Remark:           fingerling; pH 6.5, water hardness 8, water temperature 12
                  degrees Centigrade
Result:           Test result: 840 µl/l
Reliability:      (2)  valid with restrictions
                  Test procedure in accordance with generally accepted
                  scientific standards and described in sufficient detail
30-AUG-2001                                                            (76)

Type:             flow through
Species:          Salmo salar  (Fish, fresh water, marine)
Exposure period:  24 hour(s)
Unit:             mg/l                  Analytical monitoring: no data
LC50:             = 156 -

Method:           other: acute toxicity test; "flow through bioassay"
   GLP:           no
Test substance:   other TS: formalin (solution 37%)

Remark:           fingerling; pH 6.5, water hardness 8, water temperature 12
                  degrees Centigrade
Result:           Test result: 389 µl/l
Reliability:      (2)  valid with restrictions
                  Test procedure in accordance with generally accepted
                  scientific standards and described in sufficient detail
30-AUG-2001                                                            (76)

Type:             flow through
Species:          Salvelinus namaycush  (Fish, fresh water)
Exposure period:  6 hour(s)
Unit:             mg/l                  Analytical monitoring: no data
LC50:             = 241 -

Method:           other: acute toxicity test; "flow through bioassay"
   GLP:           no
Test substance:   other TS: formalin (solution 37%)

Remark:           fingerling; pH 6.5, water hardness 8, water temperature 12
                  degrees Centigrade
Result:           Test result: 603 µl/l
Reliability:      (2)  valid with restrictions
                  Test procedure in accordance with generally accepted
                  scientific standards and described in sufficient detail
30-AUG-2001                                                            (76)
```

```
Type:              flow through
Species:           Salvelinus namaycush  (Fish, fresh water)
Exposure period:   24 hour(s)
Unit:              mg/l                   Analytical monitoring: no data
LC50:              = 56.4 -

Method:            other: acute toxicity test; "flow through bioassay"
   GLP:            no
Test substance:    other TS: formalin (solution 37%)

Remark:            fingerling; pH 6.5, water hardness 8, water temperature 12
                   degrees Centigrade
Result:            Test result: 141 µl/l
Reliability:       (2)  valid with restrictions
                   Test procedure in accordance with generally accepted
                   scientific standards and described in sufficient detail
30-AUG-2001                                                              (76)

Type:              flow through
Species:           Salvelinus namaycush  (Fish, fresh water)
Exposure period:   96 hour(s)
Unit:              mg/l                   Analytical monitoring: no data
LC50:              = 40 -

Method:            other: acute toxicity test; "flow through bioassay"
   GLP:            no
Test substance:    other TS: formalin (solution 37%)

Remark:            fingerling; pH 6.5, water hardness 8, water temperature 12
                   degrees Centigrade
Result:            Test result: 100 µl/l
Reliability:       (2)  valid with restrictions
                   Test procedure in accordance with generally accepted
                   scientific standards and described in sufficient detail
30-AUG-2001                                                              (76)

Type:              semistatic
Species:           Morone saxatilis  (Fish, estuary, marine)
Exposure period:   96 hour(s)
Unit:              mg/l                   Analytical monitoring: no data
LC50:              = 6.7 -

Method:            other: acute toxicity test; "static bioassay"
  Year:            1969
   GLP:            no data
Test substance:    other TS: solution of 37%, by weight, of formaldehyde gas in
                   water; 10-15% methanol added

Result:            Test result: 18 ppm
Reliability:       (2)  valid with restrictions
                   Test procedure in accordance with generally accepted
                   scientific standards and described in sufficient detail
Flag:              Critical study for SIDS endpoint
21-SEP-2001                                                             (699)

Type:              static
Species:           Anguilla rostrata  (Fish, estuary)
Exposure period:   96 hour(s)
Unit:              mg/l                   Analytical monitoring: no data
```

```
LC50:             = 31.1 -

Method:           other: acute toxicity test; "static bioassay"
   GLP:           no data
Test substance:   other TS: formaldehyde; no data on purity of the compound

Remark:           American eel, glass stage
                  Reliability: 2 (reliable with restrictions)
30-AUG-2001                                                  (321) (322) (323)

Type:             static
Species:          Anguilla rostrata  (Fish, estuary)
Exposure period:  96 hour(s)
Unit:             mg/l                   Analytical monitoring: no data
LC50:             = 83.1 -

Method:           other: acute toxicity test; "static bioassay"
   GLP:           no data
Test substance:   other TS: formaldehyde; no data on purity of the compound

Remark:           American eel, black stage
                  Reliability: 2 (reliable with restrictions)
30-AUG-2001                                                  (321) (322) (323)

Type:             static
Species:          Anguilla rostrata  (Fish, estuary)
Exposure period:  96 hour(s)
Unit:             mg/l                   Analytical monitoring: no data
LC50:             = 122.1 -

Method:           other: acute toxicity test; "static bioassay"
   GLP:           no data
Test substance:   other TS: formaldehyde; no data on purity of the compound

Remark:           American eel, yellow stage
                  Reliability: 2 (reliable with restrictions)
30-AUG-2001                                                  (321) (322) (323)

Type:             static
Species:          Brachydanio rerio  (Fish, fresh water)
Exposure period:  96 hour(s)
Unit:             mg/l                   Analytical monitoring: no data
LC50:             = 41 -

Method:           other: acute toxicity test; "static bioassay"
   GLP:           no data
Test substance:   other TS: formaldehyde; no data on purity of the compound

Remark:           Reliability: 2 (reliable with restrictions)
30-AUG-2001                                                                (700)

Type:             static
Species:          Cyprinus carpio  (Fish, fresh water)
Exposure period:  2 hour(s)
Unit:             mg/l                   Analytical monitoring: no data
LC50:             = 74 -

Method:           Directive 84/449/EEC, C.1  "Acute toxicity for fish"
   GLP:           no data
```

```
Test substance:   other TS: formaldehyde; no data on purity of the compound

Remark:           Reliability: 2 (reliable with restrictions)
30-AUG-2001                                                          (629)

Type:             static
Species:          Ictalurus punctatus  (Fish, fresh water)
Exposure period:  24 hour(s)
Unit:             mg/l                   Analytical monitoring: no data
LC50:             = 50.7 -

Method:           other: acute toxicity test; "static bioassay"
   GLP:           no
Test substance:   other TS: formaldehyde; no data on purity of the compound

Remark:           Reliability: 2 (reliable with restrictions)
30-AUG-2001                                                          (704)

Type:             static
Species:          Ictalurus punctatus  (Fish, fresh water)
Exposure period:  48 hour(s)
Unit:             mg/l                   Analytical monitoring: no data
LC50:             = 35.5 -

Method:           other: acute toxicity test; "static bioassay"
   GLP:           no
Test substance:   other TS: formaldehyde; no data on purity of the compound

Remark:           Reliability: 2 (reliable with restrictions)
30-AUG-2001                                                          (704)

Type:             static
Species:          Lepomis gibbosus  (Fish, fresh water)
Exposure period:  24 hour(s)
Unit:             mg/l                   Analytical monitoring: no data
LC50:             = 53.7 -

Method:           other: acute toxicity test; "static bioassay"
   GLP:           no data
Test substance:   other TS: formaldehyde; no data on purity of the compound

Remark:           fingerling
                  Reliability: 2 (reliable with restrictions)
30-AUG-2001                                                          (591)

Type:             static
Species:          Lepomis gibbosus  (Fish, fresh water)
Exposure period:  24 hour(s)
Unit:             mg/l                   Analytical monitoring: no data
LC50:             = 68.5 -

Method:           other: acute toxicity test; "static bioassay"
   GLP:           no
Test substance:   other TS: formaldehyde; no data on purity of the compound


Remark:           fingerling
                  Reliability: 2 (reliable with restrictions)
30-AUG-2001                                                          (704)
```

```
Type:              static
Species:           Lepomis gibbosus  (Fish, fresh water)
Exposure period:   48 hour(s)
Unit:              mg/l                    Analytical monitoring: no data
LC50:              = 34 -

Method:            other: acute toxicity test; "static bioassay"
   GLP:            no
Test substance:    other TS: formaldehyde; no data on purity of the compound

Remark:            fingerling
                   Reliability: 2 (reliable with restrictions)
30-AUG-2001                                                            (591)

Type:              static
Species:           Lepomis gibbosus  (Fish, fresh water)
Exposure period:   48 hour(s)
Unit:              mg/l                    Analytical monitoring: no data
LC50:              = 51.8 -

Method:            other: acute toxicity test; "static bioassay"
   GLP:            no
Test substance:    other TS: formaldehyde; no data on purity of the compound

Remark:            fingerling
                   Reliability: 2 (reliable with restrictions)
30-AUG-2001                                                            (704)

Type:              static
Species:           Lepomis gibbosus  (Fish, fresh water)
Exposure period:   96 hour(s)
Unit:              mg/l                    Analytical monitoring: no data
LC50:              = 25.2 -

Method:            other: acute toxicity test; "static bioassay"
   GLP:            no
Test substance:    other TS: formaldehyde; no data on purity of the compound

Remark:            fingerling
                   Reliability: 2 (reliable with restrictions)
30-AUG-2001                                                            (591)

Type:              static
Species:           Leuciscus idus  (Fish, fresh water)
Exposure period:   48 hour(s)
Unit:              mg/l                    Analytical monitoring: no data
LC50:              = 22 -

Method:            other: acute toxicity test; "static bioassay"
   GLP:            no data
Test substance:    other TS: formaldehyde; no data on purity of the compound

Remark:            Reliability: 2 (reliable with restrictions)
30-AUG-2001                                                            (700)

Type:              static
Species:           Morone saxatilis  (Fish, estuary, marine)
Exposure period:   24 hour(s)
Unit:              mg/l                    Analytical monitoring: no data
LC50:              = 31.8 -
```

```
Method:           other: acute toxicity test; "static bioassay"
   GLP:           no data
Test substance:   other TS: solution of 37%, by weight, of formaldehyde gas in
                  water; 10-15% methanol added

Result:           Test result: 86 ppm
Reliability:      (2)  valid with restrictions
                  Test procedure in accordance with generally accepted
                  scientific standards and described in sufficient detail
30-AUG-2001                                                              (699)

Type:             static
Species:          Morone saxatilis  (Fish, estuary, marine)
Exposure period:  48 hour(s)
Unit:             mg/l                   Analytical monitoring: no data
LC50:             = 11.8 -

Method:           other: acute toxicity test; "static bioassay"
   GLP:           no data
Test substance:   other TS: solution of 37%, by weight, of formaldehyde gas in
                  water; 10-15% methanol added

Result:           Test result: 32 ppm
Reliability:      (2)  valid with restrictions
                  Test procedure in accordance with generally accepted
                  scientific standards and described in sufficient detail
30-AUG-2001                                                              (699)

Type:             static
Species:          Rasbora heteromorpha  (Fish, marine)
Exposure period:  24 hour(s)
Unit:             mg/l                   Analytical monitoring: no data
LC50:             = 76 -

Method:           other: acute toxicity test; "static bioassay"
   GLP:           no data
Test substance:   other TS: formaldehyde; no data on purity of the compound

Remark:           Reliability: 2 (reliable with restrictions)
30-AUG-2001                                                                (9)

Type:             static
Species:          Rasbora heteromorpha  (Fish, marine)
Exposure period:  48 hour(s)
Unit:             mg/l                   Analytical monitoring: no data
LC50:             = 50 -

Method:           other: acute toxicity test; "static bioassay"
   GLP:           no data
Test substance:   other TS: formaldehyde; no data on purity of the compound

Remark:           Reliability: 2 (reliable with restrictions)
30-AUG-2001                                                                (9)

Type:             static
Species:          Salmo gairdneri  (Fish, estuary, fresh water)
Exposure period:  24 hour(s)
Unit:             mg/l                   Analytical monitoring: no data
LC50:             = 76.6 -
```

```
Method:           other: acute toxicity test; "static bioassay"
   GLP:           no data
Test substance:   other TS: formaldehyde; no data on purity of the compound

Remark:           Reliability: 2 (reliable with restrictions)
30-AUG-2001                                                            (704)

Type:             static
Species:          Salmo gairdneri  (Fish, estuary, fresh water)
Exposure period:  48 hour(s)
Unit:             mg/l                   Analytical monitoring: no data
LC50:             = 59.2 -

Method:           other: acute toxicity test; "static bioassay"
   GLP:           no data
Test substance:   other TS: formaldehyde; no data on purity of the compound

Remark:           Reliability: 2 (reliable with restrictions)
30-AUG-2001                                                            (591)

Type:             static
Species:          Salmo gairdneri  (Fish, estuary, fresh water)
Exposure period:  48 hour(s)
Unit:             mg/l                   Analytical monitoring: no data
LC50:             = 62.2 -

Method:           other: acute toxicity test; "static bioassay"
   GLP:           no data
Test substance:   other TS: formaldehyde; no data on purity of the compound

Remark:           Reliability: 2 (reliable with restrictions)
30-AUG-2001                                                            (704)

Type:             static
Species:          Salmo gairdneri  (Fish, estuary, fresh water)
Exposure period:  96 hour(s)
Unit:             mg/l                   Analytical monitoring: no data
LC50:             61.9 - 106

Method:           other: acute toxicity test; "static bioassay"
   GLP:           no
Test substance:   other TS: formaldehyde; no data on purity of the compound

Remark:           fingerling; pH 6.5-9.5, water temperature 12 degrees
                  Centigrade
                  Reliability: 2 (reliable with restrictions)
30-AUG-2001                                                            (110)

Type:             static
Species:          Salmo gairdneri  (Fish, estuary, fresh water)
Exposure period:  96 hour(s)
Unit:             mg/l                   Analytical monitoring: no data
LC50:             89.5 - 112

Method:           other: acute toxicity test; "static bioassay"
   GLP:           no
Test substance:   other TS: formaldehyde; no data on purity of the compound
```

```
Remark:           larvae; pH 6.5-9.5, water temperature 12 degrees Centigrade
                  Reliability: 2 (reliable with restrictions)
30-AUG-2001                                                              (110)

Type:             static
Species:          Salmo gairdneri  (Fish, estuary, fresh water)
Exposure period:  96 hour(s)
Unit:             mg/l                   Analytical monitoring: no data
LC50:             = 118 -

Method:           other: acute toxicity test; "static bioassay"
   GLP:           no data
Test substance:   other TS: formaldehyde; no data on purity of the compound

Remark:           Reliability: 2 (reliable with restrictions)
                  water hardness 20, water
                  temperature 12 degrees Centigrade
30-AUG-2001                                                              (110)

Type:             static
Species:          Salmo gairdneri  (Fish, estuary, fresh water)
Exposure period:  96 hour(s)
Unit:             mg/l                   Analytical monitoring: no data
LC50:             565 - 1020

Method:           other: acute toxicity test; "static bioassay"
   GLP:           no
Test substance:   other TS: formaldehyde; no data on purity of the compound

Remark:           green eegs; pH 6.5-9.5, water temperature 12 degrees
                  Centigrade
                  Reliability: 2 (reliable with restrictions)
30-AUG-2001                                                              (473)

Type:             static
Species:          Salmo salar  (Fish, fresh water, marine)
Exposure period:  96 hour(s)
Unit:             mg/l                   Analytical monitoring: no data
LC50:             = 173 -

Method:           other: acute toxicity test; "static bioassay"
   GLP:           no
Test substance:   other TS: formaldehyde; no data on purity of the compound

Remark:           pH 6.5, water temperature 12 degrees
                  Centigrade
                  Reliability: 2 (reliable with restrictions)
30-AUG-2001                                                              (473)

Type:             static
Species:          Salmo trutta  (Fish, fresh water, marine)
Exposure period:  24 hour(s)
Unit:             mg/l                   Analytical monitoring: no data
LC50:             = 120.3 -

Method:           other: acute toxicity test; "static bioassay"
   GLP:           no
Test substance:   other TS: formaldehyde; no data on purity of the compound
```

```
Remark:           Reliability: 2 (reliable with restrictions)
30-AUG-2001                                                          (704)

Type:             static
Species:          Salmo trutta  (Fish, fresh water, marine)
Exposure period:  48 hour(s)
Unit:             mg/l                  Analytical monitoring: no data
LC50:             = 68.5 -

Method:           other: acute toxicity test; "static bioassay"
   GLP:           no
Test substance:   other TS: formaldehyde; no data on purity of the compound

Remark:           Reliability: 2 (reliable with restrictions)
30-AUG-2001                                                          (704)

Type:             static
Species:          Salvelinus fontinalis  (Fish, estuary, fresh water)
Exposure period:  24 hour(s)
Unit:             mg/l                  Analytical monitoring: no data
LC50:             = 72.5 -

Method:           other: acute toxicity test; "static bioassay"
   GLP:           no
Test substance:   other TS: formaldehyde; no data on purity of the compound

Remark:           Reliability: 2 (reliable with restrictions)
30-AUG-2001                                                          (704)

Type:             static
Species:          Salvelinus fontinalis  (Fish, estuary, fresh water)
Exposure period:  48 hour(s)
Unit:             mg/l                  Analytical monitoring: no data
LC50:             = 58.1 -

Method:           other: acute toxicity test; "static bioassay"
   GLP:           no
Test substance:   other TS: formaldehyde; no data on purity of the compound

Remark:           Reliability: 2 (reliable with restrictions)
30-AUG-2001                                                          (704)

Type:             static
Species:          Salvelinus namaycush  (Fish, fresh water)
Exposure period:  24 hour(s)
Unit:             mg/l                  Analytical monitoring: no data
LC50:             = 81.4 -

Method:           other: acute toxicity test; "static bioassay"
   GLP:           no
Test substance:   other TS: formaldehyde; no data on purity of the compound

Remark:           fingerling
                  Reliability: 2 (reliable with restrictions)
30-AUG-2001                                                          (704)

Type:             static
Species:          Salvelinus namaycush  (Fish, fresh water)
Exposure period:  48 hour(s)
```

```
Unit:              mg/l                    Analytical monitoring: no data
LC50:              = 61.8 -

Method:            other: acute toxicity test; "static bioassay"

   GLP:            no
Test substance:    other TS: formaldehyde; no data on purity of the compound

Remark:            fingerling
                   Reliability: 2 (reliable with restrictions)
30-AUG-2001                                                            (704)

Type:              other
Species:           Cyprinus carpio  (Fish, fresh water)
Exposure period:   72 hour(s)
Unit:              mg/l                    Analytical monitoring: no data
LC50:              > 26.6 -

Method:            other: acute toxicity test
   GLP:            no
Test substance:    other TS: formaldehyde; no data on purity of the compound

Remark:            Reliability: 2 (reliable with restrictions)
30-AUG-2001                                                            (312)

Type:              other
Species:           Ictalurus melas  (Fish, fresh water)
Exposure period:   72 hour(s)
Unit:              mg/l                    Analytical monitoring: no data
LC50:              = 17.1 -

Method:            other: acute toxicity test
   GLP:            no
Test substance:    other TS: formaldehyde; no data on purity of the compound

Remark:            fingerling
Reliability:       (2)  valid with restrictions
30-AUG-2001                                                            (312)

Type:              other
Species:           Ictalurus punctatus  (Fish, fresh water)
Exposure period:   96 hour(s)
Unit:              mg/l                    Analytical monitoring: no data
LC50:              = 25.5 -

Method:            other: no data
   GLP:            no
Test substance:    other TS: formaldehyde; no data on purity of the compound

Remark:            Reliability: 2 (reliable with restrictions)
30-AUG-2001                                                     (142) (143)

Type:              other
Species:           Lepomis cyanellus  (Fish, fresh water)
Exposure period:   72 hour(s)
Unit:              mg/l                    Analytical monitoring: no data
LC50:              > 34.2 -

Method:            other: acute toxicity test
   GLP:            no
```

```
Test substance:   other TS: formaldehyde; no data on purity of the compound

Remark:           fingerling
Reliability:      (2)  valid with restrictions
30-AUG-2001                                                          (312)

Type:             other
Species:          Lepomis cyanellus  (Fish, fresh water)
Exposure period:  96 hour(s)
Unit:             mg/l                   Analytical monitoring: no data
LC50:             = 173 -

Method:           other: acute toxicity test
   GLP:           no
Test substance:   other TS: formaldehyde; no data on purity of the compound

Remark:           water temperature 12 degrees Centigrade
Reliability:      (2)  valid with restrictions
30-AUG-2001                                                          (473)

Type:             other
Species:          Lepomis cyanellus  (Fish, fresh water)
Exposure period:  48 hour(s)

Unit:             mg/l                   Analytical monitoring: no data
LC50:             = 32.4 -

Method:           other: no data
   GLP:           no
Test substance:   other TS: formaldehyde; no data on purity of the compound

Reliability:      (2)  valid with restrictions
30-AUG-2001                                                          (369)

Type:             other
Species:          Lepomis gibbosus  (Fish, fresh water)
Exposure period:  72 hour(s)
Unit:             mg/l                   Analytical monitoring: no data
LC50:             > 30.4 -

Method:           other: acute toxicity test
   GLP:           no
Test substance:   other TS: formaldehyde; no data on purity of the compound

Remark:           fingerling
Reliability:      (2)  valid with restrictions
30-AUG-2001                                                          (312)

Type:             other
Species:          Leuciscus idus  (Fish, fresh water)
Exposure period:  48 hour(s)
Unit:             mg/l                   Analytical monitoring: no data
LC50:             = 15 -

Method:           other: no data
   GLP:           no data
Test substance:   other TS: formaldehyde; no data on purity of the compound

Reliability:      (2)  valid with restrictions
30-AUG-2001                                                          (369)
```

```
Type:             other
Species:          Micropterus salmoides  (Fish, fresh water)
Exposure period:  72 hour(s)
Unit:             mg/l                   Analytical monitoring: no data
LC50:             > 38 -

Method:           other: acute toxicity test
   GLP:           no
Test substance:   other TS: formaldehyde; no data on purity of the compound

Remark:           fingerling
Reliability:      (2)  valid with restrictions
30-AUG-2001                                                          (312)

Type:             other
Species:          Salmo gairdneri  (Fish, estuary, fresh water)
Exposure period:  24 hour(s)
Unit:             mg/l                   Analytical monitoring: no data
LC50:             214 - 7200

Method:           other: acute toxicity test
   GLP:           no
Test substance:   other TS: formaldehyde; no data on purity of the compound

Remark:           pH 7.5, water hardness 40-48,
                  water temperature 12 degrees Centigrade
Reliability:      (2)  valid with restrictions
30-AUG-2001                                                     (473) (510)

Type:             other
Species:          Salmo gairdneri  (Fish, estuary, fresh water)
Exposure period:  96 hour(s)
Unit:             mg/l                   Analytical monitoring: no data
LC50:             > 47.2 -

Method:           other: acute toxicity test
   GLP:           no
Test substance:   other TS: formaldehyde; no data on purity of the compound

Remark:           fingerling
Reliability:      (2)  valid with restrictions
30-AUG-2001                                                          (312)

Type:             other
Species:          Salmo gairdneri  (Fish, estuary, fresh water)
Exposure period:  96 hour(s)
Unit:             mg/l                   Analytical monitoring: no data
LC50:             440 - 618

Method:           other: acute toxicity test
   GLP:           no
Test substance:   other TS: formaldehyde; no data on purity of the compound

Remark:           pH 7.5-8.2, water hardness
                  30-245, water temperature 12 degrees Centigrade
Reliability:      (2)  valid with restrictions
30-AUG-2001                                                          (473)
```

```
Type:             other
Species:          Salmo gairdneri  (Fish, estuary, fresh water)
Unit:                                   Analytical monitoring: no data

Method:           other: no data
   GLP:           no
Test substance:   other TS: formaldehyde; no data on purity of the compound

Remark:           In rainbow trouts, toxicity of formaldehyde was increased
                  with raising water temperature, decreasing water hardness,
                  and increasing pH values; changes of gill function,
                  hypochloremia, decreased contents of both calcium and carbon
                  dioxide in plasma, lowered pH of blood and reduced
                  consumption of oxygen were observed.
Reliability:      (2)  valid with restrictions
30-AUG-2001                                                              (77)

Type:             other
Species:          Salmo salar  (Fish, fresh water, marine)
Exposure period:  96 hour(s)
Unit:             mg/l                  Analytical monitoring: no data
LC50:             198 - 435

Method:           other: acute toxicity test
   GLP:           no
Test substance:   other TS: formaldehyde; no data on purity of the compound

Remark:           "eyed eggs"; pH 6.5-9.5, water temperature 12 degrees
                  Centigrade
Reliability:      (2)  valid with restrictions
30-AUG-2001                                                            (473)

Type:             other
Species:          Salmo salar  (Fish, fresh water, marine)
Unit:                                   Analytical monitoring: no data

Method:           other: no data
   GLP:           no
Test substance:   other TS: formaldehyde; no data on purity of the compound

Remark:           Changes of gill function, hypochloremia, decreased contents
                  of both calcium and carbon dioxide in plasma, lowered pH of
                  blood and reduced consumption of oxygen, increased levels of
                  both hemoglobin and glucose in blood, increased protein
                  concentration in plasma, and increased "packed" cell
                  volumina were observed.
Reliability:      (2)  valid with restrictions
30-AUG-2001                                                      (510) (697)

Type:             other
Species:          other: Golden Shiner
Exposure period:  72 hour(s)
Unit:             mg/l                  Analytical monitoring: no data
LC50:             = 23.6 -

Method:           other: acute toxicity test
   GLP:           no
Test substance:   other TS: formaldehyde; no data on purity of the compound

Reliability:      (2)  valid with restrictions
```

30-AUG-2001 (312)

Type: other
Species: other: Tilapia
Exposure period: 72 hour(s)
Unit: mg/l Analytical monitoring: no data
LC50: > 38 -

Method: other: acute toxicity test
GLP: no
Test substance: other TS: formaldehyde; no data on purity of the compound

Reliability: (2) valid with restrictions
30-AUG-2001 (312)

4.2 Acute Toxicity to Aquatic Invertebrates

Species: Daphnia magna (Crustacea)
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring:
EC0: = 27 -
EC50: = 52 -
EC100: = 77 -

Method: other: Mobilization Inhibition Test
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Test result: 52 mg/l formalin solution (35%) correspond to 18.2 mg/l pure substance
Test condition: tap water as test medium, free from chlorine; pH 7.6-7.7; 20-22 deg C
Reliability: (2) valid with restrictions
Test procedure in accordance with generally accepted scientific standards and described in sufficient detail
07-SEP-2001 (99)

Species: Daphnia pulex (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring:
EC10 : = 1.9 -
EC50 : = 5.8 -
EC90 : = 16.8 -

Method: other: according to the OECD standard
GLP: no data
Test substance: other TS: formaldehyde 37 % v/v

Result: EC50 (48 h) = 4.3 - 7.8 (confidental limit)
Test condition: test temperature 20 +/- 1 °C,
the standard stock solutions were prepared according to Standard Methods: APHA-AWWA-WEF, 1992 and Leithe, 1974, daphnids cultured in 3-L-aquariumsand beakers were illuminatedfor 12 hr per day
Reliability: (2) valid with restrictions
2.1; accepatable study, meets basic scientific principles
Flag: Critical study for SIDS endpoint
08-AUG-2002 (652)

```
Species:          Daphnia magna  (Crustacea)
Exposure period:  24 hour(s)
Unit:             mg/l                   Analytical monitoring:
TLm :             > 100 - 1000

Method:           other: Acute Toxicity Test
   GLP:           no

Remark:           TLm = Median Tolerance Limit
Test condition:   Reference Dilution Water
Reliability:      (2)  valid with restrictions
23-OCT-2000                                                          (200)

Species:          Daphnia magna  (Crustacea)
Exposure period:  24 hour(s)
Unit:             mg/l                   Analytical monitoring: no
EC0:              = 33 -
EC50:             = 42 -
EC100:            = 53 -

Method:           other: Static Acute Toxicity Test (Open System)
   GLP:           no
Test substance:   other TS: aqueous solution of formaldehyde (35 %)

Remark:           Test result: 42 mg/l formalin solution (35%) correspond to
                  14.7 mg/l pure substance
Result:           EC-values were determined graphically assuming normal
                  distribution of data
Test condition:   Test vessel:          50 ml beakers
                  Test volume:          20 ml
                  Test medium:          artifical fresh water according to
                                        DIN 38412, Part 11 (draft)
                  Concentration of
                  stock solution:       not indicated
                  Dilution factor:      starting with 1:2. If this result in
                                        less than 3 dilutions steps between
                                        EC0 and EC100, additional dilutions
                                        (1:1.4 or 1:1.1) were investigated
                  pH-adjustment:        no
                  Solvents/emulsifiers: no
                  Number of test
                  replicates:           2
                  Numer of control
                  replicates:           not indicates
                  Age of animals:       max. 24 h
                  Number of animals/
                  treatment:            10
                  Feeding:              no
                  pH:                   8.0 +/- 0.2
                  Temperature:          20 °C
                  Dissolved oxygen:     > 2.0 mg/l
                  Illumination:         15 h darkend, 9 h artificial ill.
                  Measurements:         swimming ability of the daphnids was
                                        checked after 24 h of exposure
Reliability:      (2)  valid with restrictions
                  Test procedure in accordance with generally accepted
                  scientific standards and described in sufficient detail
Flag:             Critical study for SIDS endpoint
20-AUG-2001                                                          (100)
```

```
Species:          Daphnia magna  (Crustacea)
Exposure period:  1 hour(s)
Unit:             mg/l                   Analytical monitoring:
EC50:             = 39 -

   GLP:           no

Method:           Juvenile Daphnia magna was exposed to a toxicant dilution
                  series for 1 h, after which the substrate was added and the
                  enzymatic inhibition (absence of fluorescence) was observed
                  visually, using a long wave UV light (385 mm).
Remark:           In order to compare the results of the screening test with
                  the results of a conventional test, an acute toxicity test
                  was conducted according to OECD Guideline No. 202
                  Test results (immobilzation; mean concentrations of
                  formaldehyde):
                  EC50 (24 h) = 57 mg/l
                  EC50 (48 h) = 29 mg/l
Reliability:      (2)  valid with restrictions
16-JUN-2003                                                              (358)

Species:          other aquatic mollusc: Mytilus edulis

Remark:           The effects of sublethal concentrations of organic
                  pollutants on intracellular energy-rich phosphates in blue
                  mussels, Mytilus edulis, were investigated by in vivo P-NMR.
Result:           30 and 10 mg/l formaldehyde (96h exposition) caused
                  reduction of byssal thread formation and reduction of ATP.
                  No effect with 1 mg/l.
Reliability:      (2)  valid with restrictions
23-OCT-2000                                                               (35)

Type:             semistatic
Species:          other aquatic crustacea: Cypridopsis vidua
Exposure period:  96 hour(s)
Unit:             mg/l                   Analytical monitoring: yes
EC50:             = 68.6 -

Method:           other
   GLP:           no

Remark:           A second test was conducted at a temperature of 16 °C with
                  the following result:
                  EC50(96 h): 54.4 mg/l
                  The 16° C temperature was selected in order to reproduce the
                  test of Bills et al. (1977).
Test condition:   The test was conducted at 25 °C using ostracodes retained on
                  300 and 400 µm filters.
                  Test organisms were not fed during the 96-h tests
Reliability:      (4)  not assignable
                  Secondary Literature (Cooney and Bourgoin, 2001 as cited in
                  Hohreiter and Riggs, 2001)
25-JUN-2003                                                              (326)

Species:          other aquatic crustacea: Palaemonetes kadiakensis
Exposure period:  24 hour(s)

Method:           other: Acute Toxicity Test
   GLP:           no
```

```
Test substance:   other TS: formaline 37%

Result:           LC50 (24h) = 1105 ul/l
                  Toxicity based on immobility
Test condition:   soft water at 16 deg C
Reliability:      (2)  valid with restrictions
23-OCT-2000                                                        (78)

Species:          other aquatic crustacea: Penaeus sp.

Remark:           The 96 h LD50s for formaline under the conditions of these
                  tests were 235 ppm at 28 deg C and 270 ppm at 22 deg C for
                  the 60-70 mm and postlarval pink shrimp, respectively.
                  Application levels of 25 ppm would be save for treatments of
                  indefinite duration. Based on a 96 h observation period
                  following dipping, 30 min dip treatments indicated treatment
                  in the range of 150-250 ppm would be usable at temperatures
                  of 22 deg C and below. Tests that utilized post-larval
                  shrimp of poor condition and at 21 deg C showed no loss in
                  excess of controls when given the same testing routine.
Test condition:   4 sizes of shrimps; artificial sea salt (Instant ocean)
Reliability:      (2)  valid with restrictions
23-OCT-2000                                                       (367)

Species:          other: Anodonta cygnea and Daphnia magna

Remark:           The effects of some ecotoxical model substances on the
                  activity of frontal gill cilia of freshwater mussel Anodonta
                  cygnea were studied in 1 and 24 h experiments with the
                  results of standard Daphnia magna EC50 tests with the same
                  substances.
Result:           Toxicity of formaldehyde on the ciliary activity in Anodonta
                  gills and on Daphnia magna:
                  EC (minimum, 2h) = 2 mg/l (Anodonta gills)
                  EC50 (24h / 48h) = 5 / 14 mg/l (Daphnia magna)
Test substance:   Concentrations calculated as formaldehyde
Reliability:      (2)  valid with restrictions
16-JUN-2003                                                       (414)

Species:          other: Corbicula sp.
Exposure period:  24 hour(s)

Method:           other: Acute Toxicity Test
   GLP:           no
Test substance:   other TS: formaline 37%

Result:           LC50 (24h) = 800 ul/l
                  Toxicity based on ability to resist attempts to open valves
                  and respond to tactile stimulus
Test condition:   soft water at 16 deg C
Reliability:      (2)  valid with restrictions
23-OCT-2000                                                        (78)

Species:          other: Cypridopsis sp.
Exposure period:  24 hour(s)

Method:           other: Acute Toxicity Test
   GLP:           no
Test substance:   other TS: formaline 37%
```

```
Result:           LC50 (24h) = 1.15 ul/l
                  Toxicity based on immobility
Test condition:   soft water at 16 deg C
Reliability:      (2)  valid with restrictions
30-AUG-2001                                                          (76)

Species:          other: Helisoma sp.
Exposure period:  24 hour(s)

Method:           other: Acute Toxicity Test
   GLP:           no
Test substance:   other TS: formaline 37%

Result:           LC50 (24h) = 710 ul/l
                  Toxicity based on ability to respond to tactile stimulus
Test condition:   soft water at 16 deg C
Reliability:      (2)  valid with restrictions
30-AUG-2001                                                          (76)

Species:          other: Notonecta sp.
Exposure period:  24 hour(s)

Method:           other: Acute Toxicity Test
   GLP:           no
Test substance:   other TS: formaline 37%

Result:           LC50 (24h) = 4500 ul/l
                  Toxicity based on ability to respond to tactile stimulus
Test condition:   soft water at 16 deg C
Reliability:      (2)  valid with restrictions
30-AUG-2001                                                          (76)

Species:          other: Streptocephalus seali
Exposure period:  24 hour(s)
Unit:             mg/l                   Analytical monitoring:
EC0:              > 25 -

Method:           other: Acute Toxicity Test
   GLP:           no
Test substance:   other TS: formaline 37%

Result:           EC10 (48h) = 25 mg/l
Test condition:   Static test in well water at 24 deg C
Reliability:      (2)  valid with restrictions
23-OCT-2000                                                         (496)
```

4.3 Toxicity to Aquatic Plants e.g. Algae

```
Species:          Scenedesmus quadricauda  (Algae)
Endpoint:         biomass
Exposure period:  192 hour(s)
Unit:             mg/l                   Analytical monitoring: no
Toxicity Threshold :
                  = 2.5 -

Method:           other: Static Cell Multiplication Inhibition Test
  Year:           1978
   GLP:           no
```

Test substance: other TS: aqueous solution of formaldehyde (35%)

Remark: Test result: 2.5 mg/l formalin (35% solution) correspond to 0.88 mg/l pure substance

Result: Toxic threshold is defined in this investigation as the concentration of test substance causing 3 % inhibition of cell multiplication compared to untreated controls.

Test condition:

Test vessel:	Kapsenberg cultivation tubes (18 x 180 mm)
Test volume:	10 ml
Concentration of stock solution:	not indicated
Dilution:	1:2
Pre-treatment of test solution:	neutralisation if necessary
Inoculum:	cell density adjusted to TE/F = 20 (formazin turbidity equivalents at 578 nm)
Number of test replicates:	3
Numer of control replicates:	1
Illumination:	constant artifical light (Osram L 40/30)
Temperature:	27 °C
Agitation:	once daily
Measurements:	photometric determination of cell density 578 nm after 192 h of exposure

Reliability: (2) valid with restrictions
Test procedure in accordance with generally accepted scientific standards and described in sufficient detail

Flag: Critical study for SIDS endpoint

24-SEP-2001 (95)

Species: Scenedesmus sp. (Algae)
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring:
TGK : = .3 -

GLP: no

Result: Starting inhibition of cell multiplication
Test condition: 25 deg C; pH 7.5-7.8
Reliability: (2) valid with restrictions

23-OCT-2000 (94)

Species: Scenedesmus quadricauda (Algae)
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring: no data
EC10: = 3.6 -
EC50: = 14.7 -
EC90 : = 60.3 -

Method: other
GLP: no data
Test substance: other TS: formaldehyde 37 %, v/v

Method: Toxicity to algae was evaluted by measuring the oxygen production and consumption rates following exposure to the test media and calculating the 24-hr net assimilation by the algae.

The oxygen production and consu,ption rates were measured on Warburg apparatus (type 85G, B.Braun, Germany).
The effective concentrations were using linear regression analysis.

Test condition: test temperature 20 +/- 1 °C,
the standard stock solutions were prepared according to Standard Methods: APHA-AWWA-WEF, 1992 and Leithe, 1974, cultured in the nutrient solution prepared according to Holm Hansen (Bringmann and Kühn, 1980) under continuous illumination (3000 lx)

Reliability: (2) valid with restrictions
2.1; accepatable study, meets basic scientific principles

Flag: Critical study for SIDS endpoint

08-AUG-2002 (652)

4.4 Toxicity to Microorganisms e.g. Bacteria

Type: aquatic
Species: activated sludge
Exposure period: 3 hour(s)
Unit: mg/l Analytical monitoring:
IC50 : = 20.4 -

Method: other: Respiration Inhibition Test (OECD)
GLP: no

Remark: Probit-transformation analysis

23-OCT-2000 (395)

Type: aquatic
Species: activated sludge, industrial
Exposure period: 30 minute(s)
Unit: mg/l Analytical monitoring: no
EC10: > 1995 -
EC20 : > 1995 -

Method: other: Activated Sludge Respiration Inhibition Test
Year: 1979
GLP: no
Test substance: other TS: formaldehyde 35%

Remark: industrial activated sludge (BASF): 1 g/l dry weight;
tested concentrations: 15,75,150,750,1500,1995 mg/l formaldehyde 35%;

Result: 1995 mg/l formaldehyde 35% correspond to 700 mg/l pure substance; support of respiration

Reliability: (2) valid with restrictions
Documented test parameters in accordance with the relating standard methods

13-DEC-2001 (39)

Type: aquatic
Species: activated sludge, industrial
Unit: mg/l Analytical monitoring:
EC50: = 1.714 -
EC20 : = 1.429 -
EC80 : = 4.286 -

Method: other: Toximeter experiments (model WWTP)

```
 Year:            1979
   GLP:            no
Test substance:    other TS: formaldehyde 100% (calculation)

Remark:            influent: industrial sewage (BASF)
                   activated sludge: industrial (BASF) 2 g/l dry weight
                   outcome: stimulation with less than 1.429 mg/l TOC
Reliability:       (2)  valid with restrictions
                   Study not in accordance with a defined standard method, but
                   meets generally accepted scientific principles
23-OCT-2000                                                              (38)

Type:              aquatic
Species:           Alcaligenes sp.  (Bacteria)
Exposure period:   72 hour(s)
Unit:              mg/l                    Analytical monitoring:
MIC :              = 50 -

Method:            other: Acute Toxicity Test
  Year:            1995
Test substance:    other TS: Formaldehyde 37%

Remark:            MIC = Minimum Inhibitory Concentration
Test condition:    25 deg C
Reliability:       (2)  valid with restrictions
                   Study not in accordance with a defined standard method, but
                   meets generally accepted scientific principles
23-OCT-2000                                                             (373)

Type:              aquatic
Species:           Chilomonas paramaecium  (Protozoa)
Exposure period:   48 hour(s)
Unit:              mg/l                    Analytical monitoring:
TGK :              = 4.5 -

Method:            other: Cell Multiplication Inhibition Test
   GLP:            no
Test substance:    other TS: formaline 35%

Test condition:    pH 6.9; bidest. water; 20 deg C
Reliability:       (2)  valid with restrictions
                   Test procedure in accordance with generally accepted
                   scientific standards and described in sufficient detail
23-OCT-2000                                                              (96)

Type:              aquatic
Species:           Entosiphon sulcatum  (Protozoa)
Exposure period:   72 hour(s)
Unit:              mg/l                    Analytical monitoring:
TGK :              = 22 -

Method:            other: Cell Multiplication Inhibition Test
   GLP:            no
Test substance:    other TS: formaline 35%

Test condition:    pH 6.9; bidest. water; 25 deg C
Reliability:       (2)  valid with restrictions
                   Test procedure in accordance with generally accepted
                   scientific standards and described in sufficient detail
23-OCT-2000                                                             (101)
```

```
Type:              aquatic
Species:           Escherichia coli  (Bacteria)
Exposure period:   24 hour(s)
Unit:              mg/l                    Analytical monitoring:
TGK :              = 1 -

   GLP:            no

Result:            Starting inhibition of glucose inhibition
Test condition:    25 deg C; pH 7.5-7.8
23-OCT-2000                                                          (94)

Type:              aquatic
Species:           Microcystis aeruginosa  (Bacteria)
Exposure period:   8 day(s)
Unit:              mg/l                    Analytical monitoring:
TGK :              = .39 -

Method:            other: Cell Multiplication Inhibition Test
   GLP:            no
Test substance:    other TS: formaline 35%

Test condition:    pH 7.0; bidest. water; 27 deg C
Reliability:       (2)  valid with restrictions
                   Test procedure in accordance with generally accepted
                   scientific standards and described in sufficient detail
23-OCT-2000                                                          (95)

Type:              aquatic
Species:           Photobacterium phosphoreum  (Bacteria)
Exposure period:   30 minute(s)
Unit:              mg/l                    Analytical monitoring:
EC50:              ca. 16.5 -

Method:            other: Microtox Toxicity Test
   GLP:            no

23-OCT-2000                                                         (474)

Type:              aquatic
Species:           Pseudomonas fluorescens  (Bacteria)
Exposure period:   16 hour(s)
Unit:              mg/l                    Analytical monitoring:
TGK :              = 14 -

Method:            other: Modification of DEV L8 (1960)
   GLP:            no
Test substance:    other TS: formaline 35%

Remark:            Glucose assimilation was measured
Test condition:    25 deg C; bidest. water; pH 7.0
23-OCT-2000                                                          (93)

Type:              aquatic
Species:           Pseudomonas fluorescens  (Bacteria)
Exposure period:   24 hour(s)
Unit:              mg/l                    Analytical monitoring:
TGK :              = 2 -
```

```
   GLP:            no

Result:            Starting inhibition of glucose inhibition
Test condition:    25 deg C; pH 7.5-7.8
23-OCT-2000                                                          (94)

Type:              aquatic
Species:           Pseudomonas putida  (Bacteria)
Exposure period:   16 hour(s)
Unit:              mg/l                   Analytical monitoring:
TGK :              = 14 -

Method:            other: Cell Multiplication Inhibition Test
   GLP:            no
Test substance:    other TS: formaline 35%

Result:            Toxic threshold is defined in this investigation as the
                   concentration of test substance causing 3 % inhibition of
                   cell multiplication compared to untreated controls.
Test condition:    Test vessel:          300 ml Erlenmeyer flasks
                   Test volume:          100 ml
                   Concentration of
                   stock solution:       not indicated
                   Dilution factor:      1:2
                   Pre-treatment of
                   stock solution:       neutralisation if necessary
                   Solvents/emulsifiers: no
                   Inoculum:             cell density adjusted to TE/F = 10
                                         (formazin turbidity equivalents at
                                         436 nm)
                   Number of test
                   replicates:           3
                   Numer of control
                   replicates:           1
                   pH:                   8 +/- 0.2
                   Temperature:          25 °C
                   Dissolved oxygen:     saturated solution
                   Illumination:         not indicated
                   Measurements:         photometric determination of cell den-
                                         sity at 436 nm after 16 h of exposure
Reliability:       (1)  valid without restriction
                   Test procedure in accordance with generally accepted
                   scientific standards and described in sufficient detail
Flag:              Critical study for SIDS endpoint
20-AUG-2001                                                          (98)

Type:              aquatic
Species:           Uronema parduzci  (Protozoa)
Exposure period:   20 hour(s)
Unit:              mg/l                   Analytical monitoring:
TGK :              = 6.5 -

Method:            other: Cell Multiplication Inhibition Test
   GLP:            no
Test substance:    other TS: formaline 35%

Test condition:    pH 6.9; bidest. water; 25 deg C
Reliability:       (2)  valid with restrictions
                   Test procedure in accordance with generally accepted
                   scientific standards and described in sufficient detail
```

23-OCT-2000 (97)

Type: aquatic
Species: other bacteria: Pseudomonas putida, not pre-acclimated
Unit: mg/l Analytical monitoring:
NOEC : = 30 -

Method: other: Respiration Inhibition Test, modified
Year: 1990
GLP: no

23-OCT-2000 (248)

Type: aquatic
Species: other bacteria: Vibrio harveyi (marine organism)
Exposure period: 1 hour(s)
Unit: mg/l Analytical monitoring:
EC50: = 1.2 -

Method: other: Bioluminescent Direct Assay
Year: 1993
GLP: no

Result: unit: ppm
23-OCT-2000 (649)

Type: aquatic
Species: other bacteria: Vibrio harveyi (marine organism)
Exposure period: 5 hour(s)
Unit: mg/l Analytical monitoring:
EC50: = 3.7 -

Method: other: Bioluminescent Growth Assay
Year: 1993
GLP: no

Result: unit: ppm
23-OCT-2000 (649)

Type: aquatic
Species: other protozoa: Colpoda aspera
Exposure period: 72 hour(s)
Unit: mg/l Analytical monitoring:
EC10: = 2.1 -
EC50: = 5.39 -

Method: other: Acute Toxicity Test
Year: 1995
Test substance: other TS: Formaldehyde 37%

Test condition: 25 deg C
Reliability: (2) valid with restrictions
Study not in accordance with a defined standard method, but meets generally accepted scientific principles
23-OCT-2000 (373)

4.5 Chronic Toxicity to Aquatic Organisms

4.5.1 Chronic Toxicity to Fish

4.5.2 Chronic Toxicity to Aquatic Invertebrates

TERRESTRIAL ORGANISMS

4.6.1 Toxicity to Sediment Dwelling Organisms

4.6.2 Toxicity to Terrestrial Plants

Species: other terrestrial plant: Lilium longiflorum

Method: other
GLP: no
Test substance: other TS: formaldeyde

Remark: Pollen germination has been shown to be sensitive to various air pollutants. Masaru et al. sowed lily pollen grains (Lilium longiflorum) on culture medium. After beeing exposed to formaldeyhde in a fumigation chamber, for 24 h, pollen tube length was measured. A 5 h exposure to formaldehyde at 0.44 mg/m3 (0.37 ppm) resulted in a significant reduction in pollen-tube length, whereas a 1 h or 2 h exposure was innocuous. When formaladeyde concentration was increased to 2.88 mg/m3 (2.4 ppm), a 1 h exposure caused a decrease in tube length.

Pollen tube length (after 24 h) after exposure to formaldehyde for 1, 2 or 5 h at 28 °C:

Concentration (ppm)	Ratio of A to B (%) Pollen exposured for 1 h	2 h	5 h
0.37	100.0	100.0	27.7
1.40	86.5	67.3	0.0
2.4	62.5	41.6	0.0

(A = pollen tube length after exposure to various concentrations of formaldehyde; B = pollen tube length after exposure to fresh air (pollution-free air))

Reliability: (2) valid with restrictions
acceptable study meets basic scientific principles
Flag: Critical study for SIDS endpoint
30-AUG-2001 (467)

4.6.3 Toxicity to Soil Dwelling Organisms

4.6.4 Toxicity to other Non-Mamm. Terrestrial Species

Species: other

Method: other
GLP: no

Result: Persson studied the antiparasitic effect of formalin (40 % formaldehyde solution) on the eggs and larvae of Ostertagia ostertagi and Cooperia oncophora in liquid cattle manure. Formalin was tested in concentrations between 0.1 % and 5 %. Formalin in the solutions of 0.1 % and 0.5 % in liquid cattle manure did not influence the viability of the investigated eggs and larvae. Addition of formalin in 1.0 %, or higher, solution killed the eggs immediately. Formalin in 1.0 % solution had no or slight effect on the viability of the larvae. A 2.0 % solution killed the larvae after 14 d at 20 °C but did not influence their motility at 3 °C.

A 5 % solution killed the larvae after 1 day at 20 °C and reduced the number of viable larvae at 3 °C.
Test substance: other: 40 % formaldeyde solution (formalin)
Reliability: (2) valid with restrictions
acceptable study meets basic scientific principles
28-AUG-2001 (542)

Species: other: Nematodes

Method: other
GLP: no
Test substance: other TS: 37 % formaldehyde solution (formalin)

Result: Nematodes in peat were killed by application of 370 g formaldehyde/l solution at 179 ml/m3 (5 ml/ft3):

Nematodes counts in peat exposed on a conveyor belt to drip treatment with 37 % formaldehyde and packaged in sealed polyethylene bags:

treatment:	Avg. no.(*) mematodes/lb of peat 1-14 days after treatment: day 1	day 7	day 14
Formaldehyde, 5 ml/ft3, added after drying	0	0	0
Formaldehyde, 5 ml/ft3, added before drying	9	21	3
Untreated control, packaged after drying	15	18	6
Untreated control, packaged without drying	12	69	579

(*) Avg of 3 12 ft3 bags.
Reliability: (2) valid with restrictions
acceptable study meets basic scientific principles
Flag: Critical study for SIDS endpoint
30-AUG-2001 (434)

4.7 Biological Effects Monitoring

4.8 Biotransformation and Kinetics

4.9 Additional Remarks

5.0 Toxicokinetics, Metabolism and Distribution

Type: Toxicokinetics

Remark: Detailed data on toxikokinetics an metabolism are presented in chapter 5:11 "Additional Remarks"

Conclusion: Formaldehyde is produced endogenously during the metabolism of amino acids and xenobiotics. In rodents, absorption of inhaled formaldehyde occurs primarily in the nasal passages, while in humans this occurs also in the oral cavity, the trachea and bronchus. At the site of first contact, formaldehyde produces DNA protein crosslinks (DPC). It is also rapidly metabolised to formate by a number of enzymatic reactions. Detoxification by formaldehyde dehydrogenase occurs subsequent to formation of a formaldehyde-glutathione conjugate. Formaldehyde and formate are incorporated into the one-carbon pathway. Much is eliminated in the expired air shortly after exposure. The other major route of elimination is excretion of formate in the urine.

25-APR-2003

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type: LD50
Species: rat
Value: 100 - 200 mg/kg bw

Method: other: no data
GLP: no
Test substance: no data

Remark: secondary literature, source not available
Test substance: formaldehyde; no data on purity of the compound
Reliability: (3) invalid
17-AUG-2001 (683)

Type: LD50
Species: rat
Value: = 600 - 700 mg/kg bw

GLP: no
Test substance: other TS

Method: Male Wistar rats of 100 to 200 g body weight were used. A single dose of 2 and 4% aqueous solutions of formaldehyde were administered by oral gavage. Rats were observed 1 week post application.
Multiple tests with 2 and 4% aqueous solutions with and without methanol (for stabilisation) were performed. In total 400 rats were used.
The LD50 was calculated according to the method of Litchfield (linear regression with confidence limits).

```
Result:           Most rats died within 24 hours.
                  The LD50 obtained with 4% solution was 675 mg/kg b.w.
                  The results of one typical test were:
                  875 mg/kg b.w.: 16/16 rats died
                  675 mg/kg b.w.:  9/16 rats died
                  530 mg/kg b.w.:  2/16 rats died
                  400 mg/kg b.w.:  3/16 rats died
                  There were no significant differences of LD50 between tests
                  with formaldehyde and the methanol containing formalin.
                  An overall LD50 of 600 - 700 mg/kg b.w. was the
                  comprehensive result of all experiments.
Test substance:   formaldehyde; no data on purity of the compound
Reliability:      (2)  valid with restrictions
Flag:             Critical study for SIDS endpoint
25-APR-2003                                                            (662)

Type:             LD50
Species:          rat
Value:            800 mg/kg bw

Method:           other: no data
   GLP:           no
Test substance:   other TS: formaldehyde, no data on purity

Test condition:   2% aqueous solution, most death occurred within the first
                  two study days, no details concerning clinical symptoms
Reliability:      (2)  valid with restrictions
                  Tabulated data for several compounds
Flag:             Critical study for SIDS endpoint
22-OCT-2002                                                            (613)

Type:             LD50
Species:          mouse
Value:            = 42 mg/kg bw

Method:           other: no data
   GLP:           no
Test substance:   no data

Remark:           Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; no data on purity of the compound
Reliability:      (4)  not assignable
                  Secondary citation
25-APR-2003                                                            (505)

Type:             LD50
Species:          guinea pig
Sex:              male/female
Value:            = 260 mg/kg bw

Method:           other: no data
   GLP:           no
Test substance:   no data

Remark:           2% aqueous solution, most death occurred within the first
                  two study days, no details concerning clinical symptoms
Test substance:   formaldehyde; no data on purity of the compound
Reliability:      (2)  valid with restrictions
                  Tabulated data for several compounds
```

25-APR-2003 (613)

5.1.2 Acute Inhalation Toxicity

Type: LC50
Species: rat
Exposure time: 30 minute(s)
Value: = 1 mg/l

Method: other: no data
GLP: no
Test substance: no data

Method: Measured amounts of the formaldehyde solution were dripped into a vaporizer heated to 120°C in an oil bath. The vapours were taken up in a measured flow of compressed air and passed via a mixing vessel into the exposure chamber. Samples of the exhaust air were analysed for formaldehyde using the sodium sulfite method.
Eight rats (110 -150 g, sex not specified) per concentration were exposed to a concentration range of 0.6 - 1.7 mg/l.
The LC50 was derived by the probit method.
Clinical examination, necropsy and histopathology of selected organs was performed.
Result: Lachrymation, nasal secretion and severe respiratory irritation (repiratory sounds and gasping) were observed (no data on concentration-effect relation presented). Lethality mainly occured in the post exposure observation period on the basis of pathologically confirmed lung edema.
Test substance: 35,5% solution (Baker, analytic quality)
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
25-APR-2003 (610)

Type: LC50
Species: rat
Exposure time: unspecified
Value: = .203 mg/l

Method: other: no data
GLP: no
Test substance: no data

Remark: LC50 = 168 ppm
Test substance: formaldehyde; no data on purity of the compound
Reliability: (4) not assignable
22-OCT-2002 (574)

Type: LC50
Species: rat
Exposure time: 4 hour(s)
Value: = .588 mg/l

GLP: no
Test substance: no data

Method: Twenty-one test groups of 6-10 male white rats in the body weight range of 180 - 240 g were used. No details on exposure and analytical methods.

Remark: LC50 = 490 ppm
Result: Concentrations of 280-430 mg/m³ did not cause lethality, a part of the animals died at concentrations between 390 and 940 and most or all above 900 mg/m³. Lethality mainly occurred 1 or 2 days after exposure. Clinically restlessness, excitations, laboured breathing and gasping as well as lateral position before death were observed.
Test substance: formaldehyde; no data on purity of the compound
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
15-MAY-2003 (501)

Type: other
Species: rat
Exposure time: 4 hour(s)

Method: other: no data
GLP: no data
Test substance: no data

Result: The acute toxic effects of the test substance were studied in 8 male Sprague-Dawley rats. Six animals were exposed to 0.0124 mg/l (10 ppm) for 4 h; 3 rats each were sacrificed immediately after termination of exposure or 24 h later. Two rats remained unexposed (control). The nasal cavities of the rats were examined by scanning electron-microscopy.
In exposed rats, destruction of cilia, cell separation in both nasal cavity and maxillary sinus, cellular swelling and secretion of mucus of globlet cells was observed.
According to the authors, the severity of the nasal lesions due to formaldehyde were dependent on the localisation and on the cell type. The lesions observed in the nasal cavities of exposed rats which were sacrificed immediately after termination of exposure were more severe then the lesions found in rats sacrificed after 24 h of observation.
Histopathology confirmed the findings observed by electronmicroscopy (increase of cell volumina, separation of cells. and ciliar lesions).
Test substance: formaldehyde; no data on purity of the compound
Reliability: (2) valid with restrictions
16-JUN-1998 (73)

Type: other: RD50
Species: rat
Exposure time: 15 minute(s)
Value: = .017 mg/l

Method: other: sensory irritation according to Alarie, Y.; (no further data)
Year: 1966
GLP: no data
Test substance: no data

Remark: RD50 = 13.8 ppm; male CRL rats were used; RD50 = concentration of the test substance producing a 50% decrease in respiratory rate
Reliability: 2 (reliable with restrictions)
Test substance: formaldehyde; no data on purity of the compound
11-FEB-1997 (243)

```
Type:              other: RD50
Species:           rat
Exposure time:     10 minute(s)
Value:             = .016 mg/l

Method:            other: sensory irritation according to Alarie, Y.; (no further
                   data)
  Year:            1966
   GLP:            no
Test substance:    no data

Remark:            RD50 = 13.1 ppm; male Fischer 344 rats were used; RD50 =
                   concentration of the test substance producing a 50% decrease
                   in respiratory rate
                   Reliability: 2 (reliable with restrictions)
Test substance:    formaldehyde; no data on purity of the compound
11-FEB-1997                                                                (137)

Type:              other: RD50
Species:           rat
Exposure time:     10 minute(s)
Value:             = .04 mg/l

Method:            other: sensory irritation according to Alarie, Y.; (no further
                   data)
  Year:            1966
   GLP:            no
Test substance:    no data

Remark:            RD50 = 31.7 ppm; male Fischer 344 rats were used; RD50 =
                   concentration of the test substance producing a 50%
                   decreasein respiratory rate
                   Reliability: 2 (reliable with restrictions)
Test substance:    formaldehyde; no data on purity of the compound
11-FEB-1997                                                                (136)

Type:              other: RD50
Species:           rat
Value:             .012 mg/l

Method:            other: no data
   GLP:            no data
Test substance:    no data

Remark:            Reliability: 2 (reliable with restrictions)
Result:            Sensory irritation of formaldehyde, acrolein, and
                   acetaldehyde, was measured by Decrease in Breathing
                   Frequency (DBF) in nose-only-exposed male Wistar rats using
                   either the neat test substances or mixtures of them. A
                   maximum DBF was observed withing 3 minutes of exposure
                   followed by a marked desensitization during the next few
                   minutes. During a 10-min. post-exposure period, the rats
                   recovered partially.
                   In all groups exposed to mixtures, the DBF was more
                   pronounced than in groups exposed to the neat test
                   substances. However the DBF was significantly lower than the
                   mean predicted by summation of the DBFs of single compounds.
                   No desensitization occured. Both partial and full recovery
                   was observed during the 10-min post-exposure period. The
                   authors attributed the differences in the DBF of mixtures
```

compared to the predicted DBF calculated by summation of the DBFs of single compounds as a result of competition for a common receptor (trigeminal nerve).
Test substance: formaldehyde; no data on purity of the compound
17-JUN-1998 (130)

Type: LC50
Species: mouse
Exposure time: 2 hour(s)
Value: = .505 mg/l

Method: other: no data
GLP: no
Test substance: no data

Method: Forteen test groups of 6-8 white mice of both sexes in the body weight range of 18 - 24 g were used. No details on exposure and analytical methods.
Remark: LC50 = 421 ppm
Result: Concentrations of 79-120 mg/m³ did not cause lethality, 12.5 -83.3% of the animals died at concentrations between 134 and 916 and all between 917 and 1008 mg/m³.
Test substance: formaldehyde; no data on purity of the compound
Reliability: (2) valid with restrictions
15-MAY-2003 (500)

Type: LC50
Species: mouse
Exposure time: unspecified
Value: = .4 mg/l

Method: other: no data
GLP: no
Test substance: no data

Remark: LC50 = 332 ppm
Reliability: 2 (reliable with restrictions)
Test substance: formaldehyde; no data on purity of the compound
11-FEB-1997 (356)

Type: other: RD50
Species: mouse
Exposure time: 10 minute(s)
Value: = .004 mg/l

Method: other: sensory irritation according to Alarie, Y.; (no further data)
Year: 1966
GLP: no
Test substance: no data

Remark: RD50 = 3.2 ppm; male Swiss Webster mice were used; RD50 = concentration of the test substance producing a 50% decrease in respiratory rate
Reliability: 2 (reliable with restrictions)
Test substance: formaldehyde; no data on purity of the compound
16-JUN-1998 (376)

Type: other: RD50
Species: mouse

```
Exposure time:    5 minute(s)
Value:            = .007 mg/l

Method:           other: sensory irritation according to Alarie, Y.; (no further
                  data)
  Year:           1966
   GLP:           no data
Test substance:   no data

Remark:           RD50 = 5.3 ppm; male OF1 mice were used; RD50 =
                  concentration of the test substance producing a 50%
                  decrease in respiratory rate
                  Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; no data on purity of the compound
16-JUN-1998                                                              (178)

Type:             other: RD50
Species:          mouse
Exposure time:    10 minute(s)
Value:            = .006 mg/l

Method:           other: sensory irritation according to Alarie, Y.; (no further
                  data)
  Year:           1966
   GLP:           no data
Test substance:   no data

Remark:           RD50 = 4.9 ppm; male B6C3F1 mice were used; RD50 =
                  concentration of the test substance producing a 50% decrease
                  in respiratory rate
                  Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; no data on purity of the compound
27-NOV-1997                                                              (137)

Type:             other: RD50
Species:          mouse
Sex:              male
Exposure time:    30 minute(s)
Value:            4 - 8.2 ppm

Method:           other: sensory irritation test according to Alarie
   GLP:           no data
Test substance:   other TS

Method:           Four male mice per test group, 15 min baseline measurement,
                  30 min exposure, 15 min recovery, only graphical
                  presentation of tested concentrations
Remark:           strain: BALB/c mice
                  frequency: single
Result:           The decrease in respiratory rate was due to sensory
                  irritantion, clear signs of bronchoconstriction above 4 ppm
Test substance:   Formaldehyde from Paraformaldehyde
Reliability:      (2)  valid with restrictions
10-SEP-2001                                                              (170)
```

5.1.3 Acute Dermal Toxicity

```
Type:             LD50
Species:          rabbit
```

Value: ca. 270 mg/kg bw

Remark: Value: = 270 ul/kg/bw
Test substance: formaldehyde; no data on purity of the compound
Reliability: (4) not assignable
only secondary literature and no details available
22-OCT-2002 (426)

5.1.4 Acute Toxicity, other Routes

Type: LDLo
Species: mouse
Route of admin.: i.p.
Value: = 16 mg/kg bw

Test substance: other TS

Test substance: formaldehyde; no data on purity of the compound
Reliability: (2) valid with restrictions
30-JUN-1998 (217)

Type: LD50
Species: rat
Route of admin.: s.c.
Value: = 420 mg/kg bw

Method: other: no data
GLP: no
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Test substance: formaldehyde; no data on purity of the compound
10-AUG-1999 (611)

Type: LD50
Species: mouse
Route of admin.: s.c.
Value: = 300 mg/kg bw

Method: other: no data
GLP: no
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Test substance: formaldehyde; no data on purity of the compound
11-FEB-1997 (611)

Type: LDLo
Species: rabbit
Route of admin.: s.c.
Value: = 240 mg/kg bw

Test substance: other TS

Test substance: formaldehyde; no data on purity of the compound
Reliability: (2) valid with restrictions
30-JUN-1998 (573)

```
Type:             LDLo
Species:          dog
Route of admin.:  s.c.
Value:            = 350 mg/kg bw

Test substance:   other TS

Test substance:   formaldehyde; no data on purity of the compound
Reliability:      (2)  valid with restrictions
30-JUN-1998                                                        (571)

Type:             LD50
Species:          mouse
Route of admin.:  i.v.
Value:            = 87 mg/kg bw

Method:           other: no data
   GLP:           no
Test substance:   no data

Remark:           Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; no data on purity of the compound
11-FEB-1997                                                        (416)

Type:             LDLo
Species:          rabbit
Route of admin.:  i.v.
Value:            = 48 mg/kg bw

Test substance:   other TS

Test substance:   formaldehyde; no data on purity of the compound
Reliability:      (2)  valid with restrictions
30-JUN-1998                                                        (570)

Type:             LDLo
Species:          cat
Route of admin.:  i.v.
Value:            = 30 mg/kg bw

Test substance:   other TS

Test substance:   formaldehyde; no data on purity of the compound
Reliability:      (2)  valid with restrictions
30-JUN-1998                                                        (569)

Type:             LDLo
Species:          dog
Route of admin.:  i.v.
Value:            = 70 mg/kg bw

Test substance:   other TS

Test substance:   formaldehyde; no data on purity of the compound
Reliability:      (2)  valid with restrictions
30-JUN-1998                                                        (571)

Type:             LCLo
Species:          cat
```

Route of admin.: other: inhalation
Value: = .4 mg/l

Test substance: other TS

Remark: 2 hours exposure
Test substance: formaldehyde; no data on purity of the compound
Reliability: (2) valid with restrictions
16-JUN-1998 (572)

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

Species: rabbit
Result: irritating

Remark: formaldehyde solutions (0.1-20%) were applied; according to the authors, the skin irritations were mild to moderate
Test substance: formaldehyde; no data on purity of the compound
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
19-MAR-2003 (507)

Species: guinea pig
Result: irritating

Method: other: no data
GLP: no data
Test substance: no data

Remark: application of 1% solution
Test substance: formaldehyde; no data on purity of the compound
Reliability: (2) valid with restrictions
12-DEC-1997 (507)

5.2.2 Eye Irritation

Species: rabbit
Result: irritating

Method: other: no data
GLP: no
Test substance: no data

Remark: Application of 0.005 ml of a 5% and 15% aqueous solution; scores were read 18-20 hours post application; the degree of eye irritation was up to a score of 8 (maximum score: 10) based on corneal injury and amount and concentration of test substance applied
Test substance: formaldehyde; no data on purity of the compound
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
25-APR-2003 (119)

5.3 Sensitization

Type: Buehler Test
Species: guinea pig
Result: sensitizing

GLP: no data
Test substance: no data

Remark: challenge concentration might have been irritating
Result: Ten Dunkin-Hartley guinea pigs were topically induced by applying 5% formalin dissolved in the detergent ABS (aqueous solution of tetrapropylene benzene sulfonate) once a week for 6 weeks under occlusive conditions. After a resting period of another 2 weeks, the animals were challenged with 5% formalin. Sensitization rate was 3/10 (30%).
Test substance: formalin; no data on purity or formaldehyde content
Reliability: (3) invalid
17-AUG-2001 (113) (114)

Type: Buehler Test
Species: guinea pig
Result: not sensitizing

GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: Reliability: 2 (reliable with restrictions)
Result: Three groups of 10 female Dunkin-Hartley guinea pigs were topically induced by applying 5% formalin dissolved in pysiological saline and were challenged with 1.25% formadehyde in saline. No sensitization was observed.
Test substance: formalin; formaldehyde content 37%
16-JUN-1998 (466)

Type: Buehler Test
Species: guinea pig
Result: sensitizing

GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Reliability: (2) valid with restrictions
30-JUN-1998 (55)

Type: Buehler Test
Species: guinea pig
Result: sensitizing

GLP: no data
Test substance: other TS

Remark: strain: Dunkin-Hartley, animal nos. don't meet OECD 406 requirements
Result: Induction: topical - occlusive 6h 5% in 0.9% NaCl (1x/week for three weeks).
Challenge: topical occlusive 6h, 1% in 0.9% NaCl (12-14 d later).
Number of animals with skin reactions: 7/10 (70%) no

```
                    reactions in vehicle control animals after challenge.
Test substance:     formalin; formaldehyde content 37%
Reliability:        (2)  valid with restrictions
30-JUN-1998                                                          (320)

Type:                 Draize Test
Species:              guinea pig
Result:               not sensitizing

   GLP:             no
Test substance:     no data

Remark:             Reliability: 2 (reliable with restrictions)
Result:             The sensitizing potency of formalin was tested in 10
                    Dunkin-Hartley guinea pigs (males and females). For
                    induction, the animals were injected with 1% formalin
                    suspended in ABS (aqueous solution of tetrapropylene
                    benzenesulfonate) 3 times per week for 3 weeks (totally 9
                    injections). After a resting period of 2 weeks, the animals
                    were injected intradermally with 1% formalin forchallenge.
                    Sensitization rate was 1/10 (10%).
Test substance:     formalin; no data on purity or formaldehyde content
16-JUN-1998                                                          (113)

Type:                 Draize Test
Species:              guinea pig
Result:               not sensitizing

   GLP:             no
Test substance:     no data

Remark:             Reliability: 2 (reliable with restrictions)
Result:             Twenty male Dunkin-Hartley guinea pigs were induced by
                    intradermal injection of 0.1% formalin dissolved in saline
                    3 times per week for a total of 10 injections. Two weeks
                    after the last induction dose, the animals were injected
                    intradermally with 0.1% formalin for challenge.
                    Sensitization rate was 1/20 (5%).
Test substance:     formalin; no data on purity or formaldehyde content
16-JUN-1998                                                          (446)

Type:                 Draize Test
Species:              guinea pig
Result:               ambiguous
Classification:       not sensitizing

   GLP:             no
Test substance:     as prescribed by 1.1 - 1.4

Remark:             Reliability: 2 (reliable with restrictions)
Result:             Groups of 20 female Dunkin-Hartley guinea pigs were induced
                    by 7 intradermal injections of 0.1% formalin during 3 weeks.
                    Three weeks after the last induction dose, the animals were
                    injected intradermally with 0.1% formalin for challenge. Two
                    experimental runs were performed; readings were carried out
                    after 24 h. Sensitization rates were 15% (3/20 animals) and
                    32% (5-6/20 animals) in the first and second tests,
                    respectively. The degree of sensitization was evaluated by a
                    grading system established by the authors.
```

Mean reaction scores were given as 51 and 40 in the first and second experimental run, respectively. According to the authors, these results suggested that formaldehyde did not lead to sensitization in the first test and was not definitely sensitizing in the second test.
Test substance: formalin; formaldehyde content 37%
16-JUN-1998 (338)

Type: Draize Test
Species: guinea pig

GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: challenge concentration might have been irritating
Result: Groups of 10 inbred DNCB-sensitive guinea pigs were induced by a single intradermal injection of 0.375% formalin. Challenge was performed by intradermal injection of 0.15% formalin and open topical application of 40% formalin 14 days later.
Solutions for injection were dissolved in physiological saline; solutions for topical application were prepared in distilled water. Two experimental runs were carried out. In the first test, 1/10 animals (10%) were sensitized; in the repeated test, 7/10 animals (70%) showed positive reactions. (According to the authors, these results indicated that formaldehyde was a moderate sensitizer.)
Test substance: formalin; formaldehyde content 40%
Reliability: (3) invalid
16-JUN-1998 (264)

Type: Draize Test
Species: guinea pig
Result: sensitizing

GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: Reliability: 2 (reliable with restrictions)
Result: Groups of 10 female Dunkin-Hartley guinea pigs were used in the study. For induction, a 0.1% formalin solution was injected 3 times per week (totally 10 injections). Challenge was performed by intradermal injection of 0.1% formalin two weeks after the last inducing dose. All solutions were prepared in physiological saline. Three experimental runs were carried out. Positive skin reaction was observed in 6/10, 1/10, and 3/10 animals in the first, second, and third experiment, respectively. The cumulative response was 10/30 (33%).
Test substance: formalin; formaldehyde content 37%
30-JUN-1998 (466)

Type: Freund's complete adjuvant test
Species: guinea pig

Method: other: no data
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Remark: challenge concentration might have been irritating
Result: Groups of 10 Dunkin-Hartley guinea pigs were used in the study. Induction was initiated by injection of a 5% solution in Freund's Complete Adjuvant at days 0, 2, 4, 7, and 9. Challenge was carried out by topical application of the same concentration under occlusive conditions on days 21 or 35. Skin samples were taken for histopathological examination. Macroscopically, skin sensitization was observed in 3/10 animals challenged on day 21 and in 2/10 animals challenged on day 35. Doubtful results were observed in 4/10 animals challenged on day 35. Histopathology revealed incidences of 3/10 and 4/10 in the 21- and 35-day-group, respectively.
Test substance: formalin; formaldehyde content 37%
Reliability: (3) invalid
14-JAN-1998 (285) (286)

Type: Guinea pig maximization test
Species: guinea pig
Result: sensitizing

Method: Directive 84/449/EEC, B.6 "Acute toxicity (skin sensitization)"
GLP: no
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: Twenty female Dunkin-Hartley guinea pigs were used. Induction was carried out by injecting 5% formaldehyde in petrolatum (emulsified in Freund's Complete Adjuvant) intradermally and, one week later by topical application of the same formalin solution under occlusive conditions. Challenge was carried out two weeks later by an application of 2% formalinunder occlusive conditions. Sensitization rate was 16/20 (80%).
Test substance: formalin, dissolved in petrolatum; no data on formaldehyde content
10-AUG-1999 (446)

Type: Guinea pig maximization test
Species: guinea pig
Concentration 1st: Induction 5 % intracutaneous
2nd: Induction 5 % occlusive epicutaneous
3rd: Challenge 4 % occlusive epicutaneous
Vehicle: water
Result: sensitizing
Classification: sensitizing

Method: OECD Guide-line 406 "Skin Sensitization"
Year: 1983
GLP: yes
Test substance: other TS

Method: Female Pirbright-white guinea pigs were used. The induction application was performed by 2 intradermal injections of 0.1 ml of a 5% solution in the presesence and absence of Freund's Complete Adjuvant (FCA), followed by dermal application of 0.5 ml of a 5% solution for 48 h (days 9-11) under occlusive conditions.

Challenge was performed dermally on days 22 and 36 (0.5 ml 2 and 4%; occlusively for 24 h)
Remark: formaldehyde; >37% aqueous solution (monitored)
Result: According to the authors, the test substance was sensitizng at both concentrations: a challenge concentration of 4% resulted in 100% reaction at both challenges; a concentration of 2% resulted in 80 and 25% reaction at the first and second challenge, respectively.[2]
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
18-DEC-2000 (324)

Type: Guinea pig maximization test
Species: guinea pig
Result: sensitizing

Method: other
GLP: no data
Test substance: no data

Remark: formaldehyde; no data on purity of the compound
Reliability: (2) valid with restrictions
12-DEC-1997 (469)

Type: Guinea pig maximization test
Species: guinea pig
Result: sensitizing

Method: other
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: Reliability: 2 (reliable with restrictions)
24-JAN-1997 (53)

Type: Guinea pig maximization test
Species: guinea pig
Result: sensitizing

Method: other
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: Reliability: 2 (reliable with restrictions)
24-JAN-1997 (54)

Type: Guinea pig maximization test
Species: guinea pig
Result: sensitizing

GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: Reliability: 2 (reliable with restrictions)
Result: Ten male and ten female Pirbright guinea pigs were used. Induction was carried out with 5% formalin (intradermal application followed by topical application); challenge was performed with 2% formalin under occlusive conditions 2 weeks after induction. Sensitization rate was 9/20 (45%). Physiological saline was used as solvent.

Test substance: formalin; formaldehyde content 35%
30-JUN-1998 (471)

Type: Guinea pig maximization test
Species: guinea pig
Result: sensitizing

GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: challenge concentration might have been irritating
Result: Ten inbred DNCB-sensitive guinea pigs were induced by intradermal injection of 0.5% formalin (diluted with physiological saline) followed by topical application of 10% formalin. Challenge was performed topically with 5% formalin under occlusive conditions. Sensitization rate was 10/10 (100%). Mean test reaction score was 2.5; possible maximum score was 3.0.
Test substance: formalin; formaldehyde content 40%
Reliability: (3) invalid
16-JUN-1998 (264)

Type: Guinea pig maximization test
Species: guinea pig
Result: not sensitizing

GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: challenge concentration might have been irritating
Result: Groups of 20 female Dunkin-Hartley guinea pigs were used. Induction was carried out by intradermal injection of 0.1 or 0.2% formalin dissolved in water followed by topical application of 5% formalin. Animals injected with 0.2% formalin were applied sodium lauryl sulfate 24 hours prior to the topical induction. Challenge was performed with 5% formalin under occlusive conditions. Sensitization rates were 0/20 (0%) among the animals injected with 0.1% and 5/20(25%) among the animals injected with 0.2%.
Test substance: formalin; formaldehyde content 37%
Reliability: (3) invalid
16-JUN-1998 (338)

Type: Guinea pig maximization test
Species: guinea pig
Result: not sensitizing

GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: Reliability: 2 (reliable with restrictions)
Result: Three groups of 8, 10, and 10 female Dunkin-Hartley guinea pigs were used. Induction was carried out by intradermal injection of 5% formalin (37% aqueous formaldeyde solution, dissolved in physiologic saline) followed by topical application of 5% formalin; challenge was performed at a concentration of 1.25%. Sensitization rates were 2/8 (25%), 1/10 (10%), and 2/10 (20%); cumulative response was 5/28 (18%).

Test substance: formalin; formaldehyde content 37%
16-JUN-1998 (466)

Type: Guinea pig maximization test
Species: guinea pig
Result: sensitizing

GLP: no data
Test substance: no data

Remark: challenge concentration might have been irritating
Result: Twenty female Dunkin-Hartley guinea pigs were used. Induction was carried out by intradermal injection of 5% formalin dissolved in de-ionized water followed by topical application of 5% formalin; challenge was performed with 5% formalin under occlusive conditions. Additionally, skin samples were examined histopathologically. Macroscopically, 20/20 animals showed positive skin reactions (sensitization rate 100%), however, histopathologically, allergic reaction was observed in only 14/20 animals (70%).
Test substance: formalin; formaldehyde content 37%
Reliability: (3) invalid
16-JUN-1998 (285) (286)

Type: Guinea pig maximization test
Species: guinea pig
Result: sensitizing

GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: Groups of 20 female SSc:AL guinea pigs were used. Induction was carried out by intradermal injection of a 1% aqueous solution followed by topical application of a 5% solution; challenge was performed on day 21 by topical application of a 0.1, 0.5, and 1% solution. Sensitization rates were 0/20 (0%), 2/20 (10%), and 10/20 (50%) in the low, mid, and high challenge dose group, respectively, at the 48 h readings.
Test substance: formaldehyde; no data on purity of the compound
16-JUN-1998 (24)

Type: Guinea pig maximization test
Species: guinea pig
Result: sensitizing

GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: Nineteen female Dunkin-Hatley guinea pigs were used. Induction was carried out by intradermal injection of a 0.1% aqueous solution followed by topical application of a 5% solution; challenge was performed on day 21 by topical application of a 1% solution. Sensitization rate was 17/19 (90%) at the 48 h reading.
Test substance: formaldehyde; no data on purity of the compound
16-JUN-1998 (24)

Type: Guinea pig maximization test
Species: guinea pig
Result: sensitizing

GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: Reliability: 2 (reliable with restrictions)
Result: A dose-response study was performed with 18 groups of 6 SSc:AL guinea pigs each. On day 0, intradermal induction was performed by injection of solutions containing 0.01% (groups 1-3), 0.03% (groups 4-6), 0.1% (groups 7-9), 0.3% (groups 10-12), 1.0% (groups 13-15), or 3.0% formaldehyde (groups 16-18). On day 7, topical induction was performed by application of 0.5% (groups 1, 7, 13), 1.0% (groups 4, 10, 16), 2.0% (groups 2, 8, 14), 5.0% (groups 5, 11, 17), 10.0% (groups 3, 9, 15), or 20.0% (groups 6, 12, 18). On day 21, challenge was performed topically with a concentration of 1%. Readings were carried out at 72 h. The sensitization rates differed between 0/6 and 6/6 and were dependent on the concentration of the intradermal induction mainly. No clear dose-response relationship was observed for topical induction. In some cases, the highest sensitization rates were found in animals that hadreceived low topical induction doses.
In a second dose-response experiment, guinea pigs of the Dunkin-Hartley strain were treated in the same manner. Again, no dose-response relationship was observed. The sensitization rates differed between 1/6 and 6/6 showing the same dependecies as observed in the SSC:AL strain. No inducation occurred at 0.01% i.d. in the SSc:AL strain,but Dunkin-Hartley guinea pigs showed some induction at that concentration. Intradermal concentrations
giving maximum response of ca. 80% was calculated as 0.46% (48 h) or 0.65% (72 h) for the SSc:AL guinea pigs; maximum response of ca. 85% was calculated as 0.45% (48 h) or 0.34% (72 h) for the Dunkin-Hartley guinea pigs.
According to the authors, these results demonstrated that

the SSc:AL strain was less sensitive than the Dunkin-Hartley strain.
Test substance: formaldehyde; 20% aqueous solution
16-JUN-1998 (23)

Type: Guinea pig maximization test
Species: guinea pig
Result: sensitizing

GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: A dose-response study was performed with 5 groups of 5 Dunkin-Hartley guinea pigs each. Intradermal induction was performed by injection of solutions containing 0.03, 0.1, 0.3, 1.0, or 3.0% of the test substance followed by topical induction which was performed by application of a 0.1% solution to the groups given 0.03, 0.3, or 3.0% intradermally or application of a 10% solution to the groups given 0.1 or 1.0% intradermally.

Challenge was performed topically with a concentration of 1%. Readings were carried out at 72 h. The sensitization rates differed between 1/5 and 5/5; No dose-response relationship was observed; the sensitization was found to depend on the intradermal induction concentration. According to the authors, the calculated maximum response concentration was 0.8% aqueous formaldehyde solution.
Test substance: formaldehyde, dissolved in water; no data on formaldehyde content
16-JUN-1998 (22)

Type: Guinea pig maximization test
Species: guinea pig
Result: sensitizing

GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: The test substance (content not specified) was dissolved 4:1 with acetone/olive oil. For induction, the mixture was injected 0.25% intradermally in nine Dunkin-Hartley guinea pigs followed by a topical application of 10%. Challenge was carried out by topical application of 2% under occlusive conditions. Sensitization rate was 9/9.
Test substance: formaldehyde; no data on purity of the compound
16-JUN-1998 (391)

Type: Guinea pig maximization test
Species: guinea pig
Result: sensitizing

GLP: no data
Test substance: no data

Remark: no details given
Result: The test substance (no further specifications) was injected intradermally at a concentration of 0.5% into Dunkin-Hartley guinea pigs (no data on number of animals) followed by a topical application of 10% (induction). Challenge was carried out by topical application of 2% under occlusive conditions. Sensitization rate was 90%.
Test substance: formaldehyde; no data on purity of the compound
Reliability: (4) not assignable
16-JUN-1998 (47)

Type: Guinea pig maximization test
Species: guinea pig
Result: sensitizing

GLP: no data
Test substance: no data

Result: The effects of different challenge concentrations were studied groups of 10 female Dunkin-Hartley guinea pigs. The test substance was dissolved in distilled water. For induction, a 0.03% solution was injected intradermally followed by topical application of a 1% solution under occlusive conditions. Two challenges with an interval of 3 weeks were carried out by topical application of a solution

containing the test substance at concentrations of 0.03, 0.1, or 0.3%. Readings were carried out 24, 48, and 72 h after each challenge application. After the first challenge, sensitization rates were 0/10-4/10, 6/10-9/10, and 10/10 in the low, mid, and high dose group, respectively. After the second challenge, sensitization rates were 0/10-3/10, 0/10-7/10, and 6/10-10/10 in the low, mid, and high dose group, respectively. According to the authors, sensitization rates showed a clear dose-response relationship, but the second challenge did not increase the incidences of sensitization.
Test substance: formaldehyde; special grade, no further data
Reliability: (2) valid with restrictions
16-JUN-1998 (378)

Type: Guinea pig maximization test
Species: guinea pig
Result: sensitizing

GLP: no data
Test substance: no data

Remark: no details, challenge concentration might have been irritating
Result: Dunkin-Hartley guinea pigs were induced with the test substance intradermally at a concentration of 5% followed by topical induction at a concentration of 100%. Challenge was performed by topical application of the test substance at a concentration of 10%. According to the authors, the degree of sensitization was moderate to strong. No further data.
Test substance: formaldehyde; no data on purity of the compound
Reliability: (3) invalid
16-JUN-1998 (212)

Type: Guinea pig maximization test
Species: guinea pig
Result: sensitizing

Test substance: other TS

Remark: strain: Dunkin-Hartley, animal nos. don't meet OECD 406 requirements

Result: Induction:
intradermal - 6 injections 0.25% in FCA in 0.9% NaCl
topical - occlusive 48h 10% in 0.9% NaCl
Challenge: occlusive 24h, 2% in 0.9% NaCl
Number of animals with skinreactions: 10/10 (100%) no reactions in vehicle control animals after challenge
Test substance: formalin; formaldehyde content 37%
Reliability: (2) valid with restrictions
16-JUN-1998 (320)

Type: Mouse ear swelling test
Species: mouse
Result: ambiguous

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: Reliability: 2 (reliable with restrictions)
Result: In this study, different varieties of the mouse-ear swelling test protocol were evaluated in male and female Balb/c mice.
In the first test, formalin was dissolved in 70% ethanol; 12 male mice were topially applied with a 10% solution onto the shaved abdomen for 4 consecutive days. Additionally, Freund's Complete Adjuvant was injected intraperitoneally prior to each application. After a resting period, the animals were challenged by a topical application of a 10% solution onto the dorsum of the right ear at day 9; the vehicle was applied to the left ear.
In the second test, 7 mice received a repeated application twice weekly for 6 weeks prior to challenge using the same concentrations and procedures for induction and challenge as described in the protocol of the first test.
The third test was performed with 7 female mice which were initially applied a 15% solution without injection of Freund's Complete Adjuvant for 2 consecutive days and challenged by topical application of 10% onto the ear at day 6; the vehicle was acetone.
In the fourth test, 7 female mice were treated as described in the protocol of the third test, additionally they were given a vitamin A acetate enriched diet for 4 weeks prior to sensitizing and were maintained on this diet during the whole experimental period.
In every test, ear thickness was measured prior to challenge and 24, and 48 h after challenge.
In the first, second and third test, no increase in ear thickness was observed despite of the relatively high formalin concentrations applied. Only in the fourth test group which was given vitamin A enriched diet a statistically significant increase of the ear thickness was measured.
Test substance: formalin; formaldehyde content 37%
15-JAN-1998 (579)

Type: Mouse local lymphnode assay
Species: other: BALB/c mice

Method: other
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Method: Sensitization: 50 µl of 50% formaldehyde in acetone on both shaved flanks on day 1 and 5. Starting with day 10 25 µl of the substance preparation on the dorsum of both ears for further 3 days.
Examination: Cytokine expression patterns in draining lymph node cells cultures (IFN-g, IL-4, IL-10)
Result: Formaldehyde-activated lymph node cells produced high levels of the T-helper cell 1 type cytokine IFN-g, but little of the T-helper cell 2 type products IL4 and IL-10, showing that formaldehyde does not have a significant potential to cause allergic sensitization of the respiratory tract.
Reliability: (2) valid with restrictions
23-AUG-2001 (177)

Type: Mouse local lymphnode assay
Species: other: mouse and guinea pig

Method: other: no data
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: The local lymph node assay was performed in groups of CBA/Ca mice and Dunkin-Hartley guinea pigs (3 animals per group, each). Formalin was dissolved in a 4:1 mixture of acetone and olive oil. The test solutions were topically applied onto the dorsum of the ear daily for 3 consecutive days. The mice were treated with concentrations of 1 and 2%; additionally guinea pigs received 0.5 and 5%. Four days after the initial treatment, the animals were sacrificed. The draining auricular lymph nodes were excised, pooled, and single cell suspensions were prepared. The cell cultures were maintained for up to 48 h in the presence and absence of human recombinant interleukin-2 (IL-2), then 3H-methylthymidine was added for another 24 h. Thereafter, the cell cultures were examined for incorporation of 3H-methylthymidine using a beta-scintillation counting technique.
In mice, only the high dose (2%) caused an increase of the proliferation index and of the stimulation index. In guinea pigs, a positive reaction was observed at concentrations of 1% or more. However, no definite dose-response relationship was evaluated and addition of IL-2 had no effect. The mean lymph node weights indicated no substance-related effect at any concentration. According to the authors, formalin caused only slight reactions since even the highest doses caused only 2-fold increases in stimulating index and proliferation index in the positive animals.
Test substance: formalin; special grade, no further data on formaldehyde content
07-MAY-1998 (471)

Type: Mouse local lymphnode assay
Species: mouse
Result: sensitizing
Classification: sensitizing

Method: other: no data
GLP: no data
Test substance: other TS: formalin; special grade, no further data on formaldehyde

Method: The local lymph node assay was performed in groups of 4 CBA/Ca mice by different working groups. Formalin was dissolved in a 4:1 mixture of acetone and olive oil. Concentrations of 5, 10, and 25% were topically applied onto the dorsum of the ear daily for 3 consecutive days. Four days after the initial treatment, the mice were injected with a buffered solution of 3H-methylthymidine into the tail vein and were sacrificed 5 hours later.

The draining auricular lymph nodes were excised and pooled. Single cell suspension preparations of these lymph nodes were examined for incorporation of 3H-methylthymidine using a beta-scintillation counting technique.
Remark: Reliability: 2 (reliable with restrictions)
Result: Formalin was identified a contact sensitizer by all working groups. A no observed effect concentration (NOEC) was not evaluated. The incorporation of 3H-methylthymidine was increased showing a trend to dose-dependency, however, a clear dose-response relationsship could not be evaluated; the individual results varied 2-fold when expressed in disintegrations per minute (dpm) or calculated stimulation index (SI).
Flag: Critical study for SIDS endpoint
26-OCT-2000 (47) (48) (391) (392)

Type: Open epicutaneous test
Species: guinea pig
Result: sensitizing

GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: Reliability: 2 (reliable with restrictions)
Result: Fourteen groups of 6-8 guinea pigs (strain not specified) were used. Formalin was applied onto the uncovered skin at induction concentrations of 0.03, 0.1, 0.3, 1, 3, 10, and 30%. At the 24-h readings after the applications, slight skin irritation was observed in some animals even at the lowest concentration. Challenge was carried out on days 21 and 35 either at concentrations of both 0.03 and 1% (given to groups induced with 0.03 - 0.1%) 0.3 and 1% (given to groups induced with these concentratoins) and at concentrations of both 3 and 10% (given to groups induced with 3-30%). No skin reactions were observed in the groups induced or challenged with 1% or less. Induction or challenge with 3% or more resulted in sensitization: 3/8-7/8 animals were sensitized; the highest incidence of positive animals was observed at a concentration of 10% (induction and challenge). (Maibach, 1978).
In another test using a closed patch for application, 12 groups of 6-8 animals were used; one group each was induced with 0.03 or 0.1% (6 animals per group); two groups each were induced with 0.3 (6 animals per group), 1 (6 animals per group), 3 (8 animals per group), 10 (8 animals per group), or 30% (7 animals per group). The animals were challenged with 1% (the 2 groups induced with 0.03 and 0,1%, respectively), or with both 0.3 and 1% (groups induced with 0.3% and more). Sensitization was observed starting with induction concentrations of 0.3% (1/6 challenged with 0.3% and 2/6 challenged with 1%). (Maibach, 1978; Maibach, 1983).
However, according to the authors, no clear dose-response relationship could be observed in any experiment.
Test substance: formalin; formaldehyde content 40%
16-JUN-1998 (448) (449)

Type: Open epicutaneous test
Species: guinea pig
Result: ambiguous

GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Remark: Reliability: 2 (reliable with restrictions)
Result: Eight Dunkin-Hartley guinea pigs (males and females) were induced and challenged with a 5% formalin solution in de-ionized water. Additionally, skin samples were taken for histopathological examination. After the first challenge, no clear skin reaction was observed, however, 3/8 were scored as doubtful results. After the second challenge, 4/8 animals were clearly negative, while 4/8 showed doubtful reactions. In every case, histopathology revealed no signs of sensitization. Thus, according to the authors, these results suggested that formaldehyde was not sensitizing in the Open Epicutaneous Test.
Test substance: formalin; formaldehyde content 37%
16-JUN-1998 (285) (286)

Type: Split adjuvant test
Species: guinea pig
Result: not sensitizing

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: Reliability: 2 (reliable with restrictions)
Result: Groups of 10 female Dunkin-Hartley guinea pigs were used. Occluded patches containing the test solution were applied for 2 days followed by a second 2 day patch. On days 3 and 6 new patches were applied. On day 4 Freund's Complete Adjuvant was injected intradermally. After a resting period of 2 weeks, the animals were challenged with an occluded patch. The induction concentration was 5%, the challenge concentrations was 1.25%; all solutions were prepared in physiological saline. Three experimental runs were carried out. In two tests, no animal was sensitized; in one test, 2/10 animals showed positive skin reaction. The cumulative sensitization rate was 2/30 (7%). Thus, according to the authors, the sensitizing potency was rather low.
Test substance: formalin; formaldehyde content 37%
16-JUN-1998 (466)

Type: Split adjuvant test
Species: guinea pig
Result: ambiguous

Method: other: no data
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Remark: challenge concentration might have been irritating
Result: A modified Split Adjuvant Test protocol was used in groups of 10 Dunkin-Hartley guinea pigs of both sexes. Induction and challenge were performed at a concentration of 5%. Challenge was carried out 3 times (on days 21, 35, and 42). Skin samples were taken for histopathological examination. After the first challenge on day 21, none of the animals showed a clearly positive skin reaction, 7/10 were doubtful, and 3/10 were clearly negative. After the second challenge on day 35, 2/10

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                    animals showed a clearly positive reaction, 3/10 were
                    doubtful, and 5/10 were definitely negative. After the
                    third challenge on day 42, none of the animals showed a
                    clearly positive skin reaction, 3/10 were doubtful, and 7/10
                    were definitely negative. Histopathology confirmed postive
                    results only for 1 animal each after the first and second
                    challenge, respectively.
Test substance:     formalin; formaldehyde content 37%
Reliability:        (4)  not assignable
16-JUN-1998                                                          (285) (286)

Type:                 Split adjuvant test
Species:              guinea pig
Result:               sensitizing

Method:             other: no data
   GLP:             no data
Test substance:     as prescribed by 1.1 - 1.4

Remark:             challenge concentration might have been irritating
Result:             The sensitizing potency of formaldehyde was studied in
                    groups of 20 female Dunkin-Hartley guinea pigs using a
                    modified Split Adjuvant Test protocol. Two tests were
                    carried out. In the first experimental run, the initial
                    induction concentration of 37% was reduced to 10%,
                    challenge was performed at a concentration of 10%. In the
                    second run, a concentration of 5% was used for both
                    induction and challenge. In the first test, 85% of the
                    animals  (17/20) showed clearly positive skin reaction while
                    in the second test only 5% (1/20) showed positive skin
                    reaction.
Test substance:     formalin; formaldehyde content 37%
Reliability:        (4)  not assignable
16-JUN-1998                                                              (338)

Type:                 other: AP2-test
Species:              guinea pig
Result:               sensitizing
Classification:       sensitizing

Method:             other: new method
   GLP:             no data
Test substance:     no data

Remark:             Reliability: 2 (reliable with restrictions)
Result:             The aim of the study was to develop the Adjuvant and 24-h
                    occlusive patch 2x test (abbreviated AP2 test), a new
                    short-period method for delayed contact hypersensitivity in
                    groups of 10 female Dunkin-Hartley guinea pigs.
                    Formaldehyde was diluted with injectable distilled water.
                    For induction, the protocol combined an intradermal
                    injection of Freund's Complete Adjuvant and a 24 h
                    occlussive patch test; this procedure was carried out twice
                    with an interval of 4 days. The concentration for induction
                    was 1%. The animals were challenged 3 times. The first
                    challenge was performed 11 days after induction, the second
                    challenge was performed 3 weeks after the first one, and the
                    third challenge was carried out 1 week after the second one.
                    For the first and second challenges, the test substance was
                    administered by a non-occlusive topical application.
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The third challenge was applied with a 24 h occlusive patch. Challenge concentrations were 1% (1st and 2nd challenge) followed by 0.03 % (3rd challenge); 3% (1st and 2nd challenge) followed by 0.1% (3rd challenge); and 10% (1st and 2nd challenge) followed by 0.3% (3rd challenge). The skin reactions were examined 24, 48, and 72 h after each challenge.
Application of formaldehyde resulted in a dose-dependent skin sensitization; a no observed effect concentration (NOEC) was not obtained. No biologically relevant differences were observed after the first and second challenges, or at the different time-points of readings. The incidences of animals with positive skin reactions were 3-4/10, 4-7/10, and 8-9/10 in the groups challenged with 1, 3, and 10%, respectively at the first challenge. Only the animals that received a third challenge concentration of 0.03% (after 1% at the first and second challenge) showed no signs of sensitization.
Test substance: formaldehyde; special grade, no further data
23-JAN-1998 (379)

Type: other: CPA/FCA - Test
Species: guinea pig

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: large deviation of results
Result: The sensitizing potency of formaldehyde was studied in groups of 8 or 10 Dunkin-Hartley guinea pigs. Three days prior to induction, the animals received an intradermal injection of 150 mg/kg cyclophosphamide. Formalin was dissolved in physiological saline and was topically applied under occlusive conditions at a concentration of 5% on days 1, 2, 3, 4, and 9 (induction). On day 4, Freund's Complete Adjuvant was injected twice intradermally. Two weeks later, challenge was performed by topical application of 1.25% formalin under occlusive conditions. The test was carried out 3 times.
Positive skin reactions were observed in 4/8, 0/10, and 0/10 in the first, second, and third test runs, respectively. Thus, cumulative response was 4/28 (14%).
Test substance: formalin; formaldehyde content 37%
Reliability: (3) invalid
16-JUN-1998 (466)

Type: other: Cumulative contact enhancement test
Species: guinea pig
Result: ambiguous

Method: other: no data
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: The effects of several induction concentrations and several challenge concentration were studied in groups of 10 guinea pigs (males and females; no data on strain).

The animals received 1-4 induction applications and 1 challenge application. For induction, the animals were applied solutions containing the test substance at concentrations of 0.2, 1, or 5% under occlusive conditions on days 0, 2, 7, and 9. On day 7, the guinea pigs received a single intradermal injection of Freund's Complete Adjuvant. Eleven days after the last induction application, challenge was performed with closed patches containing 0.2, 1, 5, and 10% aqueous formalin.
The sensitization incidence was generally low; no clear dose-response relation was observed. According to the authors, the highest no observed effect concentrations (NOEC) were 5% for induction and 1% for challenge. However, even the challenge concentration of 5% caused only a low number of positive skin reactions up to 20%. Only challenge with 10% resulted in incidences above 20%. According to the authors,the results indicated that a higher sensitization incidence could be obtained by a higher application frequency. However, the overall conclusion was drawn, that formaldehyde was only slightly sensitzing in the Cumulative Contact Enhancement Test.

Test substance: aqueous formalin; no data on formaldehyde content

16-JUN-1998 (663)

Type: other: Cumulative contact enhancement test
Species: guinea pig
Result: sensitizing
Classification: sensitizing

Method: other: no data
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: Three groups of 10 female guinea Dunkin-Hartley pigs were induced by topical occlusive application (2 x 4h on 4 days) of 1% formalin dissolved in distilled water. Two challenge procedures were performed by non-occlusive application of 1, 3, and 10% with an interval of 3 weeks. Readings were carried out 48 h after challenge application. No significant differences were observed when comparing the results after the first and the second challenge. After the second challenge, sensitization rates were 5/10, 10/10, and 10/10 in the groups challenged with 1, 3, and 10%, respectively. A dose-dependency was observed. NOEC (no observed effect concentration) could not be evaluated under the test conditions because the lowest challenge concentration (1%) already caused 50% sensitization.

Test substance: formalin; no data on purity or formaldehyde content

16-JUN-1998 (378)

Type: other: Cytokine production by draining mouse lymph node cells
Species: mouse
Result: sensitizing
Classification: sensitizing

GLP: no data
Test substance: other TS

Result: Induction: topical application on both shaved flanks, repitition at day 5, 10%, 25%, 50% in DMF, 10% Trimellitic Anhydride in acetone/olive oil (4:1)
Challenge: at day 10, topical application on the dorsum of the ears, daily repitition for three days, 10%, 25%, 50% in DMF, 10% in Trimellitic Anhydride in acetone/olive oil (4:1)
Determination of Interferon-gamma and IL-10 after 48 - 120h lymph-node cell culture; formaldehyde at 10% induced significant levels of IFN-gamma but not of IL-10, indicative for skin sensitization; Trimellitic Anhydride in acetone/olive oil (4:1) induced significant levels of IL-10 but only moderate level of IFN-gamma indicative, indicative for respiratory sensitization.
Test substance: formalin; formaldehyde content 37%
Reliability: (2) valid with restrictions
17-JUN-1998 (320)

Type: other: Dossou-Sicard test
Species: guinea pig
Result: ambiguous

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: challenge concentration might have been irritating
Result: The study procedure used two different induction methods. In any case, both induction and challenge was carried out with a 5% solution; 2 groups of 12 Dunkin-Hartley guinea pigs were used. In the first group, the animals received an intradermal injection of Freund's Complete Adjuvant at day 0 and were induced by open topical application of the test solution at days 0, 2, and 4. In the second group, induction was performed by an intradermal injection of a 5% emulsion in Freund's Complete Adjuvant. After a resting period of 6 days, challenge was carried out by an open topical application at day 15. Skin samples were taken for histopathological examination. Macroscopically, the intradermal induction caused skin sensitization was in 6/12 animals while none of the topically induced animals showed any skin reaction. Histpathology confirmed the positive macroscopic findings of only 2/12 animals.
Test substance: formalin; formaldehyde content 37%
Reliability: (3) invalid

23-JAN-1998 (285) (286)

Type: other: Guillot-Brulos test
Species: guinea pig
Result: sensitizing

Method: other: no data
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Remark: challenge concentration might have been irritating

Result: Twenty Dunkin-Hartley guinea pigs were were given an intradermal injection of Freund's Complete Adjuvant at day 0 of the study. They were induced by 48 h occlusive topical application of a 5% aqueous solution at days 0, 2, 4, 7, 9, 11, and 14. After a resting period of 12 days, challenge was performed with by occlusive topical application of a 5% solution for 48 h. Skin samples were taken for histopathological examination. Macroscopically, a clearly positve skin reaction was observed in 7/20 animals, another 5/20 animals showed doubtful reactions. Histopathology only confirmed the clearly positive responses. Thus, according to the authors, a definite allergic reaction was observed in 7/20 (35%) of the animals.
Test substance: formalin; formaldehyde content 37%
Reliability: (3) invalid
16-JUN-1998 (285) (286)

Type: other: Guinea pig optimisation test
Species: guinea pig
Result: sensitizing

GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: Reliability: 2 (reliable with restrictions)
Result: Ten male and 10 female Pirbright guinea pigs were given an intradermal induction concentration of 0.1% formaldehyde (35%) dissolved in saline in the first week; in the second and third week, the same amount of the test substance was administered as a solution in Freund's Complete Adjuvant. For challenge, the animals were injected intradermally with 0.1% formaldehyde solution; sensitization rate was 20/20 (100%). Two weeks after this intradermal challenge, the animals were challenged topically with 2% formaldehyde solution, and 10/20 (50%) showed a positive reaction.
Test substance: formalin; formaldehyde content 35%
16-JUN-1998 (470)

Type: other: Guinea pig optimisation test
Species: guinea pig
Result: sensitizing

GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Remark: challenge concentration might have been irritating
Result: Ten male and ten female Dunkin-Hartley guinea pigs were given a 5% dilution of formalin (37% formaldehyde) in de-ionized water. Intradermally induction was carried out at days 0, 2, and 4 using water as, and on days 7, 9, 11, 14,16, and 18 using a 50% mixture of Freund's Complete Adjuvants solvent. Intradermal challenge was performed on day 35 and topical challenge on day 49 with a 5% solution; additionally, skin amples were examined histopathologically after the second challenge. After the first challenge, sensitization rate was 20/20 (100%); all animals showed positive skin reaction. However, after the second challenge, only 2/20 animals (10%) showed a clearly positive skin reaction, 16/20 animals (80%) had a questionable reaction, and 2/10 animals (10%) were not

sensitized. Histopathology revealed no allergic reaction.
Test substance: formalin; formaldehyde content 37%
Reliability: (4) not assignable
16-JUN-1998 (285) (286)

Type: other: Immuno globuline E test for respiratory sensitisation
Species: mouse
Result: not sensitizing

GLP: no data
Test substance: other TS: formalin; formaldehyde content 37%

Method: Induction: single topical application on both shaved flanks, 10%, 25%, 50% in DMF, DMF and acetone/olive oil (4:1) and 1% Dinitrochlorobenzene as negative control, 25% Trimellitic Anhydride as positive control in acetone/olive oil (4:1)
Challenge: at day 7 topical application on the dorsum of the ears, 5%, 12.5%, 25% in DMF, DMF and acetone/olive oil (4:1) and 0.5% Dinitrochlorobenzene as negative control, 12.5% Trimellitic Anhydride as positive control in acetone/olive oil (4:1)
Remark: strain: BALB/c
Result: Comments: at day 14 immuno globuline E measurement (6 animals/group), formaldehyde and Dinitrochlorobenzene: no increase in immuno globuline E conc.
Trimellitic Anhydride: stat. sig. increase in immuno globuline E conc.
Immuno globulin E: increase is indicative for respiratory sensitization
Conclusion formaldehyde has no potential to cause respiratory sensitization in the mouse
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
18-DEC-2000 (320)

Type: other: Local lymph node assay
Species: mouse
Result: sensitizing

GLP: no data
Test substance: other TS

Remark: strain: BALB/c
Result: Induction: topical application on the dorsum of the ears, daily for three days, 10%, 25%, 50% in DMF, DMF control, 1% Dinitrochlorobenzene (DNCB) as positive control dissolved in Acetone/olive oil (4:1)
Challenge: no challenge
Comments: at 10% increase in [3H]-methyl-thymidine incorporation in lymph node cells (4 animals/group), indicative for a clear sensitizing response, 3 fold less than DNCB induced increase in [3H]-thymidine incorporation in lymph node cells (3 animals/group)

Test substance: formalin; formaldehyde content 37%
Reliability: (2) valid with restrictions
16-JUN-1998 (320)

Type: other: Mouse immuno globuline E test
Species: mouse
Result: not sensitizing

GLP: no data
Test substance: other TS

Remark: strain: BALB/c
Result: Induction: single topical application on both shaved flanks, 10%, 25%, 50% in DMF, DMF and acetone/olve oil (4:1) and 1% Dinitrochlorobenzene as negative control, 25% Trimellitic Anhydride as positive control in acetone/olve oil (4:1)

Challenge: at day 7 topical application on the dorsum of the ears, 5%, 12.5%, 25% in DMF, DMF and acetone/olve oil (4:1) and 0.5% Dinitrochlorobenzene as negative control, 12.5% Trimellitic Anhydride as positive control in acetone/olive oil (4:1)

Comments: at day 14 immuno globuline E measurement (6 animals/group), formaldehyde and Dinitrochlorobenzene: no increase in immuno globuline E conc.
Trimellitic Anhydride: stat. sig. increase in immuno globuline E conc.

Immuno globulin E: increase is indicative for respiratory sensitization

Conclusion formaldehyde has no potential to cause respiratory sensitization in the mouse
Test substance: formalin; formaldehyde content 37%
Reliability: (2) valid with restrictions
24-SEP-2001 (320)

Type: other: Single injection adjuvant test
Species: guinea pig
Result: sensitizing

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: challenge concentration might have been irritating
Result: Ten inbred DNCB-sensitive guinea pigs were induced by intradermal injection of 0.5% formalin mixed with Freund's Complete Adjuvant. Challenge was performed 12 to 14 days later by open topical application of 10%. The challenge procedure was repeated weekly up to a total of 3-4 applications. Solutions for injection were dissolved in physiological saline; solutions for topical application were prepared in distilled water. All 10 animals (100%) showed positive skin reaction; the mean patch test reaction score was 1.85 (possible maximum score: 3.0). Thus, according to the authors, formaldehyde was assessed as moderately sensitizing.

Test substance: formalin; formaldehyde content 40%
Reliability: (3) invalid
16-JUN-1998 (264)

Type: other: specially designed study
Species: guinea pig

Method: other: no data
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
The aim of the study was to evaluate the most likely route to cause sensitization and the potency of formaldehyde as a sensitizing agent. Thus, groups of male English smooth-haired guinea pigs were exposed to the test substance by inhalation, dermally, or by intradermal injection.
The different groups were treated as follows:
- Group 1 (4 shaved and depilated animals): induction by inhalation of 6 ppm (ca. 0.007 mg/l) 6 h/day for 5 consecutive days; challenge: dermally by topical application of 2% (20 ul) on day 9 and pulmonary by inhalation of 2 ppm (ca. 0.002 mg/l) on day 7 for 1 h; blood samples were taken on days 14 and 22.
- Group 2 (4 shaved and depilated animals): induction by inhaling 10 ppm (ca. 0.012mg/l) 6 h/day for 5 consecutive days; challenge: dermally by topical application of 2% (20 ul) on day 9 and pulmonary by inhalation of 4 ppm (ca. 0.005 mg/l) on day 7 for 1 h; blood samples were taken on days 14 and 22.
- Group 3 (4 animals): induction by inhalation of 10 ppm (ca. 0.012 mg/l) 8 h/day on 5 consecutive days; challenge: dermally by topical application of 2% (20 ul) on day 31 and pulmonary by inhalation of 4 ppm (ca. 0.005 mg/l) on days 7, 22, and 29 for 4 h; blood samples were taken on days 22 and 29.
- Group 4 (8 animals): dermal induction by topical application of 0.1 ml of 37% solution on days 1 and 3 (total dose: 74 mg); challenge: dermally by topical application of 2% (20 ul) on day 7 and pulmonary by inhalation of 4 ppm (ca. 0.005 mg/l) on day 22 for 1 h; blood samples were taken on day 14.
- Group 5 (8 animals): dermal induction by topical application of 0.012 mg on day 1; challenge: dermally by topical application of 2% (20 ul) on day 7.
- Group 6 (8 animals): dermal induction by topical application of 0.12 mg on day 1; challenge: dermally by topical application of 2% (20 ul) on day 7.
- Group 7 (8 animals): dermal induction by topical application of 1.2 mg on day 1; challenge: dermally by topial application of 2% (20 ul) on day 7.
- Group 8 (8 animals): dermal induction by topical application of 5.1 mg on day 1; challenge: dermally by topical application of 2% (20 ul) on day 7.
- Group 9 (8 animals): dermal induction by topical application of 9.3 mg in day 1; challenge: dermally by topical application of 2% (20 ul) on day 7.

- Group 10 (4 animals): intradermal induction by injection of 0.2 ml of a 27% solution in Freund's Complete Adjuvant (total dose: 37 mg); challenge: dermally by topical application of 2% (20 ul) and pulmonary by inhalation of 4 ppm (ca. 0.005 mg/l) on day 19 for 1 h; blood samples were taken on day 14.

Skin sites were examined for erythema 1, 6, 24, and 48 h after challenge; respiratory rates were monitored continuously prior to challenge and during 24 h post challenge; the animals were exposed to vapors of the test substance. Blood samples were examined serologically.

Result: The animals induced inhalationally with 10 ppm (groups 2 and 3) revealed a depression in respiratory rates (up to 45%) with 2 different patterns indicating sensory irritation followed by pulmonary irritation. Brochial provocation failed to elicit either immediate or delayed respiratory reaction in groups 1-3. After skin testing, no contact sensitivity was observed in groups 1 and 2; while in group 3, 2/4 animals showed mild skin reactions. No antibodies were found in the blood samples.

After topical application, no respiratory response by inhalation challenge was seen (group 4), however, all animals showed extensive skin reactions after dermal challenge. No antibodies were found in the blood samples. The animals treated only dermally (groups 5-9) showed dose-dependent contact sensitivity. Sensitization rates were 1/8, 3/8, 4/8, 5/8, and 7/8 in groups 5, 6, 7, 8, and 9, respectively. The severity of the skin reaction ranged from grade 1 (groups 5 and 6) to grade 1-4 (group 9).
All animals which were injected with the test substance (group 10) showed extensive positive skin reaction after dermal challenge but no signs of allergy were observed after pulmonary challenge. In the blood samples of 2/4 animals, low titer cytophilic antibodies were detected on day 14. However, the antibodies reacted only after a special preparation of the formaldehyde serum with a reducing
agent (sodium cyanoborohydride); without this agent, no antibodies could be detected. Thus, the detection of antibodies was rather questionable. Preimmunization sera were negative.

According to the authors, these results indicated that formaldehyde was a skin sensitizer but did not induce respiratory hypersensitivity in the studied guinea pigs. The immunogenic activity of the test substance was assessed to be very low or questionable because of the detecting procedure.

Test substance: formaldehyde; no data on purity of the compound

27-NOV-1997 (419)

5.4 Repeated Dose Toxicity

Species: rat Sex: male
Strain: Wistar
Route of administration: inhalation
Exposure period: 3 days

Frequency of treatment: 22 h/d
Post exposure period: none
Doses: ca. 0.0001, 0.0012, 0.0037 mg/l (0.1, 1, 3 ppm)
Control Group: yes, concurrent no treatment
NOAEL: = .0012 mg/l
LOAEL: = .0037 mg/l

Method: other: no data
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: Ten rats were used per dose group. Examinations on general health state and nasal histopathology were carried out. Additionally, cell proliferation (the percentage of labelled cells in the nasoturbinales after a single injection of 3H-thymidine) was measured in 5 animals per group.
In the highest dose group, disarrangement and both hyperplasia and metaplasia of the respiratory epithelium in the nasal levels II and III were recorded. Cell proliferation was statistically significantly increased at nasal level II but not at nasal level III. Coexposure to ozone did not lead to any change of the lesions observed.
In the mid and low dose group, no findings were recorded.
Test substance: formaldehyde; no data on purity of the compound
10-AUG-1999 (561)

Species: rat Sex: male
Strain: Fischer 344
Route of administration: inhalation
Exposure period: up to 4 days
Frequency of treatment: 6 h/d
Post exposure period: none
Doses: ca. 0.0006, 0.0027, 0.0073, 0.0184 mg/l (0.5, 2.2, 5.9, 14.8 ppm)
Control Group: yes, concurrent no treatment
NOAEL: = .0027 mg/l
LOAEL: = .0073 mg/l

Method: other: no data
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: The ultrastructural chances of nasal epithelium caused by inhalational exposure to the test substance were studied in groups of 3-5 rats. After exposure, nasal epithelium was examined by transmission electron microscopy.
In the 2 high dose groups (14.8 and 5.9 ppm), degenerative changes differentially expressed in various cell types indicating squamous metaplasia and inflammatory processes were observed. In the 2 low dose groups (2.2 and 0.5 ppm), blebbing of the membranes in some cilia of the respiratory epithelial cells were found. According to the authors, the findings of the 2 groups exposed to 0.5 and 2.2 ppm were not considered as epithelial injury. Thus, NOAEL was given as 2.2 ppm.
Test substance: formaldehyde; no data on purity of the compound
27-NOV-1997 (486)

Species: rat Sex: male
Strain: Wistar
Route of administration: inhalation
Exposure period: 4 weeks
Frequency of treatment: 5 d/w
Post exposure period: none
Doses: ca. 0.006, 0.012, 0.024 mg/l (5, 10, 20 ppm)
Control Group: yes, concurrent no treatment
NOAEL: < .006 mg/l

Method: other: no data
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: The aim of the study was to find out whether treatment-related effects were determined by the total dose or by the exposure concentration. Thus, the cytotoxic effects of inhalational exposure to the test substance on the nasal epithelium were studied in groups of 10 rats. Two groups were exposed continuously to 5 or 10 ppm 8 hours/day 5 days/week for 4 weeks; another 2 groups were exposed to 10 or 20 ppm 4 hours/day in intervals of 30 minutes interrupted by 30 minutes without exposure for 4 weeks (5 days/week); control rats remained untreated. After 4 weeks of treatment, autopsy and nasal histopathology were performedwith 4 rats per group, the remaining 6 rats per group were examined for nasal cell proliferation.

In the group continuously exposed to 10 ppm (total daily dose 80 ppmh/d), rhinitis and focal thinning were observed in a few rats; squamous metaplasia and basal hyperplasia of the respiratory epithelium were found in most of the animals. In the group intermittently exposed to 20 ppm (total daily dose 80 ppmh/d, too), rhinitis, focal thinning,squamous metaplasia and basal hyperplasia of the respiratory epithelium were found in all or most of the animals. The lesions found in this group were more severe than those found in rats continuously exposed to 10 ppm.

In the group continuously exposed to 5 ppm (total daily dose 40 ppmh/d), rhinitis, squamous metaplasia and basal hyperplasia of respiratory epithelium was found in some rats. In the group intermittently exposed to 10 ppm (total daily dose 40 ppmh/d, too), rhinitis, focal thinning and disarrangement was observed in few rats, squamous metaplasia and basal hyperplasia of respiratory epithelium were present in most of the animals. The lesions found in this group weremore severe than those observed in rats continuously exposed to 5 ppm.

According to the authors, these results suggested that the severity of cytotoxic effects to the nasal epithelium was rather determined by the exposure concentration than by the total dose.

Test substance: formaldehyde; no data on purity of the compound
27-NOV-1997 (706)

Species: rat Sex: male
Strain: other: albino
Route of administration: inhalation
Exposure period: 6 weeks to 3 months
Frequency of treatment: no data specified
Post exposure period: none
Doses: ca. 0.002, 0.006, 0.1 mg/l (1.6, 4.6, 8.1 ppm)
Control Group: yes, concurrent vehicle
NOAEL: = .002 mg/l
LOAEL: = .006 mg/l

Method: other: no data
GLP: no data
Test substance: no data

Remark: Reliability: 3 (not reliable)
Result: Seventy-five rats were exposed to the test-substance (no data on number of rats per treatment group), 75 controls remained untreated. Data on general health state, selected organ weights and number and activity of lavaged macrophages were determined.
In the highest dose group, clinical irritation of the eyes and of the upper respiratory tract, reduced food consumption and reduced body weight gains, decreased relativeliver weights, and reduction of alveolar macrophages and their phagocytic capacity were observed. In the mid dose group, exposure to formaldehyde resulted in reduced body weight gains. In the low dose group, no substance-related effects were found.
Test substance: formaldehyde; no data on purity of the compound
27-NOV-1997 (202)

Species: rat Sex: male
Strain: Fischer 344
Route of administration: inhalation
Exposure period: 12 weeks (whole body exposure) plus 3 hours (nose-only exposure)

Frequency of treatment: 5 d/w, 6 h/d
Post exposure period: none
Doses: ca. 0.0009, 0.0026, 0.0073, 0.0124, 0.0.018 mg/l (0.7, 2.1, 5.9, 10.0, 14.5 ppm)
Control Group: yes, concurrent vehicle
NOAEL: = .0026 mg/l
LOAEL: = .0073 mg/l

Method: other: no data
GLP: no data
Test substance: no data

Remark: Another aim of the study was to evaluate protein DNA cross links in unexposed and subchronically preexposed rats.
Reliability: 2 (reliable with restrictions)

Result: Several groups of 10 rats per concentration were exposed to the test substance for 12 weeks followed by a 3-hours nose-only exposure to the 14C- or unlabelled formaldehyde. After termination of the treatment, gross inspection of the nasal cavity and histopathologic examination of the nose were carried out in 1 or 2 animals per group.

Grossly, keratinizing epithelial plaques were observed in the highest dose group. No grossly visible lesions were recorded in the other groups.
At 14.5 ppm, histopathology revealed generalized and severe epithelial lesions extending to the nasopharyngeal meatus, lateral meatus (high tumor site); epithelial erosion, transitional epithelial hyperplasia, squamous metaplasia, intraluminal and mucosal inflammatory infiltration, keratinizing plaques with subepithelial inflammation, thickening of underlying periosteum, and edema and hyperemia of lamina propria were recorded. At 10 ppm, squamous metaplasia of the lateral meatus and the medial maxilloturbinate, epithelial hyperplasia and inflammatory cell infiltration of the midseptum were observed. At 5.9 ppm, multifocal epithelial hypertrophy, hyperplasia and squamous metaplasia of the lateral meatus were present. No histopathologic lesions were found at 2.1 and 0.7 ppm.
Test substance: formaldehyde; no data on purity of the compound
04-JUL-1997 (122)

Species: rat Sex: male/female
Strain: Wistar
Route of administration: inhalation
Exposure period: 13 weeks
Frequency of treatment: 5 d/w, 6 h/d
Post exposure period: none
Doses: ca. 0.0004, 0.0012, 0.0037 mg/l (0.3, 1, 3 ppm)
Control Group: yes, concurrent no treatment
NOAEL: = .0012 mg/l
LOAEL: = .0037 mg/l

Method: other: no data
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: Twenty-five rats of each sex were used per dose group. Studies on general health state, nasal histopathology and electronmicroscopical examinations were carried out. Histopathology revealed changes in about 50% of the animals of both sexes exposed to 3 ppm; squamous metaplasia at the nasal level II were present at 3 ppm only, disarrangement orslight hyperplasia of the respiratory epithelium in the anterior part of the nose (transitional zone) were found in all groups. Electron microscopy revealed ultrastructural changes at 3 ppm comprising loss of cilia, indented and disarranged nuclei, glandularization of globlet cells, foci of keratinized squamous epithelium. No distinct differences to control were found at 1 and 0.3 ppm.

Test substance: formaldehyde; no data on purity of the compound
27-NOV-1997 (733)

Species: rat Sex: male/female
Strain: Wistar
Route of administration: inhalation
Exposure period: 13 weeks
Frequency of treatment: 5 d/w, 6 h/d
Post exposure period: none
Doses: ca. 0.0012, 0.012, 0.025 mg/l (1, 9.7, 19.8 ppm)

Control Group: yes, concurrent no treatment
NOAEL: <= .0012 mg/l

Method: other: no data
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: The effects of inhalational exposure to the test substance on the respiratory tract were studied in 10 rats/sex/group. After 13 weeks of treatment, autopsy and nasal histopathology were performed; alterations in general health state were recorded.

In the high dose group, impairment of general health accompanied by unspecific findings in clinical pathology; rhinitis; diffuse squamous metaplasia, focal hyperplasia, disarrangement and keratinization of the respiratory epithelium; focal thinning, squamous metaplasia and keratinization of the olfactory epithelium were observed in males and females. Additionally, squamous metaplasia of the lanryx epithelium was found in males, but not in females.

In the mid dose group, rhinitis, focal squamous metaplasia, hyperplasia, disarrangement and keratinization of the respiratory epithelium were observed.

In the low dose group, rhinitis was observed in 2 males; minimal hyperplasia and squamous metaplasia was found in 2 males and 1 female. However, according to the authors, the substance-relation of these findings was questionable.
Test substance: formaldehyde; no data on purity of the compound
08-NOV-1996 (713)

Species: rat Sex: male
Strain: other: albino
Route of administration: inhalation
Exposure period: up to 22 weeks
Frequency of treatment: no data
Post exposure period: none
Doses: no data specified
Control Group: yes, concurrent no treatment

Method: other: no data
GLP: no data
Test substance: other TS

Remark: Reliability: 4 (not assignable)
Result: Groups of rats were inhalationally exposed to a "vaporizing" 10% formalin solution; anayltical monitoring of the inhalation atmosphere was not carried out. Three treated and 1 control rat each were sacrificed after 2, 4, 8, 17, and 22 weeks of exposure. Data on general health were recorded, histopathology of the trachea was performed.
Three of the rats died during 22 weeks of exposure. Morphological alterations of the tracheal epithelium and submucosa were observed. No further data.
Test substance: 10% formalin solution
04-JUL-1997 (8)

Species: rat Sex: male/female
Strain: Fischer 344
Route of administration: inhalation
Exposure period: 26 weeks
Frequency of treatment: 7 d/w, 22 h/d
Post exposure period: none
Doses: ca. 0.0002, 0.0012, 0.0037 mg/l (0.19, 0.98, 2.95 ppm)
Control Group: yes, concurrent no treatment
NOAEL: .0012 mg/l
LOAEL: .0037 mg/l

Method: other: no data
GLP: no data
Test substance: no data

Remark: Reliability: 3 (not reliable)
Result: Five groups of 20 rats of each sex were used in the study; 2 control groups remained untreated. After termination of exposure, the animals were examined macroscopically and electronmicroscopically; histopathological investigation of the nose, trachea and lung were performed.

In the high dose group, decreased body weight gains and decreased absolute and relative liver weight were observed. Histopathology revealed basal cell hyperplasia of the respiratory epithelium which was most pronounced in the middle region of the nasotubinate.

According to the authors, randomly distributed rhinitis was observed in all 5 groups.
Test substance: formaldehyde; no data on purity of the compound
27-NOV-1997 (576)

Species: rat Sex: male
Strain: Wistar
Route of administration: inhalation
Exposure period: 13 and 52 weeks
Frequency of treatment: 5 d/w, 6 h/d
Post exposure period: up to 1 week
Doses: ca. 0.0001, 0.0012, 0.012 mg/l (0.1, 1.0, 9.4 ppm)
Control Group: yes, concurrent no treatment
NOAEL: .0012 mg/l
LOAEL: .012 mg/l

Method: other: no data
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: The different effects of inhaled formaldehyde on damaged and undamaged nose was studied in 16 groups of 10 rats. Four groups were used per concentration level: 0 (control), 0.1, 1.0, and 9.4 ppm, respectively. In each concentration level, 1 group with nose damage and 1 group without nose damage each was exposed to either 13 or 52 weeks. Nose damage was set by bilateral electro-coagulation of the anterior nasal cavity ca. 20 h prior to the first exposure. After termination of the exposure, investigations on general health, clinical pathology, autopsy, measurement of organ weights, and histopathology of the respiratory tract

and other organs were performed.

The electro-coagulation without exposure resulted in necrosis, hemorrhages, perforation of the nasal septum, and loss of turbinates; epithelial repair followed the pattern of wound healing. Residues found 14 weeks after damaging were rhinitis, nest-like infolds and basal cell hyperplasia and squamous metaplasia of the respiratory epithelium. In week 53 after damaging, rhinitis and basal cell hyperplasia of the respiratory epithelium were still present.

Exposure to 9.4 ppm for 13 weeks resulted in growth retardation, focal rhinits, and squamous metaplasia and basal cell hyperplasia of the respiratory epithelium in rats with undamaged noses. In rats with damaged noses, the same histopathological lesions were found, however, these lesions were more severe. Additionally, thinning and disarrangement and basal cell hyperplasia of the olfactory epithelium were found. Growth retardation and decreased liver protein and glutathione content due to exceptional high control values were recorded.

Exposure to 9.4 ppm for 52 weeks resulted in growth retardation, oliguria, focal rhinitis, squamous metaplasia and basal cell hyperplasia of the respiratory epithelium, and low incidence of thinning and disarrangement and basal cell hyperplasia of the olfactory epithelium in rats with undamaged noses. In rats with damaged noses, the same histopathological lesions were found, however, the alterations of the olfactory epithelium were more pronounced.

According to the authors, no substance-related lesions were found in the mid and low dose groups.

Test substance: formaldehyde; no data on purity of the compound

13-MAY-1998 (28)

Species: rat Sex: male
Strain: Wistar
Route of administration: inhalation
Exposure period: up to 13 weeks
Frequency of treatment: 5 d/w, 6 h/d
Post exposure period: none or up to week 131 of the study
Doses: ca. 0.012, 0.025 mg/l (10, 20 ppm)
Control Group: yes, concurrent no treatment
NOAEL: < .012 mg/l

Method: other: no data
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: The effects of inhalation exposure to the test substance on the nasal epithelium was studied in groups of 50-55 rats. The rats were exposed for 4, 8, and 13 weeks with sacrifices immediately after termination of exposure and after an observation period up to study week 131. Control rats remained untreated. Investigations on general health, autopsy and histopathology of the nose were performed.

In all treated groups, decreased body weight gains were observed, except the group exposed to 10 ppm for 4 weeks. The depression of body weight gain was mostly reversible during the observation period and had no influence on the mortality rates.

In rats exposed to 20 ppm and sacrificed immediately after termination of treatment, rhinitis, hyperplasia and squamous metaplasia of the respiratory epithelium and dissarrangement, thinning, cuboidal, or squamous metaplasia of the olfactory epithelium were observed. The intensity of the lesions increased with duration of exposure. Among the rats exposed to 20 ppm and sacrificed after the observation period, increased incidences of rhinitis, focal hyperplasia and stratified metaplasia were found in all exposure groups;alterations of the olfactory epithelium were present after 8 and 13 weeks of exposure.

In rats exposed to 10 ppm for 13 weeks and sacrificed immediately after treatment, rhinitis was found; lesions of the respiratory epithelium were more focal and less pronounced than at 20 ppm; no alterations of the olfactory epithelium were observed. In rats exposed to 10 ppm for 13 weeks and sacrificed after the observation period, increased incidences of focal hyperplasia and stratified metaplasia were observed.

According to the authors, no statisitically significant increased incidence of nasal epithelial lesions was observed at all other exposure times.

Increased numbers of tumors were observed in the groups exposed to 20 ppm (for further data see chapter 5.7 Carcinogenicity).

Test substance: formaldehyde; no data on purity of the compound

27-NOV-1997 (225)

Species: rat Sex: male/female
Strain: Fischer 344
Route of administration: inhalation
Exposure period: 3 months
Frequency of treatment: 5 d/w, 6 h/d
Post exposure period: 25 months
Doses: ca. 0.0001, 0.0012, 0.012 mg/l (0.1, 1.0, 9.4 ppm)
Control Group: yes, concurrent no treatment
NOAEL: .0012 mg/l
LOAEL: .012 mg/l

Method: other: no data
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: The different effects of inhaled formaldehyde on the intact or damaged nasal epithelium were studied. Groups of 30 rats with intact noses and groups of 60 rats with damaged noses were used. Nose damage was set by electro-coagulation of the nasal cavity. After termination of both exposure and postobservation period, investigations on general health, autopsy, measurement of organ weights, and histopathology ofthe nose were performed.

The electro-coagulation without exposure resulted in perforation of the nasal septum, loss of turbinates, high incidence of squamous metaplasia (increase of up to 46%), hyperplasia of the respiratory epithelium (11%), and rhinitis (50%).

Exposure to 9.4 ppm for 3 months followed by 25-months observation resulted in growth retardation, rhinits (50%), squamous metaplasia (increase of up to 65%) and basal cell hyperplasia (15%) of the respiratory epithelium in the anterior nose in rats with undamaged noses. Exposure to 9.2ppm after nasal damage caused growth retardation, squamous metaplasia (increase of up to 81%) and basal cell hyperplasia (33%) of the respiratory epithelium, degeneration of the olfactory epithelium (15%), and rhinitis(80%). In rats exposed to 1.0 ppm after nose damaging squamous metaplasia (increase of up to 58%) and basal cell hyperplasia (9%) of the respiratory epithelium, and rhinitis(45%) were observed. After exposure to 0.1 ppm, squamous metaplasia (maximum increase of 47%) and basal cell hyperplasia (15%) of the respiratory epithelium, and rhinitis (67%) were found in rats with damaged noses.
No significant influence of exposure to 1.0 or 0.1 ppm of the test substance on electro-coagulation damage was found. According to the authors, the NOAEL was 1 ppm for rats with intact nasal epithelium.

Test substance: formaldehyde; no data on purity of the compound

14-MAY-1998 (713)

Species: rat Sex: female
Strain: Sprague-Dawley
Route of administration: inhalation
Exposure period: no data specified
Frequency of treatment: no data specified
Post exposure period: no data
Doses: ca. 0.015 mg/l (12.4 ppm alone or 12.7 ppm in combination with 25 mg/m3 wood dust)
Control Group: yes, concurrent no treatment

Method: other: no data
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: The histological changes in the nasal mucosa after long term exposure to formaldehyde and wood dust were studied in groups of 15-16 rats. Sixteen rats were exposed to 12.4 ppm of formaldehyde; 15 animals were exposed to 12.7 ppm of formaldehyde combined with 25 mg/m3 of wood dust. Controls remained untreated; additionally, another group was exposed to 25 mg/m3 wood dust only. Data on general health were recorded; after termination of the exposure, nose and lungs were examined histopathologically.
In 10/16 (63%) rats exposed to formaldehyde only, squamous metaplasia partly with keratinization or dysplasia was observed; the same lesions were found in 12/15 (80%) rats exposed to the combination of formaldehyde and wood dust. In 1/16 (6%) of the group exposed to formaldehyde, nasal tumors were observed (see chapter 5.7). Exposure to wood dust alone did not lead to pronounced nasal lesions but

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                    increased the incidence of emphysema. According to the
                    authors, higher incidences of nasal lesions were observed n
                    coexposed animals, this could be interpreted as an additive
                    effect.
Test substance:     formaldehyde; no data on purity of the compound
27-NOV-1997                                                                (331)

Species:                  rat                                Sex: male
Strain:                   Sprague-Dawley
Route of administration:  inhalation
Exposure period:          lifetime
Frequency of treatment:   5 d/w, 6 h/d
Post exposure period:     none
Doses:                    ca. 0.018 mg/l (14.7 ppm) combined with ca. 0.016 mg/l
                          (10.6 ppm) HCl
Control Group:            yes, concurrent no treatment

Method:             other: no data
   GLP:             no data
Test substance:     other TS

Remark:             Reliability: 2 (reliable with restrictions)
Result:             The effects of a mixture of formaldehyde (FA) and hydrogen
                    chloride (HCl) was studied. Groups of 50 (untreated), 50
                    (sham-controls) and 99 FA + HCL exposed rats were used.
                    Studies on general health, autopsy, and histopathology of
                    nose, larynx, trachea, lung. liver, bladder, kidneys, and
                    spleen were conducted.
                    Exposure to the gases resulted in increased mortality and
                    reduced body weight gains compared to controls. Increased
                    incidences in rhinitis, epithelial hyperplasia and
                    hyperplasia with atypia (72% in the treated groups versus
                    16% in unexposed controls), and squamous metaplasia (65% in
                    the treated groups versus 0% in unexposed controls) were
                    observed. For tumor incidence see chapter 5.7.
                    According to the authors, this experiment was a preliminary
                    study.
Test substance:     formaldehyde-hydrogen chloride premix; no data on purity of
                    the compounds
16-JUN-1998                                                                (10)

Species:                  rat                                Sex: male
Strain:                   Fischer 344
Route of administration:  inhalation
Exposure period:          up to 28 months
Frequency of treatment:   5 d/w, 6 h/d
Post exposure period:     none
Doses:                    ca. 0.0004, 0.003, 0.018 mg/l (0.3, 2.2, 14.9 ppm)
Control Group:            yes, concurrent no treatment

Method:             other: no data
   GLP:             no data
Test substance:     no data

Remark:             Reliability: 2 (reliable with restrictions)
Result:             The inhalation toxicity of formaldehyde was studied in 5
                    groups of 32 rats. Three groups were exposed to the test
                    substance at dose levels of 0.3, 2.2 and 14.9 ppm, one
                    group remained unexposed (control), and one group was
                    exposed to 3.3 ppm (ca. 0.004 mg/l) of methanol,
                    correspondig to the methanol level present at the high
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concentration. Interim sacrifices (5 animals/group/ sacrifice) were carried out after 12, 18,and 24 months. Studies on general health, clinicalpathology, autopsy and histopathology of several tissues were conducted.
In the high dose group, clinical irritation during the first minutes of exposure was observed, however, this irritation vanished during the onset of exposure. Exposure to 14.9 ppm of the test substance further resulted in increased mortality, reduction of both body weight gain and food consumption, increased incidence of rhinitis (100%), squamous metaplasia (100%), epithelial cell hyperplasia (90%), epithelial cell hyperkeratosis (80%), and papillary hyperplasia (6%).
In the mid dose group, low incidence of squamous metaplasia (6%) and epithelial cell hyperplasia (28%) was observed after 24 months of exposure and more; these findings were not present in controls. The incidence of rhinitis was not significantly different from controls.
In the low dose group, low incidence of squamous metaplasia (9%) and epithelial cell hyperplasia (13%) was observed after 24 and 28 months of exposure. Rhinitis was comparable to controls.
According to the authors, the non-neoplastic lesions observed in these groups could not be attributed clearly to the test substance, since there did not exist a clear concentration relation. (For tumor incidences see chapter 5.7)

Test substance: formaldehyde, dissolved in methanol; no data on purity of the compound

16-AUG-2001 (375) (654) (666)

Species: rat Sex: male
Strain: Wistar
Route of administration: inhalation
Exposure period: 3 days
Frequency of treatment: 6 h/d
Post exposure period: none
Doses: ca. 0.0012, 0.0124, 0.0245 mg/l (1, 10, 20 ppm)
Control Group: yes, concurrent no treatment

Method: other: cell proliferation measurement
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: Cell proliferation in nasoturbinates after inhalation of formaldehyde (whole body exposure) was studied. Two rats per group were exposed to the test substance; the nasoturbinates were removed after exposure and incubated with 3H-thymidine.Cell proliferation was measured as % labelled cells. Doubling of labelled cells was observed in light microscopically unaffected regions of the respiratory epithelium; a ca. 20-fold increase was measured in regions of squamous metaplasia in material obtained from rats exposed to 10 or 20 ppm. No increase in cell turnover was found at 1 ppm.

Test substance: formaldehyde; no data on purity of the compound

14-MAY-1998 (713)

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Species:                 rat                                Sex: male
Strain:                  Wistar
Route of administration: inhalation
Exposure period:         3 days
Frequency of treatment:  22 h/d
Post exposure period:    none
Doses:                   ca. 0.001, 0.0012, 0.0037 mg/l (0.1, 1, 3 ppm)
Control Group:           yes, concurrent no treatment

Method:           other: cell proliferation measurement
   GLP:           no data
Test substance:   no data

Remark:           Reliability: 2 (reliable with restrictions)
Result:           Cell proliferation in nasoturbinates after inhalation of
                  formaldehyde (whole body exposure) was studied in groups of
                  10 rats. Cell proliferation was measured as % labelled
                  cells in nasoturbinates after a single intraperitoneal
                  injection of 3H-thymidine following the exposure to the test
                  substance. At 3 ppm, a statistically significantly increase
                  in cell proliferation was observed atnasal level II but not
                  at nasal level III.

                  Data presented in graphical form only; low labelling index
                  in controls.
Test substance:   formaldehyde; no data on purity of the compound
16-JUN-1998                                                          (561)

Species:                 rat                                Sex: male
Strain:                  Fischer 344
Route of administration: inhalation
Exposure period:         12 weeks
Frequency of treatment:  5 d/w, 5 h/d
Post exposure period:    none
Doses:                   ca. 0.0008, 0.0026, 0.0073, 0.018 mg/l (0.7, 2.1, 5.9,
                         14.5 ppm)
Control Group:           yes, concurrent no treatment

Method:           other: cell proliferation measurement
   GLP:           no data
Test substance:   no data

Remark:           Reliability: 2 (reliable with restrictions)
Result:           Cell proliferation in nasoturbinates after inhalation of
                  formaldehyde was studied in groups of 10 rats. Cell
                  proliferation was measured by determination of
                  incorporation of 14C from 14C-formaldehyde into DNA. The
                  animals were exposed (whole body exposure) to the test
                  substance for 12 weeks followed by a 3-h head nose exposure
                  to 14C-formaldehyde.
                  In the 5.9 ppm group, an increase of 14C incorporation was
                  observed in the lateral but not in the medial and the
                  posterior meatus. In the 14.5 ppm group, an increase was
                  found in lateral, medial, and posterior meatus.
Test substance:   formaldehyde; no data on purity of the compound
27-NOV-1997                                                          (122)

Species:                 rat                                Sex: male
Strain:                  Wistar
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Route of administration: inhalation
Exposure period: 13 weeks
Frequency of treatment: 5 d/w, 4 or 8 h/d
Post exposure period: none
Doses: ca. 0.0012, 0.0025, 0.0050 mg/l (1, 2, 4 ppm)
Control Group: yes, concurrent no treatment

Method: other: cell proliferation measurement
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: The aim of the study was to find out whether treatment-related effects were determined by the "dose" or by the exposure concentration. Thus, cell proliferation was measured after continuous and intermittent inhalational exposure of 5 rats/group to the test substance. Two groups were exposed continuously to 1 or 2 ppm 8 hours/day 5 days/week for 13 weeks; another 2 groups were exposed to 2 or 4 ppm 4 hours/day in intervals of 30 minutes interrupted by 30 minutes without exposure for 13 weeks (5 days/week); control rats remained untreated. Cell proliferation (% labelled cells) was measured in nasoturbinates following a single intraperitoneal injection of 3H-thymidine either after 3 exposures or at the end of the study.

In the group intermittently exposed to 4 ppm (daily dose 16 ppmh/d), ca. 3-fold increase was found after 13 weeks, however, this change was not statistically significantly. In the group continuously exposed to 2 ppm (daily dose 16 ppmh/d, too), no change was observed. In the groups exposed intermittently to 2 ppm or continuously to 1 ppm (both dose 8 ppmh/d), no change was observed. No differentiation between histopathologicallyaffected and unaffected regions was worked out. According tothe authors, an increase in cell proliferation after 13 weeks but not after 3 days was unusual.
Test substance: formaldehyde; no data on purity of the compound
07-JUL-1997 (707)

Species: rat Sex: male
Strain: Wistar
Route of administration: inhalation
Exposure period: 13 weeks
Frequency of treatment: 5 d/w, 6 h/d
Post exposure period: none
Doses: ca. 0.0004, 0.0012, 0.0037 mg/l (0.3, 1, 3 ppm)
Control Group: yes, concurrent no treatment

Method: other: cell proliferation measurement
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: Cell proliferation due to exposure to formaldehyde was measured as incorporation of 3H-thymidine into DNA (% labelled cells) in nasoturbinates following a single intraperitoneal injection of 3H-thymidine after 3 exposures and after termination of the 13-week exposure. Groups of 5 rats/sex were used.

At the high dose level, histological changes (squamous metaplasia) were found in level II; additionally, slight hyperplasia of the respiratory of respiratory epithelium of the nasal level III were observed after 3 days, but not after 13 weeks. Proliferation was observed in locations showing histological changes (ca. 10-fold increase), no increase was found at nasal level III after 13 weeks. In both the mid and low dose group, a statistical trend for concentration response relation was recorded at level III after 3-d exposure.
No differentiation was made between histopathologically affected and unaffected regions; a very low labelling index was observed in controls, large variations of individual cell proliferation response were present; thus, according to the authors differencies of individual susceptibility were concluded. Data were presented in graphical form only.

Test substance: formaldehyde; no data on purity of the compound

16-JUN-1998 (733)

Species: rat Sex: no data
Strain: Fischer 344
Route of administration: inhalation
Exposure period: 1,3 and 5 or 3 and 10 days for C x T study
Frequency of treatment: 6h/d or 36 ppm h/d as 3 ppm x 12 h, 6 ppm x 6 h, 12 ppm x 3 h for C x T study
Post exposure period: none
Doses: 0, 0.5, 2, 6, 15 ppm or 3, 6 and 12 ppm
Control Group: other: yes, concurrent

Method: other: cell proliferation measurement
GLP: no data
Test substance: no data

Remark: no clearcut concentration time response relation; data for mice in seperate entry - LI of control groups [%]
level B:
pulse 2 h post exp.: 0.22; 0.26
pulse 18 h post exp. 0.54; 0.43, 0.54, 0.26
level A:
3.0

Result: Examinations:
measurements of cell proliferation (% labeled cells) in nasoturbinate levels A (anterior) and B (mid-anterior) single i.p. injection of H-thymidine 2 or 18 h after end of exposure

Findings:

	fold increase of LI in level B
1 d/15 ppm:	about 13
1 d/6 ppm:	about 5
3 d/15 ppm:	about 13
3 d/6 ppm:	about 25
3 d/6 ppm:	about 6 from C x T study
5 d/15 ppm:	about 23
10 d/6 ppm:	about 2 from C x T study

no increase at 2 and 0.5 ppm labelling 18 h after end of exposure yielded higher fractions of labeled cells in controls and exposed animals (authors: circadian variations)

C x T study
level A: about 5-fold increase of proliferation independent from exposure regimen.
level B: concentration dependent about 3, 6 and 17 fold increase of proliferation after 3 days and about 2, 2 and 7 fold after 10 days
Test substance: formaldehyde; no data on purity of the compound
Reliability: (2) valid with restrictions
30-JUN-1998 (633)

Species: rat Sex: no data
Strain: Sprague-Dawley
Route of administration: inhalation
Exposure period: lifetime
Frequency of treatment: 5 d/w, 6 h/d
Post exposure period: none
Doses: 14.8 ppm FA only, 15.2 ppm FA + 9.9 HCL ppm premix, 14.9 ppm FA + 9.7 ppm HCl non-premix and 10.0 ppm HCl only
Control Group: other: yes, concurrent no treatment and sham exposed

Method: other: no data
GLP: no data
Test substance: other TS

Result: Findings - increased mortality and reduced body weight development in all groups (100 male rats per group) exposed to FA

nasal lesions:
incidences of rhinitis and epithelial or squamous hyperplasia about 70% and 50% resp. in all groups but more severe in FA treated groups, especially in naso-maxillary turbinate and nasal septum independent from coexposure, squamous metaplasia about 60% in FA treated groups versus about 7% in others

larynx:
epithelial hyperplasia in about 20% of substance treated animals versus about 2% in controls and squamous metaplasia in about 10% FA treated animals versus 0% in HCl treated or controls

trachea:
epithelial hyperplasia in about 25% of substance treated animals versus about 4% in controls and squamous metaplasia in about 8% of FA treated animals versus 0% in HCl treated or controls
Test substance: formaldehyde-hydrogen chloride; no data on purity of the compounds
Reliability: (2) valid with restrictions
20-MAY-1999 (596)

Species: rat Sex: male
Strain: Wistar
Route of administration: inhalation
Exposure period: 4 weeks
Frequency of treatment: 6h/d, 5d/w
Doses: 0, 0.35, 1.09, 3.1 ppm

NOAEL: 1.09 ppm

GLP: no data
Test substance: other TS

Remark: Examinations:
5 males per group, clinical examination, clinical pathology, pathology

Findings:
3.1 ppm: hyperplasia of respiratory epithelium in the nose, no systemic toxicity
1.09 ppm: NOAEL

no details on pathology; study was intended to investigate combination toxicity of 9 chemicals (oral exposure with a mixture of 7 plus inhalation exposure with a mixture of 2) combined treatment at the NOAEL of each compound (FA=1.09 ppm) showed some transitional epithelial hyperplasia, which was not present with FA alone, the authors conclude that simultaneous exposure at or below individual NOAELs does not constitute an evidently increased hazard
Test substance: formaldehyde; no data on purity of the compound
Reliability: (2) valid with restrictions
16-JUN-1998 (282) (283) (284)

Species: rat Sex: male
Strain: Fischer 344
Route of administration: inhalation
Exposure period: up to 6 weeks
Frequency of treatment: 5 d/w, 5 h/d
Post exposure period: none
Doses: ca. 0.0009, 0.0025, 0.0077, 0.0123, 0.0.0184 mg/l
(0.69, 2.0, 6.2, 9.9, 14.8 ppm)
Control Group: yes, concurrent no treatment
NOAEL: = .0025 mg/l
LOAEL: = .0077 mg/l

GLP: no data
Test substance: other TS: formaldehyde; no data on purity of the compound

Method: The effects of the test substance on the respiratory tract were studied in groups of 36 rats. In each group, rats were sacrificed after 1, 4, and 9 days and after 6 weeks of exposure. The respiratory tracts were examined histopathologically.
Result: At the two highest dose levels (9.9 and 14.8 ppm), epithelial cell vacuolar degeneration, individual cell necrosis, epithelial exfoliation, multifocal erosion, ulceration, epithelial hyperplasia, squamous metaplasia, and mixed inflammatory cell infiltrates were observed. The lesions were more severe at 14.8 ppm than at 9.9 ppm; the occurrence of increasing severity and distal expansion down to the nasopharynx of the lesions were exposure-time dependent. At the dose-level of 6.2 ppm, the lesions were much less severe that at the higher doses and were confined to the anterior part of the nose (level II) without exposure-time dependent increase in severity or local expansion. Mild individual cell necrosis, epithelial hyperplasia and squamous metaplasia were observed in the rats of this group.

No substance-related lesions were found in rats exposed to 2 ppm or less.
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
24-NOV-2000 (492) (495)

Species: rat Sex: male
Strain: Wistar
Route of administration: inhalation
Exposure period: 13 weeks
Frequency of treatment: 5 d/w
Post exposure period: none
Doses: ca. 0.0012, 0.0025, 0.005 mg/l (1, 2, 4 ppm)
Control Group: yes, concurrent no treatment
NOAEL: = .0012 mg/l
LOAEL: = .0025 mg/l

GLP: no data
Test substance: other TS: formaldehyde; no data on purity of the compound

Method: The aim of the study was to find out whether treatment-related effects were determined by the total dose or by the exposure concentration. Thus, the cytotoxic effects of inhalational exposure to the test substance on the nasal epithelium were studied in groups of 25 rats. Two groups were exposed continuously to 1 or 2 ppm 8 hours/day 5days/week for 13 weeks; another 2 groups were exposed to 2 or 4 ppm 4 hours/day in intervals of 30 minutes interrupted by 30 minutes without exposure for 13 weeks (5 days/week); control rats remained untreated. After 13 weeks of treatment, autopsy and nasal histopathology (with special regard to cell proliferation) were performed; alterations in general health state were recorded.
Result: In the group continuously exposed to 2 ppm (total daily dose 16 ppmh/d), no differences to controls were observed in any item. In the group intermittently exposed to 4 ppm (total daily dose 16 ppmh/d, too), disarrangement and squamous metaplasia in the nose were observed in about 50% of the animals.

In the group continuously exposed to 1 ppm (total daily dose 8 ppmh/d), no differences to controls were observed. In the group intermittently exposed to 2 ppm (total daily dose 8 ppmh/d, too), rhinitis, disarrangement squamous metaplasia and nest-like infolds of the respiratory epithelium were observed; globlet cell hyperplasia was present in about 50% of the animals.

For detection of cell proliferation, 3H-tymidine was injected intraperitoneally after 3 exposures and at the end of the study. Cell proliferation was observed only in rats which were intermittently exposed to 4 ppm; the percentage of labelled cells was about 3-fold increased after 13 weeks, however, this change was not statistically significant.

According to the authors, these results suggested that the severity of cytotoxic effects to the nasal epithelium was rather determinted by the exposure concentration than by the total dose.

Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
18-DEC-2000 (707)

Species: rat Sex: male/female
Strain: Fischer 344
Route of administration: inhalation
Exposure period: 28 months
Frequency of treatment: 5 d/w, 6 h/d
Post exposure period: none
Doses: ca. 0.0001, 0.0012, 0.011 mg/l (0.1, 1.0, 9.2 ppm)
Control Group: yes, concurrent no treatment
NOAEL: .0012 mg/l
LOAEL: .011 mg/l

GLP: no data
Test substance: other TS: formaldehyde; no data on purity of the compound

Method: The different effects of inhaled formaldehyde on the intact or damaged nasal epithelium were studied. Groups of 30 rats with intact noses and groups of 60 rats with damaged noses were used. Nose damage was set by electro-coagulation of the nasal cavity. After termination of the exposure, investigations on general health, autopsy, measurement of organ weights, and histopathology of the nose were performed.

Result: The electro-coagulation without exposure resulted in perforation of the nasal septum, loss of turbinates, high incidence of squamous metaplasia (increase of up to 46%), hyperplasia of the respiratory epithelium (11%), and rhinitis (50%).

Exposure to 9.2 ppm for 28 months resulted in growth retardation, focal rhinits (69%), squamous metaplasia (increase of up to 96%) and basal cell hyperplasia (54%) of the respiratory epithelium, and degeneration of the olfactory epithelium (27%) in the anterior nose in rats with undamaged noses. In rats with damaged noses, the same histopathological lesions were found, however, these lesions were more severe. Exposure to 9.2 ppm after nasal damage caused squamous metaplasia (increase of up to 82%) and basal cell hyperplasia (41%) of the respiratory epithelium, degeneration (31%), squamous metaplasia (19%) and basal cell hyperplasia (21%) of the olfactory epithelium, and rhinitis (71%). In rats exposed to 1.0 ppm after nose damaging squamous metaplasia (increaseof up to 57%) and basal cell hyperplasia (29%) of the respiratory epithelium, and rhinitis (70%) were observed. After exposure to 0.1 ppm, squamous metaplasia (maximum increase of 66%) and basal cell hyperplasia (14%) of the respiratory epithelium, and rhinitis (78%) were found in rats with damaged noses.
No significant influence of exposure to 1.0 or 0.1 ppm of the test substance on electro-coagulation damage was found. According to the authors, the NOAEL was 1 ppm for rats with intact nasal epithelium.

Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
26-OCT-2000 (713)

Species: rat Sex: male

Strain: Fischer 344
Route of administration: inhalation
Exposure period: up to 18 months
Frequency of treatment: 5 d/w, 6 h/d
Post exposure period: none
Doses: ca. 0.0009, 0.0025, 0.0075, 0.012, 0.019 mg/l (0.7, 2.0, 6.0, 9.9, 14.9 ppm)
Control Group: yes, concurrent no treatment
NOAEL: = .0025 mg/l
LOAEL: = .0075 mg/l

GLP: no data
Test substance: other TS: formaldehyde; no data on purity of the compound

Method: The effects of inhalation exposure to the test substance with special regard to nasal proliferation was studied in 6 groups of 24 rats (5 treated and 1 control group). Six rats each per group were sacrificed after 3, 6, 12, and 18 months of exposure and examined nasal-histopathologically.
Result: At 14.9 ppm, hyperplasia, squamous metaplasia and hyperplasia of the nasal epithelium, individual cell necrosis, exfoliation and neutrophilic infiltration were observed. After exposure for 12 months and more, neutrophilic exudate, turbinate-to-turbinate or turbinate-to-wall adhesions, mucosal folding, and both degeneration and atrophy of the olfactory epithelium were found. An anterior posterior gradient of these lesions were determined; 71 putative preneoplastic lesions were recorded.
After exposure to 9.9 ppm, hyperplasia, squamous metaplasia and hyperplasia of the nasal epitelium, individual cell necrosis, exfoliation, neutrophilic infiltrate were observed, however, these findings were less pronounced than in the 14.9 ppm groups. One putative preneoplasic lesion was recorded.
Exposure to 6.0 ppm resulted in subtle individual nasal epithelial cell necrosis and incidental small foci of squamous cell metaplasia. Generally, no significant lesions were observed.
Nasal tumors were found in the rats exposed to 14.9 and 9.9 ppm. Locations of non-neoplastic lesions correlated with tumor sites. Thelack of marked lesions in the 6 ppm group was interpreted as an adaptive response. A steep non-linear increase of putative preneoplastic lesions comparable to tumor incidence was determined. According to the authors, the preneoplastic lesions could be differentated from adaptive squamous metaplasia and exhibited much higher cell proliferation.
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
26-OCT-2000 (488) (489) (490) (493) (495)

Species: rat Sex: male/female
Strain: Fischer 344
Route of administration: inhalation
Exposure period: up to 24 months
Frequency of treatment: 5 d/w, 6 h/d
Post exposure period: up to 6 months
Doses: ca. 0.002, 0.007, 0.018 mg/l (2.0, 5.6, 14.3 ppm)
Control Group: yes, concurrent no treatment

NOAEL: < .002 mg/l

GLP: no data
Test substance: other TS: formaldehyde; no data on purity of the compound

Method: The inhalation toxicity of formaldehyde was studied in 4 groups of 120 rats/sex. Interim sacrifices were carried out after 6, 12, 18, 27, and 30 months. Studies on general health (including neurofunction and opthalmoscopy), clinicalpathology, autopsy, unrinalysis, and histopathology of ca. 50 tissues were conducted.
Result: Exposure to 14.3 ppm resulted in increased mortality, reduction of body weight gain during the exposure period, dyspnea, rhinitis, epithelial dysplasia and squamous metaplasia (partly papillary or with cellular atypia) in all nasal levels but most pronounced in the anterior part of the nose, as well as mild hyperplasia, dysplasia, or squamous metaplasia of the proximal tracheal epithelium.
In the mid dose group, increased mortality and slightly decreased body weight gains during the exposure period (males only), rhinitis, epithelial dysplasia and squamous metaplasia in the anterior part of the nose (levels I-III) were observed. The incidence and severity of the lesions increased with exposure duration and showed a trend for recovery during the postexposure period.
In the low dose group, rhinitis, epithelial dysplasia and squamous metaplasia in the most anterior part of the nose (level I) were observed. The incidence and severity of the lesions were exposure-duration dependent; however, there was recovery during the post exposure period.

Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
26-OCT-2000 (384) (632)

Species: rat Sex: male
Strain: Wistar
Route of administration: inhalation
Exposure period: 3 days or 4 weeks (5 d/w)
Frequency of treatment: 4 or 8 h/d
Post exposure period: none
Doses: 0.006, 0.012, 0.025 mg/l (5, 10, 20 ppm)
Control Group: yes, concurrent no treatment

Method: other: cell proliferation measurement
GLP: no data
Test substance: other TS: formaldehyde; no data on purity of the compound

Method: The aim of the study was to find out whether treatment-related effects were determined by the total dose or by the exposure concentration. Thus, cell proliferation was measured after continuous and intermittent inhalation exposure of 10 rats/group to the test substance. Two groups were exposed daily to 5 or 10 ppm 8 hours/day for 3 days or 5 days/week for 4 weeks; another 2 groups were exposed to 10 or 20 ppm 4 hours/day in intervals of 30 minutes interrupted by 30 minutes without exposure for 3 days or 4 weeks (5 days/week); control rats remained untreated.

Cell proliferation (% labelled cells) was measured in nasoturbinates following a single intraperitoneal injection of 3H-thymidine either after 3 exposures or at the end of the study.

Result: In the group continuously exposed to 10 ppm (dose 80 ppmh/d), ca. 10-fold increase was found after both exposure periods. In the group intermittently exposed to 20 ppm (dose 80 ppmh/d, too), ca. 20-fold increase was observed after both exposure periods.
In the group continuously exposed to 5 ppm (dose 40 ppmh/d), ca. 3-fold increase was found after 3 exposures and doubling was observed at the end of the study. In the group intermittently exposed to 10 ppm (dose 40 ppmh/d, too), ca. 10-fold increase were found after 3 exposures and ca. 5-fold increase was determined at the end of the study.

According to the authors, these results suggest that the cell proliferation effect was concentration-related rather than "total dose"-related. A tendency of decreasing proliferation rate with duration of exposure was pointed out; however, no differentiation between histopathologically affected and unaffected regions was worked out.

Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
20-DEC-2002 (706)

Species: rat Sex: male
Strain: Fischer 344
Route of administration: inhalation
Exposure period: 6 weeks
Frequency of treatment: 5 d/w, 6 h/d
Post exposure period: none
Doses: ca. 0.0008, 0.0025, 0.0077, 0.012, 0.018 mg/l (0.69, 2.0, 6.2, 9.9, 14.8 ppm)
Control Group: yes, concurrent no treatment

Method: other: cell proliferation measurement
GLP: no data
Test substance: other TS: formaldehyde; no data on purity of the compound

Method: Cell proliferation in nasoturbinates after inhalation of formaldehyde (whole body exposure) was studied in groups of 36 rats. The rats were sacrificed after 1, 4, 9 days and after 6 weeks. Cell proliferation was measured in nasoturbinates after a single intraperitoneal injection of 3H-thymidine after the different exposure times; the unit length labelling index (ULLI) of 5 different locations was determined; 4-6 animals were evaluated for each time point and exposure concentration.

Result: ULLI was increased at concentrations of 6.2 ppm and more at most locations investigated and already after the first exposure. An anterior-posterior gradient was found at 6.2 ppm, but not at higher concentrations. No clearcut response was determined within the same exposure time groups except in posterior locations between 6.2 and 9.9 ppm. No clearcut effects on duration of exposure on the degree of cell proliferation was observed.

Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint

24-NOV-2000 (492) (495)

Species: rat Sex: male
Strain: Fischer 344
Route of administration: inhalation
Exposure period: up to 24 months
Frequency of treatment: 5 d/w, 6 h/d
Post exposure period: none
Doses: ca. 0.0009, 0.0025, 0.0075, 0.0123, 0.0185 mg/l (0.7, 2.0, 6.0, 9.9, 14.9 ppm)
Control Group: yes, concurrent no treatment

Method: other: cell proliferation measurement
GLP: no data
Test substance: other TS: formaldehyde; no data on purity of the compound

Method: Cell proliferation due to exposure to formaldehyde (0, 0.7, 2, 6, 10, or 15 ppm, 6 h/d, 5 days/week) was determined via measurement of unit length labelling index (ULLI). Six male rats/group (6 - 7 weeks old) each were sacrificed after 3, 6, 12, and 18 months of exposure and after osmotic pump infusion of 3H-thymidine for 5 days before the sacrifices. Scoring of inflammation by intraepithelial neutrophil counts was carried out.

Cross-sectional blocks of the nasal cavity were prepared at six levels. For histoautoradiographic detection of cells in S phase, adjacent sections were cut from each block and mounted on glass slides, dipped in Kodak NTB2 emulsion, exposed at -15°C for 10 weeks, developed, fixed, washed in water, and stained with hematoxylin and eosin. The nasal cavities from all unscheduled death animals, in addition to animals euthanize at the terminal sacrifice following 24 months of exposure, were routinely procesed for histopathology.
Histoautoradiographic cell proliferation data were expressed as the number of labeled cell profiles/mm basement membrane, i.e., ULLI.
An index of the number of cells at risk of mutation in each of the locations studies was then estimated from the total cell population in each site and the ULLI. The ULLI was found previously to be highly correlated with the true labeling index.
The comparability of ULLIs among formaldehyde concentrations, nasal sites, and across time was assessed using ANOVA. The statistical significance of pairwise comparisons to controls was assessed with Dunnett's test at a = 0.05 and a = 0.01.
Result: A significant increase of cell proliferation was observed at ca. 10 and 15 ppm (max ca. 11 and 16 fold increase, respectively). Cell proliferation was enhanced in metaplastic lesions and most pronounced in preneoplastic lesions. Additionally an increase of inflammation scores was observed at these dose levels. Nasal tumors were observed (see chapter 5.7). The authors concluded that sustained enhanced cell proliferation in the target organ was associated with nasal carcinogenesis.
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint

26-OCT-2000 (488) (489) (490) (492) (493) (494) (495)

Species: rat Sex: male
Strain: no data
Route of administration: inhalation
Exposure period: 6 month
Frequency of treatment: 5 h/d, 5d/w
Post exposure period: 1 month
Doses: 0.5 mg/m³
Control Group: yes

Method: Groups of 60 animals in a weight range of 180 -240 g were used. The exposure was performed in 700 l chambers (no further details on atmosphere generation and analytics). Clinical examination and body weight determination was performed. Several physiological and functional parameters were examined and necropsy as well as weighing and histopathology of selected organs was performed in groups of 15 animals (no details on methods).
Result: No changes were observed during clinical examination. The body weight development of the animals was not changed. Differences in some physiological and functional parameters were observed during the time course of exposure, some of which persisted to the end of post exposure observation. No changes in organ weights, macroscopic and microscopic pathology were observed.
According to the authors the tested concebntration did not present a NOAEL.
Reliability: (4) not assignable
Insufficient description of methods and results for this kind of study

15-MAY-2003 (501)

Species: rat Sex: male/female
Strain: Wistar
Route of administration: drinking water
Exposure period: 4 weeks
Frequency of treatment: continuously in the drinking water
Post exposure period: none
Doses: 5, 25, 125 mg/kg bw/d
Control Group: yes, concurrent no treatment
NOAEL: = 25 mg/kg bw

Method: other: no data
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: The effects of orally administered formaldehyde was studied in rats: 3 groups of 10 rats/sex were given the test substance in the drinking water (concentration in the drinking water was not given) and 20 rats/sex remained untreated. In another group of 10 rats/sex, water was restricted. Examinations on general health, clinical pathology, autopsy, and histopathology of the nose, upper gastrointestinal tract, liver, and kidneys were performed.

No systemic toxicity was observed. In the high dose group, a decrease in water and food consumption and in body weight gain was observed. A decrease of plasma protein,

hyperkeratosis, incidental hyperplasia of the forestomach epithelium, and focal atrophic gastritis in the glandular stomach was found. Water restriction resulted in a decrease in body weight gain and in changes in several hematological and clinicochemical parameters. No substance-related effects were observed in animals treated with 25 and 5 mg/kg/d. Thus, NOAEL was given as 25 mg/kg/d.
Test substance: formaldehyde; no data on purity of the compound
25-APR-2003 (651)

Species: rat Sex: male/female
Strain: Sprague-Dawley
Route of administration: drinking water
Exposure period: 91 days
Frequency of treatment: continuously in the drinking water
Post exposure period: none
Doses: 50, 100, 150 mg/kg bw/d
Control Group: yes, concurrent no treatment

Method: other: no data
GLP: no data
Test substance: no data

Remark: In preliminary two week studies gavage of 37.5, 75, 150 and 225 mg/kg body weight reduced weight development above 75 mg/kg whereas administration of 500, 1000 and 1500 ppm (i.e. 75, 150 and 225 mg/kg body weight) did only reduce water consumption.
Reliability: 3 (not reliable)
Result: The effects of orally administered formaldehyde was studied in 4 groups of 15 rats/sex (3 treated groups, 1 control group; concentration in the drinking water was not given). Examinations on general health, clinical pathology, autopsy,and histopathology of several organs were performed.

Administration of the high dose resulted in reduction of both water consumption and body weight gain in males and females. In the mid dose group, reduction of waterconsumption and body weight gain was observed in males only.In the low dose group, decrease in water consumption was recorded.
Test substance: formaldehyde; no data on purity of the compound
25-APR-2003 (363)

Species: rat Sex: male
Strain: Wistar
Route of administration: drinking water
Exposure period: 32 weeks
Frequency of treatment: continuously in the drinking water
Post exposure period: none
Doses: ca. 450 mg/kg bw/d (5000 ppm)
Control Group: yes

Method: other: no data
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: The study was part of an initiation-promotion study; 10 rats were administered the test substance, 10 rats remained untreated. Examinations on general health, autopsy, and

histopathology of stomach and duodenum were performed.

Administration of the test substance resulted in reduction of body weight gain. Diffuse proliferative changes in the superficial epithelium of the glandular stomach, erosions and ulcers along the liming ridge of fundic mucosa was observed. For carcinogenic effects see chapter 5.7.

Test substance: formaldehyde; no data on purity of the compound

25-APR-2003 (639)

Species: rat Sex: male
Strain: Wistar
Route of administration: drinking water
Exposure period: 104 weeks
Frequency of treatment: continuously in the drinking water
Post exposure period: none
Doses: 10, 50, 300 mg/kg bw/d (200, 1000, 5000 ppm in the drinking water)
Control Group: yes
NOAEL: = 10 mg/kg bw

Method: other: no data
GLP: no data
Test substance: no data

Result: The effects of orally administered formaldehyde was studied in 4 groups of 20 rats/sex (3 treated groups, 1 control group). Interim sacrifices were carried out with 6 animals/sex/group after 12 and 18 months. Examinations on general health, clinical pathology, autopsy, and histopathology of several organs were performed.

In the high dose group (5000 ppm), poor general state, reduction of body weight gain and both food and water consumption (ca. 50%), increased mortality (ca. 50% after 12 months), and changes in various clinical parameters were recorded. Lesions of the stomach were most pronounced after 12 months of exposure: squamous and basal cell hyperplasia and hyperkeratosis (70-100%), erosions/ulcers and submucosal cell infiltration (20-30%) in the forestomach; glandular hyperplasia, erosions/ulcers (70-100%) and submucosal cell infiltration (30-50%) in the glandular stomach were found. A high incidence of renal papillary necrosis was observed in male and female animals (about 50% versus 0-10% in the other groups). This finding is ascribed to the dehydration caused by the considerable decrease of liwuid consumption.
Administration of 1000 ppm resulted in forestomach hyperkeratosis in several animals after 18 and 24 months. According to the authors, NOAEL was 10 mg/kg/d; for carcinogenicity see chapter 5.7.

Test substance: formaldehyde; no data on purity of the compound
Reliability: (2) valid with restrictions
More details are reported in the study by Til et al. 1989 and the outcome is comparable.
Flag: Critical study for SIDS endpoint

15-MAY-2003 (655)

Species: rat Sex: male
Strain: Wistar

Route of administration: drinking water
Exposure period: 104 weeks
Frequency of treatment: continuously in the drinking water
Post exposure period: none
Doses: 1.2, 15, 82 mg/kg bw/d (males), 1.8, 21, 109 mg/kg bw/d (females); i.e. average concentration of 20, 260, 1900 mg/l in the drinking water
Control Group: yes
NOAEL: ca. 260 mg/l

GLP: no data
Test substance: other TS: formaldehyde; no data on purity of the compound

Method: Formaldehyde was administered in the drinking water to groups of 70 male and 70 female Wistar rats for up to 24 months. Survivors of subgroups of ten rats/sex/group each were killed after 12 or 18 months. The mean formaldehyde doses administered were 0, 1.2, 15 or 82 mg/kg body weight/day for males, and 0, 1.8, 21 or 109 mg/kg/day for females.
At the beginning of the study the rats were 5 weeks old.
Hematology and clinical chemistry: Blood samples were collected from the tail tips of ten rats/sex/group in weeks 26 and 103 and were examined.
Urinalysis: In weeks 27, 52, 78 and 104, ten rats/sex/group were sampled.
Pathology: Before the start of the study, two subsets each of 10 male and 10 female rats and one of 50 rats of each sex were defined in each group. The survivors of the first (10 rats/sex/group), second (10 rats/sex/group) and third (50 rats/sex/group) subsets were killed in weeks 53, 79 and 105, respectively. The following organs of each rat were weighed and the organ to body weight ratios were calculated: adrenals, brain, heart, kidneys, liver, ovaries, pituitary, spleen, testes and thyroid. Samples of these organs and of the skin, skeletal muscle, mammary glands (females), Harderian and exorbital lachrymal glands, nose, lungs, aorta, parotid, submandibular and sublingual salivary glands, oesophagus, forestomach, glandular stomach, small and large intestine, pancreas, urinary bladder, epididymides, prostate, uterus, sternum, mesenteric and axillary lymph nodes, spinal cord, sciatic nerve and eyes. Detailed microscopic examinations were carried out.
In addition, the adrenals, kidneys, spleen, testes, thyroid, ovaries, pituitary and mammary glands (females) of the rats of subset three (killed in week 105) of the low- and mid-dose groups were examined .
The laboratory determinations and organ weights were evaluated by a one-way analysis of variance, followed by Dunnett's multiple comparison tests.
The mortality incidences and the histopathological changes were examined by Fisher's exact probability test (two-sided).
Result: In the high dose group (1900 mg/l; 82 and 109 mg/kg/d for males and females, respectively), decreased water (40%) and food consumption, depressed body weight gain, and minor changes in urinary densitiy and volume were recorded.

Increased incidence of papillary epithelial hyperplasia in the forestomach (60-90%) and chronic atrophic gastritis in the glandular stomach (100%) were observed. After 24 months of exposure, additionally hyperkeratosis (50-70%) and ulceration (15%) in the forestomach, focal ulceration (20%) and glandular hyperplasia in the glandular stomach (30-40%),and renal papillary necrosis (40%) were found. The forestomach lesions were mostly located in the vicinty of the limiting ridge; according to the authors, the renal papillary necrosis was due to decreased water consumption.

In the mid dose group, (260 mg/l; 15 and 21 mg/kg/d for males and females, respectively), a slight reduction of water consumption was observed. Thus, according to the authors, a concentration of 260 mg/l drinking water was considered to be the NOAEL. No evidence of carcinogenicity was found (see chapter 5.7).

Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
25-APR-2003 (651)

Species: rat Sex: male
Strain: Wistar
Route of administration: gavage
Exposure period: 4 weeks
Frequency of treatment: 5d/w
Post exposure period: no
Doses: 20, 40, 80 mg/kg bw/day

GLP: no
Test substance: other TS: formaldehyde, no further data

Method: A 28% aqueous solution of formaldehyde was tested.
Clinical examination, body weight determination
Blood: hemoglobin concentration, hematocrit, erythrocyte count total and differential leukocyte counts, albumin total protein IgG, IgA, IgM
Immune-organ weights and cellularity: spleen, thymus, mesenteric and inguinal lymphnodes
Pathology: weights: liver, kidneys, lung, brain, testes, prostate, adrenals, pituitary, heart, spleen, thymus, mesenteric and popliteal lymph node; Histopathology of lung, liver spleen, kidney, thymus, lymphnodes, small and large intestine
Immune-function: Serum hemagglutinin response, plaque forming cell assay, microbicidal and phagocytic activity

Remark: The authors interpret the findings as possible immunosuppressive effects. They indicate however that other investigators (Dean et al. 1984 and Adams et al. 1987) reported that 3 week inhalation exposure to 15 ppm did not influence the immune status of mice.

The findings observed in the animals treated with 80 mg/kg indicate some overall toxicity, which with some probability might have been cause by irritation of the gastrointestinal tract (no histopathology of stomach performed), leading to decreased water (increased hematocrit) and food consumption (decreased body weight) in the animals (data not available). This would mean that the effects are secondary to primary irritation and not caused by systemic availability of the substance.

The effects reported at 20 and 40 mg/kg are either without dose-response relationship or of doubtful biological significance.

Therefore the results of the study are should not be interpreted as presenting evidence of an immunotoxicity potential.

Result: 8% decreased final body weight at 80 mg/kg
Increased hematocrit at 40 and 80 mg/kg accompanied by some minor changes in red and white blood cell parameters at 80 mg/kg
Non-dose dependent slight increase in lymph node weights, but cellularity of lymphoid organs not influenced; dose-dependent reduction of antibody response (IgG, IgM), reduced phagocytic activity of doubtful biological significance.
Dose dependent depression of hemagglutinin titers
Some changes at 80 mg/kg in liver (vacuolization of hepatocytes) and spleen histology (e.g. narrowed thymus-dependent zones of periarterial lymphoid sheaths)

Reliability: (2) valid with restrictions
No guideline study, No GLP

Flag: Critical study for SIDS endpoint

25-APR-2003 (680)

Species: rat Sex: no data
Strain: other: no data
Route of administration: i.p.
Exposure period: single or 4 daily doses
Post exposure period: no data
Doses: 0.02 ml of a 2% solution (ca. 0.4 mg/dose)
Control Group: no data specified

Method: other: no data
GLP: no
Test substance: no data

Result: A single intraperitoneal injection to neonatal rats resulted in a decrease of cellular activity in some regions of the hypothalamus and in an accumulation of granula in neural cytoplasm. Furthermore, the nuclear volumina of adrenal cells were incresed. The latter finding was also observed after 4 treatments of the same kind. Additionally, in rats treated 4 times, pronounced degeneration and cellular atrophy of the hypothalamus was observed. Only secondary literature; no further data.

Test substance: formaldehyde; no data on purity of the compound

Reliability: (3) invalid

28-NOV-1997 (532)

Species: rat Sex: male
Strain: other: Chalres foster
Route of administration: i.p.
Exposure period: 30 days
Frequency of treatment: once per day
Post exposure period: no
Doses: 5, 10, 15 mg/kg bw

Method: other
GLP: no

Test substance: other TS

Method: Determination of body and testes weights, serum testosterone and histology of testes
Remark: Clear signs of general toxicity (body weight loss)
Result: Non-dose dependent, statistically significant reduction in body weight gain (to about 70% of control), testes weights (to about 90% of control) and structural and functional impairment of Leydig cells.
Test substance: Formaldehyde (no details)

Reliability: (3) invalid
unphysiological route of application with high general toxicity
25-APR-2003 (140)

Species: rat Sex: male
Strain: Wistar
Route of administration: i.p.
Exposure period: 30 days
Frequency of treatment: once per day
Post exposure period: no
Doses: 10 mg/kg
Control Group: other: yes (distilled water)

Method: other
GLP: no
Test substance: other TS

Method: Sperm count, motility and viability determined in minced caudae epididymides
Remark: No description if general signs of toxicity or irritation of the abdominal cavity was present.
Result: Statistically significant reduction of sperm count, viability and motility and in prostate DNA content
Test substance: Formaldehyde (no details)
Reliability: (3) invalid
unphysiological route of application with high general toxicity
10-SEP-2001 (451)

Species: mouse Sex: female
Strain: Swiss
Route of administration: inhalation
Exposure period: 4 days
Frequency of treatment: 4 h/d
Post exposure period: none
Doses: ca. 0.006 mg/l (5 ppm)
Control Group: yes, concurrent no treatment

Method: other: no data
GLP: no data
Test substance: no data

Remark: Reliability: 3 (not reliable)
The results are biologically not plausible, no clear description and explanations were given by the author.

Result: The effect of formaldehyde inhalation on alveolar macrophage Fc-mediated phagocytosis was studied. According to the authors, exposure to 5 ppm formaldeyde alone had no effect on phagocytosis.

Coexposure with 0.01 mg/l (10 mg/m3) carbon black reversibly decreased phagocytosis but did not alter bacterial elimination in the lung. Four-hour single exposure to 15, but not to <=10 ppm decreased phagocytosis; 18-h exposure to 1 but not to 0.5 ppm followed by bacterial challenge and 4-h exposure to decreased bacterial elimination in the lung.
Test substance: formaldehyde; no data on purity of the compound
16-JUN-1998 (357)

Species: mouse Sex: female
Strain: B6C3F1
Route of administration: inhalation
Exposure period: 3 weeks
Frequency of treatment: 5 d/w, 6 h/d
Post exposure period: none
Doses: ca. 0.018 mg/l (14.8 - 15.0 ppm)
Control Group: yes, concurrent no treatment

Method: other: no data
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: The effects of formaldehyde were studied in a total of 255 mice. Three experimental runs were carried aout at dose levels of 14.8, 14.8, and 15.0 ppm. Examinations on general health, thymus and spleen weights, hematology, spleen and bone marrow cellularity and colony-forming activity, cell mediated immunity by 4 different lymphocyte function tests, function tests with peritoneal macrophages and host susceptibility studies with Listeria monocytogenes and 2 lines of transplantable tumor cells were carried out. According to the authors, enhanced resistance to Listeria monocytogenes, and increased competence of peritoneal macrophages for release of hydrogen peroxide were observed.
Test substance: formaldehyde; no data on purity of the compound
04-JUL-1997 (6) (176)

Species: mouse Sex: no data
Strain: B6C3F1
Route of administration: inhalation
Exposure period: up to 10 days
Frequency of treatment: 6 h/d, 1, 3 and 5 d; 36 ppmh/d as 3 ppm x 12 h, 6 ppm x 6h, 12 ppm x 3h for 10 days
Post exposure period: none
Doses: 0, 0.5, 2, 6, 15 ppm or 3, 6 and 12ppm
Control Group: other: yes, concurrent

Method: other: cell proliferation measurement
GLP: no data
Test substance: no data

Remark: Examinations:
measurements of cell proliferation (% labeled cells) in nasoturbinate levels A (anterior) and B (mid anterior)
single i.p. injection of H-thymidine 2 or 18 h after end of exposure

Findings:
fold increase of LI in level B
1 d/15 ppm: about 8
3 d/15 ppm: about 8
5 d/15 ppm: about 13
no increase at 6, 2 and 0.5 ppm; labelling 18 h after end of exposure yielded higher fractions of labeled cells in controls and exposed animals (authors: circadian variations)

C x T study
level A: concentration dependent about 8, 4 and 1.4 fold increase of proliferation after 10 days
level B: no increase in proliferation rate

Authors try to explain inverse proportionality of proliferation versus concentration by high suceptibility of mice to sensory irritation; LI of control groups [%]
level B:
pulse 2 h post exp.: 0.12
pulse 18 h post exp.: 0.27
level A:
1.24
data for rats in seperate entry

Test substance: formaldehyde; no data on purity of the compound
Reliability: (2) valid with restrictions
20-MAY-1999 (631) (632) (633)

Species: mouse Sex: male/female
Strain: B6C3F1
Route of administration: inhalation
Exposure period: 13 weeks
Frequency of treatment: 5 d/w, 6 h/d
Post exposure period: none
Doses: ca. 0.002, 0.005, 0.012, 0.025, 0.050 mg/l (1.96, 4.1, 10.1, 20.4, 40.3 ppm)
Control Group: yes, concurrent no treatment
NOAEL: = .002 mg/l
LOAEL: = .005 mg/l

GLP: no data
Test substance: other TS: formaldehyde; no data on purity of the compound

Method: Groups of 10 male and 10 female B6C3F1 mice were exposed to 0, 2, 4, 10, 20, or 40 ppm of formaldehyde vapor 6 h/day, 5 days/week for 13 weeks.
Male and female C57BL/6 x C3H F1 mice from Charles River Breeding Laboratory were used.
The mice were 6 weeks of age at start of study. Groups of 10 male and 10 female mice were exposed 6 h/day, 5 days/week, excluding holidays, for 13 weeks at target concentrations of 2, 4, 10, 20, or 40 ppm of formaldehyde. The control group was exposed to filtered chamber air. Clinical observations were made twice daily and body weights were recorded weekly throughout the study. All mice were necropsied. Histological

examinations were performed on nasal cavity, larynx, trachea, lung, ovaries, uterus, larynx and trachea and lung.

Result: At the highest dose level (40.3 ppm), 80% lethality was observed from exposure week 5-6 onwards. Impairment of general health was recorded. In all animals, rhinitis, and squamous metaplasia of the nose, the larynx, and the trachea was observed. Some animals showed epithelial hyperplasia, purulent inflammation, and submucosal fibrosis of the trachea; bronchial squamous metaplasia, inflammation, and submucosal fibrosis were found in the lungs of some animals. Hyperplasia of ovaries and uterus was observed.
Exposure to 20.4 ppm resulted in an impairment of general health, rhinitis, and squamous metaplasia of the nose in alle animals; squamous metaplasia of the larynx and trachea and epithelial hyperplasia of the larynx was observed in some animals of this group.
In the 10.1 ppm group, squamous metaplasia was observed in in all animals; some males showed rhinitis.
Squamous metaplasia was observed in one male exposed to 4.1 ppm.
Exposure to 1.96 ppm did not result in any abnormalities.
According to the authors, death, impairment of general health, and findings in the female genital tract were related to general debility and weight loss rather than a direct target organ effect of formaldehyde.

Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
18-DEC-2000 (458)

Species: mouse Sex: male/female
Strain: B6C3F1
Route of administration: inhalation
Exposure period: up to 24 months
Frequency of treatment: 5 d/w, 6 h/d
Post exposure period: up to 6 months
Doses: ca. 0.0025, 0.007, 0.018 mg/l (2.0, 5.6, 14.3 ppm)
Control Group: yes, concurrent no treatment
NOAEL: = .0025 mg/l
LOAEL: = .007 mg/l

GLP: no data
Test substance: other TS: formaldehyde; no data on purity of the compound

Method: The effects of formaldehyde were studied in groups of ca. 120 mice/sex/group. Mice were sacrificed after month 6, 12, 18, 24, 27, and 30 of the study. Examinations on general health (including neurofunction and ophthalmoscopy), clinical pathology, urinalysis, autopsy, and histopathology of about 50 tissues were performed.

Result: An exposure-independent increase in mortality due to infections of the genitourinary tract was observed in males. At the highest dose level (14.3 ppm), a trend to decreased body weight gains was noted in the last third of exposure. Rhinitis, epithelial dysplasia and squamous metaplasia was observed from month 12 onwards. Increased incidence and severity of the findings with exposure duration and a tendency for recovery during the postexposure period was recorded.

In the mid dose group (5.6 ppm), epithelial dysplasia was observed in a few animals.
No substance-related effects were observed in mice exposed to 2.0 ppm.
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
26-OCT-2000 (384)

Species: mouse Sex: male
Strain: B6C3F1
Route of administration: gavage
Exposure period: 5 days
Frequency of treatment: daily
Post exposure period: 5 weeks
Doses: 100, 250, 500 mg/kg/d
Control Group: yes, concurrent vehicle

Method: other: no data
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
These experiments were part of a sperm morphology study.
Result: Formalin (37% formaldehyde, 10% methanol in water) was administered to groups of 10 mice for 5 consecutive days; 5 control mice were given distilled water. Five weeks after treatment, the mice were sacrificed.
According to the authors, application of the mid and high dose was lethal to all mice treated.
Test substance: formalin; 37% formaldehyde; no data on purity of the compound
28-NOV-1997 (694)

Species: mouse Sex: male/female
Strain: other: hairless (hr/hr, Oslo)
Route of administration: dermal
Exposure period: 60 weeks
Frequency of treatment: twice a week
Post exposure period: none
Doses: 2, 20 mg/animal
Control Group: no data specified

Method: other: no data
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: The effects of dermally administered formaldehyde was studied in 16 mice/sex; 200 ul of a 1 or 10% aqueous solution of the test substance (i.e. ca. 2 and 20 mg/animal,respectively) were applied. Examinations on general health, autopsy, and histopathology of brain, nasal mucosa, lungs, and skin and other tumors were performed.

Application of the 10% solution resulted in slight hyperplasia of the epidermis; skin ulcers were observed in few animals. No systemic toxicity was reported.
This study was part of an initiation-promotion study.
Test substance: formaldehyde; no data on purity of the compound

15-APR-1998 (355)

Species: mouse Sex: female
Strain: CD-1
Route of administration: dermal
Exposure period: 2-3 weeks
Frequency of treatment: daily
Post exposure period: none
Doses: 3 - 300 mg/kg
Control Group: no data specified
NOAEL: 3 mg/kg bw
LOAEL: 15 mg/kg bw

GLP: no data
Test substance: other TS: formaldehyde; no data on purity of the compound

Method: The effects of dermally administered formaldehyde was studied in 30 mice; the test substance was dissolved in acetone/water 50:50; 100 ul of 0.1, 0.5, 1, 2, 5, and 10% solutions (i.e. 0.1-10 mg/animal, i.e. 3-300 mg/kg) were applied for 2-3 weeks. Examinations on general health with special regard for skin irritation were performed.

This study was a pre-test for an initiation-promotion study. No further data.

Result: No systemic toxicity was observed. Administration of a 10% solution resulted in fissuring, sloughing and papules at the application site (moderate irritation) after 2-4 treatments. In mice exposed to 5 and 2%, mild to moderate irritation occurred after 4-5 treatments. A solution of 1% caused mild irritation beginning during the second week. A concentration of 0.5% caused slight irritation which was reversible during weekends.

Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint

26-OCT-2000 (407)

Species: mouse Sex: male/female
Strain: other
Route of administration: dermal
Exposure period: 26 weeks
Frequency of treatment: 3 times per week
Post exposure period: 26 weeks
Doses: 125 mg/kg (single dose) followed by 2.5, 12.5, 25 mg/kg/application

Control Group: no data specified
LOAEL: 3 mg/kg bw

GLP: no data
Test substance: other TS: formaldehyde; no data on purity of the compound

Method: The effects of dermally administered formaldehyde was studied in 30 mice; the test substance was dissolved in acetone/water 50:50. At the beginning of the study, 50 ul of a 10% solution (5 mg/animal = 125 mg/kg) was applied. Thereafter, 100 ul of a solution containing 0.1, 0.5, or 1% (2.5, 12.5, or 25 mg/kg, respectively) was applied 3 times a week for 26 weeks. After termination of exposure, the mice were post-observed for additional 26 weeks.

Examinationson general health and skin nodules were performed.
Result: No influence on mortality and body weight was found; minimal irritation of skin was observed.
This study was part of an initiation-promotion study (see chapter 5.7).
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
26-OCT-2000 (407)

Species: mouse Sex: male
Strain: B6C3F1
Route of administration: i.p.
Exposure period: 5 days
Frequency of treatment: daily
Post exposure period: 5 weeks
Doses: 100 mg/kg/d
Control Group: yes, concurrent vehicle

Method: other: no data
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
These experiments were part of a sperm count study.
Result: Formalin (37% formaldehyde, 10% methanol in water) was administered to 10 mice for 5 consecutive days; 5 control mice were given distilled water.
According to the authors, i.p. application of the test substance was lethal to all mice treated.
Test substance: formalin; 37% formaldehyde; no data on purity of the compound
28-NOV-1997 (694)

Species: rabbit Sex: no data
Strain: other: no data
Route of administration: other: topical application to oral mucosa ("oral tank")
Exposure period: 10 months
Frequency of treatment: 5 times a weeks for 90 min
Post exposure period: 1 month
Doses: 3% aqueous solution
Control Group: yes, concurrent vehicle

Method: other: no data
GLP: no data
Test substance: no data

Remark: According to the authors, "oral tank" was a stomatological device to hold viscose sponges in close contact to oral mucosa over prolonged periods of time.
Reliability: 3 (not reliable)
Result: The effects of topical administration of the test substance to oral mucosa using "oral tanks" was investigated using 20 rabbits (10 untreated controls, 4 "oral tank" controls = vehicle controls, 6 treated). A 3% aqueous solution was applied; histopathology of oral mucosa was performed.
Treatment with the test substance resulted in severe epithelial hyperplasia; visible leukoplakia was found in 2/6 animals and was histologicallly characterized by "preneoplasic unrest".

According to the authors, one lesion was classified as "carcinoma in situ". In "oral tank" controls, moderate hyperplasia with parakeratosis by mechanical irritation was observed.
Test substance: formaldehyde; no data on purity of the compound
04-JUL-1997 (497)

Species: Syrian hamster Sex: male
Route of administration: inhalation
Exposure period: 26 weeks
Frequency of treatment: 7 d/w, 22 h/d
Post exposure period: none
Doses: ca. 0.0002, 0.0012, 0.0037 mg/l (0.19, 0.98, 2.95 ppm)
Control Group: yes, concurrent no treatment
NOAEL: > .0037 mg/l

Method: other: no data
GLP: no data
Test substance: no data

Result: The effects of formaldehyde were studied in 5 groups of 10 hamsters/sex (3 treated groups and 2 untreated control groups). Examinations on general health, autopsy, measurements of organ weights (heart, kidneys, liver, adrenals) and histopathology of the nose, trachea and lungs were performed.
No substance-related findings were recorded.
Test substance: formaldehyde; no data on purity of the compound
Reliability: (2) valid with restrictions
28-NOV-1997 (576)

Species: Syrian hamster Sex: male
Strain: other: no data
Route of administration: inhalation
Exposure period: lifetime
Frequency of treatment: 5 h/d, 5 d/w (10 ppm) or 5 h/d, 1 d/w (30 ppm)
Post exposure period: none
Doses: ca. 0.012 mg/l (10 ppm) or 0.037 mg/l (30 ppm)
Control Group: yes, concurrent no treatment

Method: other: no data
GLP: no data
Test substance: no data

Result: The effects of formaldehyde on the respiratory tract were studied in 88 animals exposed to 10 ppm and 50 animals exposed to 30 ppm, 132 and 50 control animals remained untreated.Autopsy and histopathology or subgross stereomicroscopical examination of the respiratory tract was performed. At 10 ppm a reduced survival time (50% mortality between 80 and 90 weeks of age) was recorded. A 5% incidence of nasal epithelial hyperplasia and metaplasia was observed. No changes were found in the control group. At 30 ppm fifty percent mortality between 70 or 80 weeks of age was observed in both control and treated group.

The analytical concentration of the test substance was not reported.
Test substance: formaldehyde; no data on purity of the compound
Reliability: (2) valid with restrictions

17-JUN-1998 (168)

Species: dog Sex: male/female
Strain: Beagle
Route of administration: drinking water
Exposure period: 91 days
Doses: 0, 50, 75, 100 mg/kg bw

GLP: no data
Test substance: other TS

Remark: In prelimary studies food containing concentrations resulting in higher dosages than 100 mg/kg were not applicable (food rejection or regurgitation)
Result: Examinations:
General health, clinical pathology, autopsy, histopathology of several organs (digestive tract not mentioned)

Findings:
100 mg/kg - decrease in drinking water and food consumption and reduced body weight development

75 mg/kg - decrease in drinking water and food consumption

50 mg/kg - decrease in drinking water and food consumption
Test substance: formaldehyde; no data on purity of the compound
Reliability: (3) invalid
prelimnary study

25-APR-2003 (363)

Species: guinea pig Sex: male
Strain: Hartley
Route of administration: inhalation
Exposure period: 8 weeks
Frequency of treatment: no data specified
Post exposure period: none or 4 weeks
Doses: ca. 0.001, 0.011 mg/l (0.9, 8.8 ppm)
Control Group: yes, concurrent no treatment
NOAEL: < .001 mg/l
LOAEL: = .001 mg/l

Method: other: no data
GLP: no data
Test substance: no data

Result: The effects of formaldehyde were studied in groups of 20 animals. The guinea pigs were sacrificed either immediately after termination of exposure or 4 weeks later. Examinations on general health, nasal and tracheal mucosal clearance velocities, biochemical parameters of lung lavage fluid and lung homogenate, and histopathology of nasal cavitiy, trachea, lung and 12 other tissues were performed.
In the high dose group, behaviour indicating eye and nose irritation, a tendency to increased mucous clearance during exposure and decreased tracheal mucosal clearance during exposure which reversed to increased velocities after the end of the exposure period was recorded. Hyperkeratosis of squamous epithelium and focal squamous metaplasia of the respiratory epithelium in the anterior half of the nasal cavity which resolved to slight hyperkeratosis at the end of the recovery period.

In the low dose group, hyperkeratosis of squamous epithelium was observed.
Test substance: formaldehyde; no data on purity of the compound
Reliability: (2) valid with restrictions
28-NOV-1997 (463)

Species: guinea pig Sex: no data
Strain: no data
Route of administration: inhalation
Exposure period: 1 month
Frequency of treatment: 5h/d, 5d/w
Post exposure period: no
Doses: 0.5 mg/m³
Control Group: yes

Method: Groups of 15 animals were used. The exposure was performed in 700 l chambers concurrent with the rats (see seperate entry, no further details on atmosphere generation and analytics). Blood proteins and histamine as well as neuraminic acid levels were examined (no details on methods).
Result: There were non statistically significant tendencies of an increase in globulins, histamin and neuraminic acid as well as decrease in albumin.
Reliability: (4) not assignable
Insufficient description of methods and results for this kind of study
15-MAY-2003 (501)

Species: monkey Sex: male
Strain: other: Rhesus
Route of administration: inhalation
Exposure period: 1 or 6 weeks
Frequency of treatment: 5 d/w, 5 h/d
Post exposure period: none
Doses: ca. 0.007 mg/l (6 ppm)
Control Group: yes, concurrent no treatment

Method: other: cell proliferation measurement
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: Cell proliferation due to exposure to formaldehyde was determined via measurement of unit length labelling index (ULLI) in nasoturbinates, larynx, trachea, and carina and measurement of the Labelling Index (LI) of the terminal bronchioles. Three animals/group each were exposed to 6 ppm of the test substance for 1 or 6 weeks, then a single dose of 3H-thymidine was injected intraperitoneally.

After exposure for 1 week, an increase in proliferation of transitional and respiratory epithelium of the nose was observed; the degree of the increase was dependent on the localisation (max. 14-fold); a clear anterior-posterior gradient of labelling was recorded. A ca. 2-3 fold increase was found in the larynx, trachea, and carina.
After 6 weeks of exposure, an increase of proliferation of transitional, respiratory, and olfactory epithelium of the nose was observed (depending on the location; max. 16-fold).

A 7-9 fold increase was found in the larynx, trachea, and carina, however these alterations were not statistically significant due to huge variations.
No increase in proliferation was found in maxillary sinuses and terminal bronchioles.
Test substance: formaldehyde; no data on purity of the compound
07-MAY-1998 (491) (495)

Species: monkey Sex: male
Strain: other: Rhesus
Route of administration: inhalation
Exposure period: 1 or 6 weeks
Frequency of treatment: 5 d/w, 5 h/d
Post exposure period: none
Doses: ca. 0.007 mg/l (6 ppm)
Control Group: yes, concurrent no treatment

GLP: no data
Test substance: other TS: formaldehyde; no data on purity of the compound

Method: Nine young adult male rhesus monkeys (Macaca mulata), aged 4 - 5 years, weighing 6 - 7 kg, were used.
Exposures were conducted during the day in 15 cubicmeter stainless steel and glass inhalation chambers.
The monkeys were randomly divided into three experimental groups of three animals per group. Group one (control) was sham-exposed to biologically filtered air for 6 weeks, 6 hours per day, 5 days per week. Group two was exposed to 6 ppm formaldehyde for 1 week (i.e. 5 days), 6 hours per day. Group three was exposed to 6 ppm formaldehyde for 6 weeks, 6 hours per day, 5 days per week.
The following tissues were collected from each animal: adrenals, bone marrow (sternum), duodenum, esophagus, eyes, gallbladder, heart, kidneys, liver, lymph nodes (bronchial, mesenteric, ileac), pancreas, stomach, spleen, and tongue.
All tissues were examined by light microscopy.
Result: Exposure to the test substance resulted in ocular irritation and altered breathing pattern. In animals exposed for 1 week, loss of cilia and globlet cells, mild epithelial hyperplasia and squamous metaplasia, inflammation with a clear anterior-posterior gradient was observed in the respiratory epithelium of the nose; in larynx, trachea , andcarina, loss of cilia was found. In animals exposed for 6 weeks, mild hyperkeratosis of the squamous epithelium of thenose, and erosions, epithelial hyperplasia, and inflammationof the transitional epithelium of the nose was observed. In the respiratory epithelium of the nose, the same lesions were found after 1 week of exposure, however, these lesions were more extensive and found also in the posterior parts of the nasal cavity. The lesions were most pronounced in the middle turbinate. In larynx, trachea, and carina, loss of cilia and globlet cells, mild epithelial hyperplasia, and early squamous metaplasia were observed; these lesions were of a higher extent than in the 1-week group. No substance-related lesions were found int the maxillar sinuses or in organs outside the respiratory tract.

The results of concentration measurement of the inhalation atmosphere were not reported; no tabulation or grading of the histopathological findings.

Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
26-OCT-2000 (491) (495)

Species: monkey Sex: male
Strain: other: Cynomolgus
Route of administration: inhalation
Exposure period: 26 weeks
Frequency of treatment: 7 d/w, 22 h/d
Post exposure period: none
Doses: ca. 0.0002, 0.0012, 0.0037 mg/l (0.19, 0.98, 2.95 ppm)
Control Group: yes, concurrent no treatment
NOAEL: = .0012 mg/l
LOAEL: = .0037 mg/l

GLP: no data
Test substance: other TS: formaldehyde; no data on purity of the compound

Method: The experimental animals were exposed to test atmospheres of formaldehyde gas at nominal concentrations of 0 ppm (groups I and V), 0.20 ppm (group II), 1.0 ppm (group III), or 3.0 ppm (group IV). The exposures were conducted 22 hr/day, 7 days/week for 26 weeks.
The test animals were male Cynomolgus monkeys (Primate Imports, Port Washington, N.Y.), male and female Fischer-344 rats and male and female Syrian golden hamsters.
All animals were weighed weekly, at which time they were also given complete physical assessments. Following the 6 months of exposure, all animals were killed.
Weights of the adrenals, heart, kidneys and liver were measured. The lungs, nasal turbinates, and trachea were fixed.
Four sections of lung, one section of trachea, and four sections of nasal turbinates were prepared and examined by light microscopy. In addition, sections from the respiratory system of randomly selected rats (five/sex/group) from group I (control) and III (1.0 ppm exposure group) were examined by electron microscopy.
For multiple group comparisons, Bartlett's test was done to determine if groups had equal variance. If the variances were equal, the standard one-way ANOVA using the F distribution to assess significance was used. If significant differences among the means were indicated, Dunnett's test was used to determine which means were significantly different from control. If a non-parametric procedure for testing equality of means was needed, the Kruskal-Wallis test was used, and if differences were indicated, a summed rank test (Dunn) was used to determine which treatments differed from control.
Result: In the high dose group monkeys, increased incidence of hoarseness, congestion, nasal discharge, and squamous metaplasia of the respiratory epithelium was observed; the lesions were most pronounced in the middle region of the nasoturbinate. Rhinits was randomly distributed in all 5 groups. No detailed tabulation of data.
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
20-DEC-2002 (576)

5.5 Genetic Toxicity 'in Vitro'

```
Type:                     other: in vitro gene mutation - prokaryotes (bacteria)
System of testing:        Salmonella typhimurium TA98, TA100, UTH8413, UTH8414
Concentration:            0.02 - 0.5 mg/plate
Metabolic activation:     with and without
Result:                   positive

Method:            other: Ames test
   GLP:            no data
Test substance:    no data

Remark:            Preincubation Test with and without metabolic activation
                   with S-9 mix prepared from liver homogenate of Aroclor
                   pretreated Sprague-Dawlwey rats.
                   Reliability: 2 (reliable with restrictions)
Test substance:    formaldehyde; no data on purity of the compound
10-AUG-1999                                                          (152) (153)

Type:                     other: in vitro gene mutation - prokaryotes (bacteria)
System of testing:        Salmonella typhimurium TA98, TA100, TA102
Concentration:            0.0001 - 0.03 mg/plate
Metabolic activation:     without
Result:                   positive

Method:            other: Ames test
   GLP:            no data
Test substance:    no data

Remark:            Fluctuation Test without metabolic activation.
                   Reliability: 2 (reliable with restrictions)
Test substance:    formaldehyde; no data on purity of the compound
13-MAY-1998                                                              (418)

Type:                     other: in vitro gene mutation - prokaryotes (bacteria)
System of testing:        Salmonella typhimurium, no data on strain
Concentration:            no data
Metabolic activation:     without
Result:                   negative

Method:            other: Ames test
   GLP:            no data
Test substance:    no data

Remark:            Only abstract available; no data on doses, preparation of
                   S-9 mix, tester strain, or method.
                   Reliability: 3 (not reliable)
Test substance:    formaldehyde; no data on purity of the compound
13-MAY-1998                                                              (112)

Type:                     other: in vitro gene mutation - prokaryotes (bacteria)
System of testing:        Salmonella typhimurium TA102, TA2638
Concentration:            0.1 mg/plate
Metabolic activation:     no data

Result:                   positive

Method:            other: Ames test
   GLP:            no data
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Test substance:   no data

Remark:           Reliability: 2 (reliable with restrictions)
                  Standard Plate Test; no data on dose range or S-9 mix; weak
                  response with TA102.
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-1998                                                              (422)

Type:                     other: in vitro gene mutation - prokaryotes (bacteria)
System of testing:        Salmonella typhimurium TA97, TA98, TA100
Concentration:            0.5 - 2.0 mM (ca. 15 - 60 mg/l); no further data
Metabolic activation:     without
Result:                   positive

Method:           other: Ames test
   GLP:           no data
Test substance:   no data

Remark:           Reliability: 2 (reliable with restrictions)
                  Standard Plate Test; only abstract available; no data on
                  exact dose or test method
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-1998                                                              (194)

Type:                     other: in vitro gene mutation - prokaryotes (bacteria)
System of testing:        Salmonella typhimurium TA100, TM677
Concentration:            0.06 - 0.25 mM (ca. 1.8 - 7.5 mg/l); no further data
Metabolic activation:     without
Result:                   positive

Method:           other: Ames test
   GLP:           no data
Test substance:   no data

Remark:           Forward mutation assay, 8-azaguanidine resistance
                  (Preincubation Test); only abstract available; no data on
                  exact dose or test method
                  Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-1998                                                              (194)

Type:                     other: in vitro gene mutation - prokaryotes (bacteria)
System of testing:        Escherichia coli WP2 (pKM101), WP2 uvrA (pKM101)
Concentration:            up to 0.2 mg/plate
Metabolic activation:     without
Result:                   positive

Method:           other: Bacterial reverse mutation assay
   GLP:           no data
Test substance:   no data

Remark:           Reliability: 2 (reliable with restrictions)
                  Standard Plate Test (SPT) and Preincubation Test (PIT)
                  without metabolic activation; positive result in SPT with
                  WP2 uvrA (pKM101) strain only.
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-1998                                                              (519)

Type:                     other: in vitro gene mutation - prokaryotes (bacteria)
System of testing:        Salmonella typhimurium TM677
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Concentration:           0.33 - 20 mM (ca. 10 - 600 mg/l); no further data
Metabolic activation:    with and without
Result:                  positive

Method:           other: Ames test
   GLP:           no data
Test substance:   no data

Remark:           Forward mutation assay, 8-azaguanidine resistance
                  (Preincubation Test) with and without metabolic activation
                  with S-9 mix prepared from liver homogenate of Aroclor
                  pretreated Sprague-Dawley rats; minimum concentrations to
                  induce mutagenicity were 0.167 mM (ca. 5 mg/l) without S-9
                  or 0.33 mM (ca. 10 mg/l) with S-9; mutagenicity depended on
                  concentration and time of preincubation (between 15 and 120
                  minutes).
                  Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-1998                                                              (644)

Type:                    other: in vitro gene mutation - prokaryotes (bacteria)
System of testing:       Salmonella typhimurium TA100, TA102
Concentration:           no data
Metabolic activation:    with and without
Result:                  positive

Method:           other: Ames test
   GLP:           no data
Test substance:   no data

Remark:           Reliability: 3 (not reliable)
                  Result: mutagenic; only abstract available; no data on
                  method, S-9 mix, or exact results
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-1998                                                              (344)

Type:                    other: in vitro gene mutation - prokaryotes (bacteria)
System of testing:       Escherichia coli (gpt locus)
Concentration:           40 mM (ca. 1200 mg/l)
Metabolic activation:    with and without
Result:                  positive

Method:           other: Bacterial gene mutation assay
   GLP:           no data
Test substance:   no data

Remark:           According to the authors, 8/9 mutants analyzed were AT-to-CG
                  transitions and 1/9 was a GC-to-AT transition.
                  No details concerning method, S-9 mix, doses, exact results
                  etc. were given. Dideoxy DNA sequencing was used to
                  determine the specific base changes.
                  Reliability: 3 (not reliable)
Test substance:   formaldehyde; no data on purity of the compound
18-JUN-1998                                                              (166)

Type:                    other: in vitro gene mutation - prokaryotes (bacteria)
System of testing:       Escherichia coli AB1157 (wild type), AB1886 (uvrA),
                         AB2480 (recA/uvrA)
Concentration:           0.625 - 5 mM (ca. 18.8 - 150 mg/l)
```

```
Metabolic activation:    without
Result:                  positive

Method:           other: Bacterial forward mutation assay
   GLP:           no data
Test substance:   no data

Remark:           Preincubation Test (rifampicin resistance) without
                  metabolic activation. A dose-related mutagenicity was
                  observed in the wild type tester strain AB1157, only;
                  according to the authors, this was a characteristic shared
                  with cross-linking agents.
                  Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-1998                                                            (276)

Type:                    other: in vitro gene mutation - prokaryotes (bacteria)
System of testing:       Escherichia coli B/r WP2 Hcr+ (Trp-), B/r WP2 Hcr-
                         (Trp-)
Concentration:           40, 80, 320, 640 mM (1200, 2400, 9600, 19200 mg/l)
Metabolic activation:    without
Result:                  positive

Method:           other: Bacterial reverse mutation assay
   GLP:           no data
Test substance:   no data

Remark:           Preincubation Test without metabolic activation; Hcr+
                  strain tested with 40 and 80 mM (1200 and 2400 mg/l), Hcr-
                  strain tested with 320 and 640 mM (9600 and 19200 mg/l).
                  Induction of both types of mutations (SMr and Trp+) was
                  found only on Hcr- cells; according to the authors, these
                  resuslts indicated that the test substance produced
                  mutagenic lesionswhich were subject to cellular Hcr repair.
                  Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-1998                                                            (511)

Type:                    other: in vitro gene mutation - prokaryotes (bacteria)
System of testing:       Escherichia coli B/r WP2 Hcr+ (Trp-), B/r WP2 Hcr-
                         (Trp-)
Concentration:           40, 80, 320, 640 mM (1200, 2400, 9600, 19200 mg/l)
Metabolic activation:    without
Result:                  positive

Method:           other: Bacterial forward mutation assay
   GLP:           no data
Test substance:   no data

Remark:           Reliability: 2 (reliable with restrictions)
                  Standard Plate Test (streptomycin resistance) without
                  metabolic activation; Hcr+ strain tested with 40 and 80 mM
                  (1200 and 2400 mg/l), Hcr- strain tested with 320 and 640
                  mM (9600 and 19200 mg/l). Induction of both types of
                  mutations (SMr and Trp+) was found only on Hcr- cells;
                  according to the authors, these resuslts indicated that the
                  test substance produced mutagenic lesions which were subject
                  to cellular Hcr repair.
Test substance:   formaldehyde; no data on purity of the compound
```

13-MAY-1998 (511)

Type: other: in vitro gene mutation - prokaryotes (bacteria)
System of testing: Salmonella typhimurium BA13 (wild type), BA9 (deep rough)
Concentration: 167 - 1332 nmoles/ml (ca. 5 - 40 mg/l)
Metabolic activation: without
Result: positive

Method: other: Ames test
GLP: no data
Test substance: no data

Remark: Forward mutation assay (Preincubation Test, L-arabinose resistance) without metabolic activation; dose-dependent increase in mutant colonies (ARAR)
Reliability: 2 (reliable with restrictions)
Test substance: formaldehyde; no data on purity of the compound

13-MAY-1998 (575)

Type: other: in vitro gene mutation - prokaryotes (bacteria)
System of testing: Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538
Concentration: 0.00005 - 1 mg/plate
Metabolic activation: with and without
Result: negative

Method: other: Ames test
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Standard Plate Test with and without metabolic activation with S-9 mix prepared from liver homogenate of Aroclor induced Sprague-Dawley rats. Accoring to the author,no mutagenic response was observed, however, NTP results showed a positive response in the Preincubation assay.
Test substance: formaldehyde; no data on purity of the compound

13-MAY-1998 (111)

Type: other: in vitro gene mutation - prokaryotes (bacteria)
System of testing: Salmonella typhimurium TA100
Concentration: up to 30 umoles (ca. 0.9 mg)
Metabolic activation: without
Result: positive

Method: other: Ames test
GLP: no data
Test substance: no data

Remark: Preincubation Test without metabolic activation, the test substance was strongly mutagenic at the 5uM level (ca. 0.15 mg); cytotoxicity was observed at doses >5uM.
Reliability: 2 (reliable with restrictions)
Test substance: formaldehyde; no data on purity of the compound

13-MAY-1998 (479)

```
Type:                    other: in vitro gene mutation - prokaryotes (bacteria)
System of testing:       Salmonella typhimurium TA100
Concentration:           0.1 - 1.0 umoles/plate (ca. 0.003 - 0.03 mg/plate)
Metabolic activation:    with
Result:                  positive

Method:           other: Ames test
   GLP:           no data
Test substance:   no data

Remark:           Preincubation Test and Standard Plate Test both with
                  metabolic activation with S-9 prepared from liver
                  homogenateof Aroclor pretreated rats, both with S-9 with and
                  without cofactors. Positive reaction was only observed in
                  the Preincubation Test (60 min); the greatest effect was
                  observed using S-9 without cofactors. No further data on
                  Standard Plate Test.
                  Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-1998                                                                (546)

Type:                    other: in vitro gene mutation - prokaryotes (bacteria)
System of testing:       Salmonella typhimurium TA98, TA1535, TA1537, TA1538
Concentration:           0.1 - 0.6 umoles/plate (ca. 0.003 - 0.018 mg/plate)
Metabolic activation:    with
Result:                  positive

Method:           other: Ames test
   GLP:           no data
Test substance:   no data

Remark:           Reliability: 2 (reliable with restrictions)
                  Standard Plate Test with S-9 without cofactors. Mutagenicity
                  was observed only with tester strain TA98.
Test substance:   formaldehyde; no data on purity of the compound

13-MAY-1998                                                                (546)

Type:                    other: in vitro gene mutation - prokaryotes (bacteria)
System of testing:       Escherichia coli K12GP120, carrying the pSV2gpt plasmid
Concentration:           4 or 40 mM (ca. 120 and 1200 mg/l)
Metabolic activation:    no data
Result:                  positive

Method:           other: Bacterial gene mutation assay
   GLP:           no data
Test substance:   no data

Remark:           4 mM induced point mutations (41%), large insertions (41%),
                  and large deletions (18%); average mutation frequency was
                  2.3-fold over background. Most of the point mutations were
                  transversions at CG base pairs.
                  40 mM induced point mutations (92%), large insertions (3%),
                  and large deletions (5%); average mutation frequency was
                  3-7-fold over background. Most of the point mutations were
                  transitions at a single TA base pair.
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                  According to the authors, the test substance induced
                  different alterations at different concentrations.
                  Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-1998                                                          (165)

Type:                     other: in vitro gene mutation - prokaryotes (bacteria)
System of testing:        other: Escherichia coli K12GP120 and naked pSV2gpt
                          plasmid DNA
Concentration:            3.3 or 10 mM (ca. 100 or 300 mg/l)
Metabolic activation:     no data
Result:                   positive

Method:           other: Bacterial gene mutation assay
   GLP:           no data
Test substance:   no data

Remark:           Naked plasmid DNA was exposed and transformed into
                  Escherichia coli. Formaldehyde induced point mutations
                  (86%) and large deletions (14%). Most of the resulting
                  mutations were frameshifts.
                  Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-1998                                                          (165)

Type:                     other: in vitro gene mutation - prokaryotes (bacteria)
System of testing:        Salmonella typhimurium TA98, TA100, TA1537
Concentration:            no data
Metabolic activation:     without
Result:                   positive

Method:           other: Ames test
   GLP:           no data
Test substance:   no data

Remark:           Preincubation Test with and without metabolic activation
                  with S-9 prepared from liver homogenate of PCB (KC-400)
                  pretreated Wistar rats; mutagenic effect with TA100 without
                  S-9 mix; 2000 his+ revertants/mg.
                  Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-1998                                                          (354)

Type:                     other: in vitro gene mutation - prokaryotes (bacteria)
System of testing:        Escherichia coli DB2
Concentration:            1 - 40 mg/l
Metabolic activation:     without
Result:                   positive

Method:           other: Bacterial forward mutation assay
                  tes (bacteria)
   GLP:           no data
Test substance:   no data

Remark:           ampicillin resistance test; non-linear dose-response;
                  minimum detectable dose was ca. 6 and 9 ug/ml in the first
                  and second experimental run, respectively
                  Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; no data on purity of the compound
```

13-MAY-1998 (87)

Type: other: in vitro gene mutation - prokaryotes (bacteria)
System of testing: Salmonella typhimurium TA98, TA100, TA104
Concentration: no data
Metabolic activation: with and without
Result: positive

Method: other: Ames test
GLP: no data
Test substance: no data

Remark: Preincubation Test with and without metabolic activation; positive results in all tester strains with and without S-9. Only abstract available; no further data.
Reliability: 3 (not reliable)
Test substance: formaldehyde; no data on purity of the compound
13-MAY-1998 (380)

Type: other: in vitro gene mutation - prokaryotes (bacteria)
System of testing: Escherichia coli WP2 uvrA/pKM101
Concentration: no data
Metabolic activation: with and without
Result: positive

Method: other: Bacterial reverse mutation assay
GLP: no data
Test substance: no data

Remark: Preincubation Test with and without metabolic activation; positive results with and without S-9. Only abstract available; no further data.
Reliability: 3 (not reliable)
Test substance: formaldehyde; no data on purity of the compound
13-MAY-1998 (380)

Type: other: in vitro gene mutation - prokaryotes (bacteria)
System of testing: Escherichia coli - B tester strains H/r30R (wild-type), Hs30R (uvrA), NG30 (recA), O16 (polA)
Concentration: 0.05 - 5 mM (ca. 1.5 - 150 mg/l) or 20 mM (ca. 600 mg/l)
Metabolic activation: without
Result: positive

Method: other: Bacterial reverse mutation assay
GLP: no data
Test substance: no data

Remark: Preincubation Test without metabolic activation; dose-related increase in the number of arg+ revertants of tester strains H/r30R and O16; the repair deficient tester strains were more sensitive to the lethal effect of formaldehyde than the wild type.
Reliability: 2 (reliable with restrictions)
Test substance: formaldehyde; no data on purity of the compound
13-MAY-1998 (638)

Type: other: in vitro gene mutation - prokaryotes (bacteria)

```
System of testing:       Escherichia coli - B/r tester strains WP2 (wild-type),
                         WP2 uvrA
Concentration:           0.2 - 20 mM (ca. 6 - 600 mg/l)
Metabolic activation:    without
Result:                  positive

Method:           other: Bacterial reverse mutation assay
   GLP:           no data
Test substance:   no data

Remark:           Preincubation Test without metabolic activation;
                  dose-related increase in the number of trp+ revertants with
                  both tester strains; the repair deficient tester strain was
                  more sensitive to the lethal effect of formaldehyde than the
                  wild type.
                  Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-1998                                                                (638)

Type:                    other: in vitro gene mutation - prokaryotes (bacteria)
System of testing:       Salmonella typhimurium TA98, TA100
Concentration:           0.2 - 10 mM (ca. 6 - 300 mg/l)
Metabolic activation:    without
Result:                  positive

Method:           other: Ames test
   GLP:           no data
Test substance:   no data

Remark:           Preincubation Test without metabolic activation; only weak
                  response in both tester strains.
                  Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; no data on purity of the compound

13-MAY-1998                                                                (638)

Type:                    other: in vitro gene mutation - prokaryotes (bacteria)
System of testing:       Salmonella typhimurium TA98, TA100, TA1535, TA1537
Concentration:           (a) 0.001-0.1 mg/plate (lab. 1); (b) 0.0033-0.3
                         mg/plate (lab. 2) ; (c) 0.0033-0.3333 mg/plate (lab. 3)
Metabolic activation:    with and without
Result:                  positive

Method:           other: Ames test
   GLP:           no data
Test substance:   no data

Remark:           Preincubation Test with and without metabolic activation
                  with S-9 mix prepared from liver homogenate of both Aroclor
                  pretreated Sprague-Dawley rats and Syrian hamsters;
                  dose-related increase in the revertants was observed with
                  tester strains TA98 and TA100.
                  "Round Robin Test" with 3 different laboratories.
                  Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-1998                                                                (300)

Type:                    other: in vitro gene mutation - prokaryotes (bacteria)
System of testing:       Salmonella typhimurium TA104
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Concentration:           370 - 1500 uM (ca. 11.1 - 45 mg/l)
Metabolic activation:    with and without
Result:                  positive

Method:           other: Ames test
   GLP:           no data
Test substance:   no data

Remark:           Preincubation Test with and without metabolic activation
                  with S-9 mix prepared from liver homogenate of Aroclor
                  pretreated Sprague-Dawley rats; dose-related increase in the
                  revertants was observed with S-9.
                  Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-1998                                                              (727)

Type:                    other: in vitro gene mutation - prokaryotes (bacteria)
System of testing:       Salmonella typhimurium; no data on tester strain
Concentration:           no data
Metabolic activation:    with and without
Result:                  positive

Method:           other: Ames test
   GLP:           no data
Test substance:   no data

Remark:           Preincubation Test with and without metabolic activation
                  with S-9 mix prepared from liver homogenate of Aroclor
                  pretreated Sprague-Dawley rats; mutagenicity was observed
                  inpresence and absence of S-9; no data on doses and tester
                  strains.
                  Reliability: 3 (not reliable)
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-1998                                                              (547)

Type:                    other: in vitro gene mutation - prokaryotes (bacteria)
System of testing:       Salmonella typhimurium TA98, TA100
Concentration:           no data
Metabolic activation:    without
Result:                  negative

Method:           other: Ames test
   GLP:           no data
Test substance:   no data

Remark:           Reliability: 3 (not reliable)
                  Standard Plate Test without metabolic activation; no
                  mutagenic repsonse was observed. No further data.
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-1998                                                               (29)

Type:                    other: in vitro gene mutation - prokaryotes (bacteria)
System of testing:       Escherichia coli WP2 uvrA
Concentration:           0.02 - 10 mM (ca. 0.6 - 300 mg/l)
Metabolic activation:    without
Result:                  negative

Method:           other: Bacterial reverse mutation assay
   GLP:           no data
```

```
Test substance:   no data

Remark:           Preincubation Test without metabolic activation for 18 h;
                  no mutagenic response was observed; no further data.
                  Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-1998                                                          (315)

Type:                     other: in vitro gene mutation - prokaryotes (bacteria)
System of testing:        Salmonella typhimurium TA100, TA102
Concentration:            no data
Metabolic activation:     with and without
Result:                   positive

Method:           other: Ames test
   GLP:           no data
Test substance:   no data

Remark:           Reliability: 3 (not reliable)
                  Standard Plate Test and Preincubation Test both with and
                  without metabolic activation with S-9 mix prepared from
                  liver homogenate of Aroclor pretreated Syrian hamsters;
                  mutagenic response in presence and absence of S-9. According
                  to the authors, the results suggested that the preincubation
                  was more sensitive than the standard procedure. Only
                  abstract available; no further data.

Test substance:   formaldehyde; no data on purity of the compound
13-MAY-1998                                                          (608)

Type:                     other: in vitro gene mutation - prokaryotes (bacteria)
System of testing:        Salmonella typhimurium TA102
Concentration:            no data
Metabolic activation:     no data
Result:                   positive

Method:           other: Ames test
   GLP:           no data
Test substance:   no data

Remark:           According to the authors, the test substance was mutagenic.
                  Only abstract available; no data on method, metabolic
                  activation, doses, exact results etc.
                  Reliability: 3 (not reliable)
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-1998                                                          (703)

Type:                     other: in vitro gene mutation - prokaryotes (bacteria)
System of testing:        Escherichia coli WP2/pKM101, WP2 uvrA/pKM101
Concentration:            no data
Metabolic activation:     no data
Result:                   ambiguous

Method:           other: Bacterial reverse mutation assay
   GLP:           no data
Test substance:   no data

Remark:           Reliability: 3 (not reliable)
                  The mutagenicity of the test substance was questionable.
                  Only abstract available; no data on method, metabolic
                  activation, doses, exact results etc.
```

```
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-1998                                                          (703)

Type:                     other: in vitro gene mutation - prokaryotes (bacteria)
System of testing:        Escherichia coli K12/343/113 (uvrB+), K12/343/268
                          (uvrB-)
Concentration:            no data
Metabolic activation:     no data
Result:                   positive

Method:           other: Bacterial gene mutation assay
   GLP:           no data
Test substance:   no data

Remark:           Mutagenicity was increased 8-fold only at higher
                  concentrations while at low concentrations, no influence
                  of liquid holding was observed. The 60-fold increase over
                  control was dependent on the presence of the intact uvrB
                  function. NALres and VALres forward mutations, nad (frame
                  shift and arg reversions (point mutations) were determined.
                  Only abstract available; no further data.

                  Reliability: 3 (not reliable)
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-1998                                                          (730)

Type:                     other: in vitro gene mutation - prokaryotes (bacteria)
System of testing:        Escherichia coli K12/343/113, K12/343/268
Concentration:            up to 12 mM (ca. 480 mg/l)
Metabolic activation:     without
Result:                   positive

Method:           other: Bacterial gene mutation assay
   GLP:           no data
Test substance:   no data

Remark:           Reliability: 2 (reliable with restrictions)
                  The test substance was clearly mutagenic in the nalr system
                  of Escherichia coli K12/343/113. Maximum response was
                  observed at 2mM (ca. 60 mg/l; ca. 20-fold increase);
                  further increase after liquid holding (24 hours) up to 12 mM
                  (ca. 480 mg/l; 56-fold) was recorded.
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-1998                                                          (731)

Type:                     other: in vitro gene mutation - prokaryotes (bacteria)
System of testing:        Salmonella typhimurium TA98, TA100
Concentration:            no data
Metabolic activation:     with and without
Result:                   positive

Method:           other: Ames test
   GLP:           no data
Test substance:   no data

Remark:           Preincubation Test with and without metabolic activation
                  with liver homogenate from KC-500 pretreated rats; weak
                  response with tester strain TA100 in absence of S-9; no
                  mutagenic response in presence of S-9. Only abstract
                  available; no furhter data.
                  Reliability: 3 (not reliable)
```

Test substance: formaldehyde; no data on purity of the compound
13-MAY-1998 (584)

Type: other: in vitro gene mutation - prokaryotes (bacteria)
System of testing: Salmonella typhimurium TA100, TM 677
Concentration: 0.002 - 0.01 mg/plate
Metabolic activation: without
Result: positive

Method: other: Ames test
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Standard Plate Test (SPT) and Preincubation Test (PIT) without metabolic activation; positive response with TA 100 (3 fold) and TM 677 (7 fold) only in the PIT; only abstract available no further data.
Test substance: formaldehyde; no data on purity of the compound
13-MAY-1998 (160)

Type: other: in vitro gene mutation - prokaryotes (bacteria)
System of testing: Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538
Concentration: up to 2 umoles/plate (ca. 0.06 mg/plate)
Metabolic activation: with and without
Result: negative

Method: other: Ames test
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Standard Plate Test with and without metabolic activation with S-9 prepared from liver homogenate of Aroclor pretreated Sprague-Dawley rats; no mutagenic activity was observed.
Test substance: formaldehyde; no data on purity of the compound
13-MAY-1998 (253)

Type: other: in vitro gene mutation - prokaryotes (bacteria)
System of testing: Salmonella typhimurium TA97, TA102
Concentration: 0.025 - 0.2 mg/plate
Metabolic activation: with and without
Result: positive

Method: other: Ames test
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Standard Plate Test with and without metabolic activation with S-9 prepared from liver homogenate of Aroclor pretreated Sprague-Dawley rats; no differences in mutagenic activity was observed in the presence or absence of S-9; weakly positive response with tester strain TA102; maximum response +/-S-9 at 100 ug/plate (2-3-fold).
Test substance: formaldehyde; no data on purity of the compound
13-MAY-1998 (179) (180)

```
Type:                     other: in vitro gene mutation - prokaryotes (bacteria)
System of testing:        Salmonella typhimurium TA102
Concentration:            up to 5.0 mg/plate
Metabolic activation:     with and without
Result:                   ambiguous

Method:            other: Ames test
   GLP:            no data
Test substance:    no data

Remark:            Reliability: 2 (reliable with restrictions)
                   Standard Plate Test with and without metabolic activation
                   with S-9 prepared from liver homogenate of Aroclor
                   pretreated Sprague-Dawley rats; the test was performed as a
                   Round Robin Test in 3 different laboratories. The results
                   were conflicting: no mutagenicity was observed in 2
                   laboratories, weakly positive reaction was observed in 1
                   laboratory.
Test substance:    formaldehyde; no data on purity of the compound
02-FEB-1999                                                          (370) (498)

Type:                     other: in vitro gene mutation - prokaryotes (bacteria)
System of testing:        Salmonella typhimurium TA98, TA100, TA1535, TA1537,
                          TA1538
Concentration:            no data
Metabolic activation:     with and without
Result:                   negative

Method:            other: Ames test
   GLP:            no data
Test substance:    no data

Remark:            Reliability: 3 (not reliable)
                   Standard Plate Test with and without metabolic activation
                   with S-9 prepared from liver homogenate of Aroclor
                   pretreated Sprague-Dawley rats; no increase in the number of
                   mutant colonies was observed in the presence and absence of
                   S-9.
Test substance:    formaldehyde; no data on purity of the compound
13-MAY-1998                                                          (179) (180)

Type:                     other: in vitro gene mutation - prokaryotes (bacteria)
System of testing:        Salmonella typhimurium TA100
Concentration:            1 - 30 umoles (ca. 0.030 - 0.9 mg)
Metabolic activation:     without
Result:                   positive

Method:            other: Ames test
   GLP:            no data
Test substance:    no data

Remark:            Reliability: 2 (reliable with restrictions)
                   Standard Plate Test without metabolic activation, the test
                   substance was strongly mutagenic at the 5 uMole level (ca.
                   0.15 mg); cytotoxicity was observed at doses >5 uMole.

Test substance:    formaldehyde; no data on purity of the compound
13-MAY-1998                                                                (228)
```

```
Type:                     other: in vitro gene mutation - prokaryotes (bacteria)
System of testing:        Salmonella typhimurium TA98, TA100
Concentration:            up to 20 ul
Metabolic activation:     with and without
Result:                   positive

Method:            other: Ames test
   GLP:            no data
Test substance:    no data

Remark:            Mutagenicity was observed in the presence and absence of
                   S-9 mix (prepared from liver homogenate of Aroclor
                   pretreated Wistar rats) with both tester strains with the
                   most marked activity towards tester strain TA100. Mutagenic
                   acitivity was reduced in the presence of S-9 mix.
                   Reliability: 2 (reliable with restrictions)
Test substance:    formaldehyde; no data on purity of the compound
18-JUN-1998                                                                (529)

Type:                     other: in vitro gene mutation - lower eukaryotes
                          (yeast, fungi)
System of testing:        Saccharomyces cerevisiae TF1, EH3951
Concentration:            10 - 40 mM (ca. 300 - 1200 mg/l)
Metabolic activation:     without
Result:                   positive

Method:            other: Yeast gene mutation assay
   GLP:            no data
Test substance:    no data

Remark:            A dose-dependent weak increase of reverse mutation of yeast
                   strains lacking the SFA gene, i.e. disruption mutants was
                   observed. According to the authors, very little genetic
                   activity was observed in the diploid wild type (2 SFA
                   genes) and in multi-copy SFA-containing transformants.
                   Reliability: 2 (reliable with restrictions)
Test substance:    formaldehyde; no data on purity of the compound
13-MAY-1998                                                                (698)

Type:                     other: in vitro gene mutation - lower eukaryotes
                          (yeast, fungi)
System of testing:        Saccharomyces cerevisiae N123, UVSz, DH2252-6a,
                          XV185-14C, XV423-2A, YO14-2C
Concentration:            0.05-60 mM (ca. 1.5-1800 mg/l)
Metabolic activation:     without
Result:                   positive

Method:            other: Yeast gene mutation assay
   GLP:            no data
Test substance:    no data

Remark:            Reliability: 2 (reliable with restrictions)

                   Several concentrations were tested:
                   - No indication of a nuclear mutagenic effect was observed
                     after various periods of treatment (5-20 min.) with 60 mM
                     (ca. 1800 mg/l), however, the same test
                     concentration resulted in induction of cytoplasmatic
                     "petite" or p-mutation in tester strains N123 and UVSz
                     (no data on test duration).
```

- Concentrations of 0.1-0.7 mM (ca. 3-21 mg/l) resulted in dose-related mutagenicity. Optimum response in the fluctuation test was found in tester strain N123 at 0.2 and 0.4 mM (ca. 6 and 12 mg/l, respectively). The optimum depended on the test method.
- After tretment with concentrations of 0.05-0.2 mM (ca. 1.5-6 mg/l) or 0.4 mM (ca. 12 mg/l), a dose-related mutagenicity was observed with the tester strains N123, XV185-14C and XV423-2A (his1 gene) and with the tester strain DH2252-6a (ade5 gene). In all cases, the mutagenic action of the test substance was weak.

Test substance: formaldehyde; no data on purity of the compound
13-MAY-1998 (133)

Type: other: in vitro gene mutation - lower eukaryotes (yeast, fungi)
System of testing: Aspergillus niger A15
Concentration: 1.0% (10 mg/ml)
Metabolic activation: no data
Result: positive

Method: other: gene mutation
GLP: no
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
The spores were treated for 5, 10, 15, and 20 min.; survival and mutation rates were determined after 5 days of incubation. The increase in the mutation frequency was treatment time-dependent.
Test substance: formaldehyde; no data on purity of the compound
13-MAY-1998 (172)

Type: other: in vitro gene mutation - lower eukaryotes (yeast, fungi)
System of testing: Neurospora crassa H-12, H-59
Concentration: no data
Metabolic activation: no data
Result: positive

Method: other: gene mutation
GLP: no data
Test substance: no data

Remark: Treatment of conidial suspension resulted in an induction of ad-3 forward mutations.
Test substance: formaldehyde; no data on purity of the compound
Reliability: (3) invalid

13-MAY-1998 (185)

Type: other: in vitro gene mutation - lower eukaryotes (yeast, fungi)
System of testing: Neurospora crassa H-12, H-59, H-71
Concentration: 0.005 - 0.075%
Metabolic activation: no data
Result: positive

Method: other: gene mutation
GLP: no data

Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Tester strains H-12 and H-71 were treated with 0.01-0.075%; tester strain H-59 was treated with 0.005-0.04%. Induction of ad-3 forward mutants was about 8-11 fold over background in tester strains H-12 and H-71 and about 320 fold over background in tester strain H-59. According to the authors, formaldehyde treatment resulted in about the same killing effect in H-12 and H-71 but in a 9 fold increase in H-59.
Test substance: formaldehyde; no data on purity of the compound
13-MAY-1998 (186)

Type: other: in vitro gene mutations - eukaryotes (mammalian cells)
System of testing: human lymphoblasts TK6 (HPRT-)
Concentration: 150 uM (ca. 4.5 mg/l), 8 times
Metabolic activation: without
Result: positive

Method: other: HGPRT assay
GLP: no data
Test substance: no data

Remark: About 50% of the induced mutations had visible deletions, indicating large losses of DNA. The remainder probably consisted of point mutations or smaller insertions or deletions (characterized by Southern blot). The test substance was a weak mutagen at the hprt locus in TK6 cells (12.4 fold over background).
Reliability: 2 (reliable with restrictions)
Test substance: formaldehyde; no data on purity of the compound
18-JUN-1998 (165)

Type: other: in vitro gene mutations - eukaryotes (mammalian cells)
System of testing: human lymphoblasts TK6 (TK+/-)
Concentration: up to 150 uM (ca. 4.5 mg/l)
Metabolic activation: without
Result: positive

Method: other: HGPRT assay
GLP: no data
Test substance: no data

Remark: Induction of a significant number of F3TdR-resistant mutants was observed at 150 uM; minimum detectable concentration which induced mutants was ca. 130 uM (3.9 mg/l).
Reliability: 2 (reliable with restrictions)
Test substance: formaldehyde; no data on purity of the compound
18-JUN-1998 (259)

Type: other: in vitro gene mutations - eukaryotes (mammalian cells)
System of testing: human lymphoblasts TK6 (Oub)
Concentration: 150 uM (ca. 4.5 mg/l), 4 times
Metabolic activation: without
Result: negative

```
Method:           other: HGPRT assay
   GLP:           no data
Test substance:   no data

Remark:           No increase in the number of ouabain-resistant (Oubr) cells
                  was observed. According to the authors, this result
                  suggested that formaldehyde did not induce a wide variety of
                  base substitution mutation.
                  Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; no data on purity of the compound
18-JUN-1998                                                          (162) (163)

Type:                     other: in vitro gene mutations - eukaryotes (mammalian
                          cells)
System of testing:        CHO/HPRT (hprt locus)
Concentration:            no data
Metabolic activation:     without
Result:                   negative

Method:           other: HGPRT assay
   GLP:           no data
Test substance:   no data

Remark:           No induction of mutations in the hprt locus; only abstract
                  available; no further data.
Test substance:   formaldehyde; no data on purity of the compound
Reliability:      (3)  invalid
02-FEB-1999                                                              (620)

Type:                     other: in vitro gene mutations - eukaryotes (mammalian
                          cells)
System of testing:        AS52/XPRT (gpt locus)
Concentration:            no data
Metabolic activation:     without
Result:                   positive

Method:           other: HGPRT assay
   GLP:           no data
Test substance:   no data

Remark:           Mutagenic response at the gpt locus (i.e. mutation to TGr);
                  only abstract available; no further data.
Test substance:   formaldehyde; no data on purity of the compound
Reliability:      (3)  invalid
02-FEB-1999                                                              (620)

Type:                     other: in vitro gene mutations - eukaryotes (mammalian

                          cells)
System of testing:        AS52/XPRT
Concentration:            1 - 50 mg/l
Metabolic activation:     without
Result:                   positive

Method:           other: HGPRT assay
   GLP:           no data
Test substance:   no data
```

```
Remark:           No mutagenicity at low doses (1-10 mg/l); linear
                  increase in XPRT mutant frequencies at higher
                  concentrations; only abstract available; no
                  further data.
                  Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; no data on purity of the compound
18-JUN-1998                                                        (620)

Type:                     other: in vitro gene mutations - eukaryotes (mammalian
                          cells)
System of testing:        mouse lypmoma cells L5178Y (TK+/-)
Concentration:            140 - 260 umoles/l (ca. 4.2 - 7.8 mg/l)
Metabolic activation:     without
Result:                   positive

Method:           other: Mouse lymphoma assay
   GLP:           no data
Test substance:   no data

Remark:           Clear increase in the forward mutation frequency without
                  dose-response
                  Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; no data on purity of the compound
18-JUN-1998                                                        (691)

Type:                     other: in vitro gene mutations - eukaryotes (mammalian
                          cells)
System of testing:        mouse lypmoma cells L5178Y (TK+/-)
Concentration:            no data
Metabolic activation:     with and without
Result:                   positive

Method:           other: Mouse lymphoma assay
   GLP:           no data
Test substance:   no data

Remark:           A dose-related increase in TK forward mutation was observed
                  in the absence and presence of S-9; only abstract available;
                  no further data.
Test substance:   formaldehyde; no data on purity of the compound
Reliability:      (3)  invalid
18-JUN-1998                                                        (112)

Type:                     other: in vitro gene mutations - eukaryotes (mammalian
                          cells)
System of testing:        mouse lypmoma cells L5178Y (TK+/-)
Concentration:            0.06 - 15 mg/l (-S-9), 0.06 - 3.8 mg/l (+S-9)
Metabolic activation:     with and without
Result:                   positive

Method:           other: Mouse lymphoma assay
   GLP:           no data
Test substance:   no data

Remark:           Positive response from ca. 7.5 ug/ml and 1.9 ug/ml in the
                  absence and presence of S-9 (prepared from liver homogenate
                  of Aroclor pretreated rats), respectively. According to the
                  author, the presence of S-9 lowered the minimum effecitve
                  mutagenic concentration.
```

Reliability: 2 (reliable with restrictions)
Test substance: formaldehyde; no data on purity of the compound
18-JUN-1998 (111)

Type: other: in vitro gene mutations - eukaryotes (mammalian cells)
System of testing: mouse lypmoma cells L5178Y (TK+/-)
Concentration: 0.4-0.9 mM (ca. 1.2-27 mg/l) (+S-9), 0.07-0.2 mM (ca. 2.1-6 mg/l) (-S-9)
Metabolic activation: with and without
Result: positive

Method: other: Mouse lymphoma assay
GLP: no data
Test substance: no data

Remark: Dose-dependent increase in mutant frequency (2-18 fold). Coadministration of formaldehyde dehydrogenase and NAD+ completely eliminated both toxicity and mutagenicity; only abstract available; no further data.
Reliability: 2 (reliable with restrictions)

Test substance: formaldehyde; no data on purity of the compound
18-JUN-1998 (195)

Type: other: in vitro gene mutations - eukaryotes (mammalian cells)
System of testing: human bronchial fibroblasts
Concentration: 50 - 175 uM (ca. 1.5 - 5.25 mg/l)
Metabolic activation: without
Result: positive

Method: other: HGPRT assay
GLP: no data
Test substance: no data

Remark: A dose-related induction of 6-thioguanine-resistant (6-TGr) mutants was observed. According to the authors, formaldehyde also inhibited the repair of O6-methylguanine and potentiated the mutagenicity of N-methyl-N-nitrosourea (probably by repair inhibition).
Reliability: 2 (reliable with restrictions)
Test substance: formaldehyde; no data on purity of the compound
18-JUN-1998 (270)

Type: other: in vitro gene mutations - eukaryotes (mammalian cells)
System of testing: human fibroblasts
Concentration: 50 and 75 uM (ca. 1.5 and 2.25 mg/l)
Metabolic activation: without
Result: negative

Method: other: HGPRT assay
GLP: no data
Test substance: no data

Remark: No detectable increase in 6-thioguanine-resistant (6-TGr) mutants was observed. Cell survival was 82% and 40% at 50 and 75 uM, respectively. Only abstract available; no furtherdata.

```
                   Reliability: 2 (reliable with restrictions)
Test substance:    formaldehyde; no data on purity of the compound
02-FEB-1999                                                          (716)

Type:                      other: in vitro gene mutations - eukaryotes (mammalian
                           cells)
System of testing:         V79 cells
Concentration:             (a) 1.0-15 mg/l, 6 h; (b) 1.0-7.5 mg/l, 4 h; (c)
                           1.0-7.5 mg/l, 2x2 h; (d) 1.0-7.7 mg/l, 3x2 h
Metabolic activation:      without
Result:                    positive

Method:            other: HGPRT assay
   GLP:            no data
Test substance:    no data

Remark:            - Treatment for 6 h: a slight increase in the mutation rates
                     was observed at 15 mg/l (protocol (a)).
                   - Treatment for 4 h: a slight increase in the mutation
                     frequency was observed at >= 5 mg/l (protocol (b)).
                   - 2 treatments for 2 h (with an interval of 24 h): a clearly
                     positive and dose-dependent reaction was
                     observed already at the lowest dose (protocol (c)).
                   - 3 treatments for 2 h (with a day): a clearly
                     positive and dose-dependent reaction was observed already
                     at the lowest dose; the degree of the reaction increased
                     dose-dependently (protocol (d)).
                   According to the authors, significantly higher mutation
                   rates were observed after 2 treatments on 2 consecutive
                   days compared to 3 treatments within 1 day.
                   Reliability: 2 (reliable with restrictions)
Test substance:    formaldehyde; no data on purity of the compound
18-JUN-1998                                                          (483)

Type:                      other: in vitro gene mutations - eukaryotes (mammalian
                           cells)
System of testing:         human lymphoblasts (hprt locus)
Concentration:             150 uM (ca. 4.5 mg/l)
Metabolic activation:      without
Result:                    positive

Method:            other: HGPRT assay
   GLP:            no data
Test substance:    no data

Remark:            Visible deletions were found in 14/30 DNAs; only abstract
                   available; no further data.
Test substance:    formaldehyde; no data on purity of the compound
Reliability:       (2)  valid with restrictions
18-JUN-1998                                                          (166)

Type:                      other: in vitro gene mutations - eukaryotes (mammalian
                           cells)
System of testing:         human lymphoblasts
Concentration:             15 - 150 uM (ca. 0.45 - 4.5 mg/l)
Metabolic activation:      without
Result:                    positive

Method:            other: HGPRT assay
   GLP:            no data
```

Test substance: no data

Remark: Induction of mutants at a concentration of > 15 uM with a maximum of 4.8x10E-6 at 150 uM; cytotoxicity was detected > 50 uM; only abstract available; no further data.
Reliability: 2 (reliable with restrictions)
Test substance: formaldehyde; no data on purity of the compound
18-JUN-1998 (67)

Type: other: in vitro gene mutations - eukaryotes (mammalian cells)
System of testing: CHO/HPRT cells (hprt locus) and AS52/XRPT (gpt locus)
Concentration: 37% (w/v)
Metabolic activation: with and without
Result: positive

Method: other: HGPRT assay
GLP: no data
Test substance: no data

Remark: Equivocal results were obtained for induction of HPRT mutants without S-9; weak response with S-9 (prepared from liver homogenate of Aroclor induced rats). Significant induction of the mutant frequencies at the gpt locus was observed with and without S-9. According to the authors, mutation induction varied considerably between the 2 cell lines.
Reliability: 2 (reliable with restrictions)
Test substance: formaldehyde; no data on purity of the compound
18-JUN-1998 (619)

Type: other: in vitro gene mutations - eukaryotes (mammalian cells)
System of testing: AS52/XPRT cells (gpt locus)
Concentration: 50 mg/l
Metabolic activation: with
Result: positive

Method: other: HGPRT assay
GLP: no data
Test substance: no data

Remark: An increase in the mutant frequencies at the gpt locus was observed in the presence of S-9 prepared from liver homogenate of Aroclor induced rats.
Reliability: 2 (reliable with restrictions)
Test substance: formaldehyde; no data on purity of the compound
18-JUN-1998 (1)

Type: other: in vitro gene mutations - eukaryotes (mammalian cells)
System of testing: CHO cells (hprt locus)
Concentration: up to 0.05 mg/l
Metabolic activation: without
Result: negative

Method: other: HGPRT assay
GLP: no data
Test substance: no data

Remark: No mutagenicity was observed after exposure to vapours of the test substance for 1 h without S-9.
Reliability: 2 (reliable with restrictions)
Test substance: formaldehyde; no data on purity of the compound

18-JUN-1998 (723)

Type: other: in vitro gene mutations - eukaryotes (mammalian cells)
System of testing: mouse lypmoma cells L5178Y (TK+/-)
Concentration: no data
Metabolic activation: without
Result: positive

Method: other: Mouse lymphoma assay
GLP: no data
Test substance: no data

Remark: only abstract available; no further data.
Test substance: formaldehyde; no data on purity of the compound
Reliability: (3) invalid
18-JUN-1998 (690)

Type: other: in vitro gene mutations - eukaryotes (mammalian cells)
System of testing: human fibroblasts
Concentration: 100 mM (ca. 3000 mg/l)
Metabolic activation: without
Result: positive

Method: other: HGPRT assay
GLP: no data
Test substance: no data

Remark: Induction of 6-thioguanine-resistant mutants was observed.
Reliability: 2 (reliable with restrictions)
Test substance: formaldehyde; no data on purity of the compound
18-JUN-1998 (272)

Type: other: in vitro gene mutations - eukaryotes (mammalian cells)
System of testing: human fibroblasts
Concentration: 50, 75 uM (ca. 1.5, 2.25 mg/l)
Metabolic activation: without
Result: negative

Method: other: HGPRT assay
GLP: no data
Test substance: no data

Remark: No induction of 6-thioguanine-resistant mutants was observed.
Reliability: 2 (reliable with restrictions)
Test substance: formaldehyde; no data on purity of the compound
18-JUN-1998 (268)

Type: other: in vitro chromosomal aberrations - lower eukaryotes (yeast, fungi)
System of testing: Saccharomyces cerevisiae D61.M
Concentration: 50 - 137 nl/ml

```
Metabolic activation:    without
Result:                  ambiguous

Method:           other: Yeast Cytogenetic assay
   GLP:           no data
Test substance:   no data

Remark:           Reliability: 2 (reliable with restrictions)
                  The test substance did not clearly induce mitotic
                  chromosome loss when applied in pure form. According to the
                  authors, pure formaldehyde gave some tantalizing results
                  which indicated that it might induce chromosome loss. The
                  enhancement assay showed definitely that formaldehyde
                  combined with propionitrile induced chromosome
                  malsegregation (synergistic effect).
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-1998                                                            (732)

Type:                    other: in vitro chromosomal aberrations - eukaryotes
                         (plants)
System of testing:       Allium cepa root tips
Concentration:           33 - 1000 uM (ca. 1 - 30 mg/l)
Metabolic activation:    without
Result:                  negative

Method:           other: Anaphase-telophase test
                  aberrations - eukaryotes (plants)
   GLP:           no data
Test substance:   as prescribed by 1.1 - 1.4

Remark:           No increase in the frequency of chromosome aberrations was
                  obtained with formaldehyd of analytical grade. However,
                  application of a technical batch gave positive response.
                  Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; analytical grade
13-MAY-1998                                                            (555)

Type:                    other: in vitro chromosomal aberrations - eukaryotes
                         (plants)
System of testing:       Crepis capillaris
Concentration:           0.05, 0.1%  (ca. 0.5, 1.0 mg/ml)
Metabolic activation:    without
Result:                  positive

Method:           other: Metaphase test, Anaphase-telophase test
   GLP:           no data
Test substance:   as prescribed by 1.1 - 1.4

Remark:           Increase in chromosomal lesions, greater sensitivity of
                  metaphase scoring on seedlings of Crepis capillaris seeds.
                  Reliability: 2 (reliable with restrictions)

Test substance:   formaldehyde; no data on purity of the compound
13-MAY-1998                                                            (334)

Type:                    other: in vitro chromosomal aberrations - eukaryotes
                         (plants)
System of testing:       Allium cepa root tips
Concentration:           no data
```

Metabolic activation: without
Result: positive

Method: other: Micronucleus test
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: F1 generation of the treated cells were examined. Only abstract available; no further data.
Test substance: formaldehyde; no data on purity of the compound
Reliability: (3) invalid
13-MAY-1998 (442)

Type: other: in vitro chromosomal aberrations - eukaryotes (plants)
System of testing: Tradescantia
Concentration: 38 ppm/min (ca. 0.05 mg/l/min)
Metabolic activation: without
Result: positive

Method: other: Micronucleus test
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: Treatment of meiotic pollen mother cells with formaldehyde vapour; dose-related increase of micronucleus frequencies ranging from 8.2 (3-h treatment) to 39.2 MCN/100tetrads (36-h treatment). Only abstract available; no further data.
Test substance: formaldehyde; no data on purity of the compound
Reliability: (3) invalid
13-MAY-1998 (441)

Type: other: in vitro chromosomal aberrations - eukaryotes (plants)
System of testing: Tradescantia
Concentration: 3.3 - 330 mM (ca. 100 - 10000 mg/l)
Metabolic activation: without
Result: negative

Method: other: Micronucleus test
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: Treatment of early stages of meiotic chromosomes of pollen mother cells with formaldehyde in its liquid form for 6 h; micronuclei were analyzed 24 h after treatment in the early tetrads; treatment did not result in elevated micronucleus frequencies. Only abstract available; no further data.

Test substance: formaldehyde; no data on purity of the compound
Reliability: (3) invalid
02-FEB-1999 (440)

Type: other: in vitro chromosomal aberrations - eukaryotes (plants)
System of testing: Tradescantia
Concentration: (a) 62 ppm (ca. 0.077 mg/l), 3-6 h; (b) 1200 ppm (ca. 1.5 mg/l), 2-6 h; (c) 3100 ppm (ca. 3.9 mg/l), 20-60 min
Metabolic activation: without

```
Result:                  positive

Method:           other: Micronucleus test
   GLP:           no data
Test substance:   as prescribed by 1.1 - 1.4

Remark:           Treatment of early stages of meiotic chromosomes of pollen
                  mother cells with formaldehyde in its gaseous form;
                  micronuclei were analyzed 24 h after treatment in the early
                  tetrads; in each protocol, treatment resulted in a marked
                  increase in micronucleus frequency. Only abstract
                  available; no further data.
Test substance:   formaldehyde; no data on purity of the compound
Reliability:      (3)  invalid
02-FEB-1999                                                              (440)

Type:                    other: in vitro chromosomal aberrations - eukaryotes
                         (plants)
System of testing:       Tradescantia
Concentration:           (a) 0.5 ppm/min (ca. 0.0006 mg/l/min), 1 h; (b) 1.56
                         ppm/min (ca. 0.0019 mg/l/min), 6 h; (c) 62 ppm/min
                         (ca.0.077 mg/l/min), 3 h
Metabolic activation:    without
Result:                  positive

Method:           other: Micronucleus test
   GLP:           no data
Test substance:   as prescribed by 1.1 - 1.4

Remark:           Reliability: 2 (reliable with restrictions)
                  Treatment of early prophase-I meiotic chromosomes of pollen
                  mother cells with formaldehyde; micronuclei were analyzed 24
                  h after treatment in the early tetrads. An increase in
                  micronucleus frequency was observed at 0.5 and 1.56 ppm;
                  toxicity was observed at 62 ppm.
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-1998                                                              (443)

Type:                    other: in vitro chromosomal aberrations - eukaryotes
                         (plants)
System of testing:       Tradescantia
Concentration:           no data
Metabolic activation:    without
Result:                  positive

Method:           other: Micronucleus test
   GLP:           no data
Test substance:   as prescribed by 1.1 - 1.4

Remark:           Treatment of early prophase-I meiotic chromosomes of pollen
                  mother cells resulted in a positive response; only abstract
                  available; no further data.
Test substance:   formaldehyde; no data on purity of the compound
Reliability:      (3)  invalid
18-JUN-1998                                                              (439)

Type:                    other: in vitro chromosomal aberrations - eukaryotes
                         (non-mammalian cells)
```

System of testing: Chortophaga viridifasciata (Grasshopper) neuroblast cells
Concentration: 10E-8 M (0.0003 ppm) - 10E-3 M (30 ppm)
Metabolic activation: without
Result: positive

Method: other: Cytogenetic assay
GLP: no data
Test substance: no data

Remark: Embryos were exposed in vitro. Scoring was carried out at the late anaphase and very early telophase of the neuroblast cells. An increase in fragment and chromosome stickiness was observed. Low frequency of distinct acentric chromosome fragments was found at 7.5x10E-4 or 10E-3 M, but not at lower concentrations. No obvious dose-response was observed. The increase in the number of cells with sticky chromosomes was linear for cells with slight and moderate stickiness but not for those with severe stickiness.
Reliability: 2 (reliable with restrictions)
Test substance: formaldehyde; no data on purity of the compound
18-JUN-1998 (198) (199)

Type: other: in vitro chromosomal aberrations - eukaryotes (mammalian cells)
System of testing: CHO cells
Concentration: (a) 1.6-16 mg/l -S-9; (b) 1.6-50 mg/l +S-9; (c) 1.1-11 mg/l -S-9; (d) 1.1-11 mg/l + S-9; (e) 15-25 mg/ml + S-9
Metabolic activation: with and without
Result: positive

Method: other: Cytogenetic assay
GLP: no data
Test substance: no data

Remark: positive response at protocols (a), (b), and (e); protocol (a) at only 1 dose level; negative response at protocols (c)and (d).
With S-9 mix (prepared from liver homogenate of Aroclor pretreated Sprague-Dawley rats), high level of damage at toxic doses with marked mitotic suppression was observed.
The tests were performed by 2 laboratories (lab. 1: protocols (a) and (b), lab. 2: protocols (c) - (e)).
Test substance: formaldehyde; no data on purity of the compound
24-JUL-2002 (240)

Type: other: in vitro chromosomal aberrations - eukaryotes (mammalian cells)
System of testing: CHO cells
Concentration: no data
Metabolic activation: with and without
Result: negative

Method: other: Cytogenetic assay
GLP: no data
Test substance: no data

Remark: only abstract available; no further data
Test substance: formaldehyde; no data on purity of the compound

Reliability: (3) invalid
18-JUN-1998 (112)

Type: other: in vitro chromosomal aberrations - eukaryotes (mammalian cells)
System of testing: CHO cells
Concentration: 0.003 - 0.024 ul/ml
Metabolic activation: with and without
Result: positive

Method: other: Cytogenetic assay
GLP: no data
Test substance: no data

Remark: dose-related increase of all types of aberrations (gaps, breaks, exchanges); at all doses with and without S-9 mix; S-9 mix reduced the frequency of aberrations; all the aberrations were chromatid-type, indicating an S-phase-dependent agent; no data on toxicity.

Reliability: 2 (reliable with restrictions)
Test substance: formaldehyde; no data on purity of the compound
13-MAY-1998 (503)

Type: other: in vitro chromosomal aberrations - eukaryotes (mammalian cells)
System of testing: human lymphocytes
Concentration: 0.125 - 0.5 mM (ca. 3.75 - 15 mg/l)
Metabolic activation: without
Result: negative

Method: other: Cytogenetic assay
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Unstimulated human lymphocytes were used in the test. No increase in chromosomal changes was found in a conventional chromosome analysis in the first post-treatment metaphases. However, a dose-dependent clastogenic effect (ca. 4-5 fold) was observed using the premature chromosome condensation (PCC) technique, i.e. a high yield of fragments. No toxicity was observed.
Test substance: formaldehyde; no data on purity of the compound
13-MAY-1998 (201)

Type: other: in vitro chromosomal aberrations - eukaryotes (mammalian cells)
System of testing: human lymphocytes
Concentration: 0.032 - 1.0 mM (ca. 0.96 - 30 mg/l)
Metabolic activation: with and without
Result: positive

Method: other: Cytogenetic assay
GLP: no data
Test substance: no data

Remark: dose-related increase in the number of chromatid-type aberrations (gaps, breaks, exchanges); at 0.25 and 0.5 mM (7.5 and 15 mg/l, respectively) with and without S-9 mix

```
                    prepared from liver homogenate of Clophen A50 pretreated
                    Wistar rats; addition of S-9 mix reduced the yields; cell
                    proliferation was clearly reduced in the presence and
                    absence of S-9 with increasing formaldehyde concentrations.
                    Reliability: 2 (reliable with restrictions)
Test substance:     formaldehyde; no data on purity of the compound
13-MAY-1998                                                                (590)

Type:                       other: in vitro chromosomal aberrations - eukaryotes
                            (mammalian cells)
System of testing:          CHL cells
Concentration:              no data
Metabolic activation:       with and without
Result:                     positive

Method:             other: Cytogenetic assay
   GLP:             no data
Test substance:     no data

Remark:             Reliability: 2 (reliable with restrictions)
                    The test was performed in the presence and absence of S-9
                    mix prepared from liver homogenate of PCB (KC400)
                    pretreated Wistar rats. Clastogenic effects were observed
                    without S-9. D20 (concentration at which aberrations were
                    detected in 20%of the metaphases) = 0.018 mg/l.
Test substance:     formaldehyde; no data on purity of the compound
13-MAY-1998                                                                (354)

Type:                       other: in vitro chromosomal aberrations - eukaryotes
                            (mammalian cells)
System of testing:          CHO cells, AS52 cells
Concentration:              no data
Metabolic activation:       no data
Result:                     positive

Method:             other: Cytogenetic assay
   GLP:             no data
Test substance:     no data

Remark:             Induction of chromosome aberrations was quite similar in
                    the different cell lines and exhibits a similar threshold
                    and kinetics. Only abstract available; no further data.
                    Reliability: 2 (reliable with restrictions)
Test substance:     formaldehyde; no data on purity of the compound
02-FEB-1999                                                                (620)

Type:                       other: in vitro chromosomal aberrations - eukaryotes

                            (mammalian cells)
System of testing:          V79 cells
Concentration:              0.5 - 20 mg/l
Metabolic activation:       with and without
Result:                     positive

Method:             other: Cytogenetic assay
   GLP:             no data
Test substance:     no data

Remark:             - Exposure for 4 h: dose-related increase in chromosomal
                      aberrations at 7.5-20 mg/l without S-9 and at 10-20 mg/l
                      with S-9; weaker clastogenic response with S-9 (prepared
```

from liver homogenate of Aroclor pretreated Wistar rats); reduced mitotic index at doses >= 10 mg/l (-S-9) or at 20 mg/l (+S-9).
- Exposure for 2x4 h (with an interval of 24 h): dose-related increase on chromosomal aberrations at 7.5-20 mg/l with and without S-9.
- Exposure for 3x4 h (with an interval of 24 h): dose-related increase in chromosomal aberrations at 1.0-20 mg/l without S-9 and at 5-20 mg/l with S-9.

A dose-realted reduction in the number of mitoses was observed after multiple treatment. Weaker clastogenic and cytotoxic effects were found after the addition of S-9.
Reliability: 2 (reliable with restrictions)

Test substance: formaldehyde; no data on purity of the compound

30-JUN-1998 (483)

Type: other: in vitro chromosomal aberrations - eukaryotes (mammalian cells)
System of testing: V79 cells
Concentration: (a) 5-15 mg/l, 6 h; (b) 0.1-2.5 mg/l, 3x2 h within 1 day
Metabolic activation: without
Result: positive

Method: other: Micronucleus test
GLP: no data
Test substance: no data

Remark: After treatment of the cells for 6 h, a clear increase in micronucleated cells was found at 7-10 mg/l; a slight decrease in cell numbers was observed at doses >= 10 mg/l (protocol (a)).
After treatment for 3x2 h, a clear increase in micronucleated cells was observed at 0.1-1.0 mg/l; a slight decrease in cell numbers was found at >= 1.0 mg/l (protocol (b)).
Reliability: 2 (reliable with restrictions)

Test substance: formaldehyde; no data on purity of the compound

18-JUN-1998 (483)

Type: other: in vitro chromosomal aberrations - eukaryotes (mammalian cells)
System of testing: rat nasal epithelial cells
Concentration: 0.5-20 mg/l
Metabolic activation: with and without
Result: positive

Method: other: Cytogenetic assay
GLP: no data
Test substance: no data

Remark:
- treatment for 4 h: chromosomal aberrations only at 20 mg/l without S-9; increase in the mitotic index up to 7.5 mg/l (-S-9) or at 10 mg/l (+S-9 prepared from liver homogenate of Aroclor pretreated Wistar rats), then decrease.
- treatment for 2x4 h (with an interval of 24 h): dose-related increase in chromosomal aberrations only at doses >= 10 mg/l without S-9; increase in the mitotic index up to 5 mg/ (-S-9) or up to 10 mg/l (+S-9), then decrease.

```
                    - treatment for 3x4 h (with an interval of 24 h):
                      dose-related increase in chromosomal aberrations only at
                      doses >= 1.0 mg/l without S-9; increase in the mitotic
                      index up to 7.5 mg/l (+-S-9), then decrease.
   Reliability: 2 (reliable with restrictions)
Test substance: formaldehyde; no data on purity of the compound
18-JUN-1998                                                              (483)

Type:                     other: in vitro chromosomal aberrations - eukaryotes
                          (mammalian cells)
System of testing:        rat nasal epithelial cells
Concentration:            (a) 0.5-15 mg/l for 6 h; (b) 0.1-2.5 mg/l, 3x2 h within
                          1 day
Metabolic activation:     without
Result:                   positive

Method:            other: Micronucleus test
   GLP:            no data
Test substance:    no data

Remark:            A clear increase in micronuclei was observed at doses >10
                   and >=1.0 mg/l (protocol (a) and (b), respectively).
                   Reliability: 2 (reliable with restrictions)
Test substance:    formaldehyde; no data on purity of the compound
18-JUN-1998                                                              (483)

Type:                     other: in vitro chromosomal aberrations - eukaryotes
                          (mammalian cells)
System of testing:        human lymphocytes
Concentration:            10 - 5000 mg/l
Metabolic activation:     no data
Result:                   positive

Method:            other: Cytogenetic assay
   GLP:            no data
Test substance:    no data

Remark:            induction of polyploidy and chromosome aberrations; Russian
                   publication with English abstract
Test substance:    formaldehyde; no data on purity of the compound
Reliability:       (2)  valid with restrictions
18-JUN-1998                                                              (484)

Type:                     other: in vitro chromosomal aberrations - eukaryotes
                          (mammalian cells)
System of testing:        human lymphocytes
Concentration:            0.125 - 0.5 mM (ca. 3.75 - 15 mg/l)
Metabolic activation:     no data
Result:                   positive

Method:            other: Cytogenetic assay
   GLP:            no data
Test substance:    no data


Remark:            dose-dependent increase in premature chromosome
                   condensation (PCC) fragments in G0 lypmphocytes; only
                   abstract available; no further data
Test substance:    formaldehyde; no data on purity of the compound
Reliability:       (2)  valid with restrictions
18-JUN-1998                                                              (201)
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Type:                     other: in vitro chromosomal aberrations - eukaryotes
                          (mammalian cells)
System of testing:        rat nasal epithelial cells
Concentration:            no data
Metabolic activation:     no data
Result:                   positive

Method:            other: Micronucleus test
   GLP:            no data
Test substance:    no data

Remark:            significant increase in micronuclei formation; Japanese
                   publication with English abstract
Test substance:    formaldehyde; no data on purity of the compound
Reliability:       (3)  invalid
02-FEB-1999                                                              (237)

Type:                     other: in vitro chromosomal aberrations - eukaryotes
                          (mammalian cells)
System of testing:        CHO cells
Concentration:            up to 4 mg/l (-S-9); up to 3 mg/l (+S-9)
Metabolic activation:     with and without
Result:                   negative

Method:            other: Cytogenetic assay
   GLP:            no data
Test substance:    no data

Remark:            No chromosome aberrations both with and without S-9 mix
                   prepared from liver homogenate of Aroclor pretreated Wistar
                   rats. Higher doses were completely cytotoxic.
                   Reliability: 2 (reliable with restrictions)
Test substance:    formaldehyde; no data on purity of the compound
13-MAY-1998                                                              (111)

Type:                     other: in vitro chromosomal aberrations - eukaryotes
                          (mammalian cells)
System of testing:        CHL cells
Concentration:            15 mg/l
Metabolic activation:     no data
Result:                   positive

Method:            other: Cytogenetic assay
   GLP:            no data
Test substance:    no data

Remark:            Increase in chromosome aberrations after 48-h treatment; no
                   further data.
                   Reliability: 2 (reliable with restrictions)
Test substance:    formaldehyde; no data on purity of the compound
13-MAY-1998                                                              (353)
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```
Type:                     other: in vitro chromosomal aberrations - eukaryotes
                          (mammalian cells)
System of testing:        CHL cells
Concentration:            7.5 - 30 mg/l
Metabolic activation:     without
Result:                   positive

Method:            other: Cytogenetic assay
   GLP:            no data
Test substance:    no data

Remark:            Increase in chromosome aberrations after treatment for 24
                   and 48 h; no further data.
                   Reliability: 2 (reliable with restrictions)
Test substance:    formaldehyde; no data on purity of the compound
13-MAY-1998                                                                (352)

Type:                     other: in vitro DNA damage - prokaryotes (bacteria)
System of testing:        Escherichia coli K-12 uvrB+/recA+ (343/636), K-12
                          uvrB-/recA- (343/591)
Concentration:            up to 456 mmoles/l (ca. 13680 mg/l)
Metabolic activation:     without
Result:                   positive

Method:            other: DNA damage and repair assay
   GLP:            no data
Test substance:    no data

Remark:            Reliability: 2 (reliable with restrictions)
                   The viability of the DNA repair deficient strain was
                   significantly reduced at a lower concentration (0.456
                   mmoles/l; ca. 13.7 mg/l) than that of the DNA repair
                   proficient strain (1.52 mmoles/l; ca. 45.6 mg/l). At doses
                   >= 4.56 mmoles/l (ca. 136.8 mg/l), no surviving colonies
                   were found.
Test substance:    formaldehyde; no data on purity of the compound
18-JUN-1998                                                                (310)

Type:                     other: in vitro DNA damage - prokaryotes (bacteria)
System of testing:        Escherichia coli PQ37
Concentration:            1 - 30000 mg/l
Metabolic activation:     without
Result:                   positive

Method:            other: SOS chromotest
   GLP:            no data
Test substance:    no data

Remark:            Genotoxicity at 15-50 ug/ml, toxicity at doses >=50 ug/ml
                   Reliability: 2 (reliable with restrictions)
Test substance:    formaldehyde; no data on purity of the compound
18-JUN-1998                                                                (418)

Type:                     other: in vitro DNA damage - prokaryotes (bacteria)
System of testing:        Escherichia coli GE94, KY943 (lexA), KY945 (recA),
                          KY946 (uvrA)
Concentration:            no data
Metabolic activation:     without
Result:                   positive
```

```
Method:           other: Rec-lac test
   GLP:           no data
Test substance:   no data

Remark:           Reliability: 2 (reliable with restrictions)
                  The SOS-inducing activity was detectable in tester strains
                  GE94 and KY946, but not in tester strains KY943 and KY945.
                  Only abstract available; no further data.
Test substance:   formaldehyde; no data on purity of the compound
18-JUN-1998                                                              (516)

Type:                     other: in vitro DNA damage - prokaryotes (bacteria)
System of testing:        Escherichia coli KY945 (recA), KY946 (uvrA)
Concentration:            1.7 - 16.5 mg/l
Metabolic activation:     without
Result:                   positive

Method:           other: Rec-lac test
   GLP:           no data
Test substance:   no data

Remark:           Reliability: 2 (reliable with restrictions)
                  Tester strains KY946 and KY945 were positive (SOS
                  inducible) and negative (SOS uninducible) indicator strains,
                  respectively. A dose-dependent increase in
                  beta-galactosidase activity was observed in tester strain
                  KY946, but not in tester strain KY945.
Test substance:   formaldehyde; no data on purity of the compound
18-JUN-1998                                                              (517)

Type:                     other: in vitro DNA damage - prokaryotes (bacteria)
System of testing:        Salmonella typhimurium TA1535/pSK1002
Concentration:            no data
Metabolic activation:     no data
Result:                   positive

Method:           other: umu test
   GLP:           no data
Test substance:   no data

Remark:           positive reaction, i.e. induction of beta-galactosidase;
                  only abstract available; no further data.
Test substance:   formaldehyde; no data on purity of the compound
Reliability:      (3)  invalid
18-JUN-1998                                                              (521)

Type:                     other: in vitro DNA damage - prokaryotes (bacteria)
System of testing:        Salmonella typhimurium TA1535/pSK1002
Concentration:            3 - 30 mg/l
Metabolic activation:     without
Result:                   positive

Method:           other: umu test
   GLP:           no data
Test substance:   no data

Remark:           dose-dependent increase in beta-galactosidase activity (ca.
                  3-fold over background at 30 mg/l)
                  Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; no data on purity of the compound
```

18-JUN-1998 (522)

Type: other: in vitro DNA damage - prokaryotes (bacteria)
System of testing: Salmonella typhimurium TA1535/pSK1002
Concentration: 19 mg/ml
Metabolic activation: without
Result: positive

Method: other: umu
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
The induction of umu gene expression was defined on an increase in beta-galactosidase activity 2-fold over background level. According to the authors, the indicated concentration was the lowest one which induced umu gene expression.
Test substance: formaldehyde; no data on purity of the compound
18-JUN-1998 (502)

Type: other: in vitro DNA damage - prokaryotes (bacteria)
System of testing: Escherichia coli PQ37
Concentration: no data
Metabolic activation: no data
Result: negative

Method: other: SOS chromotest
GLP: no data
Test substance: no data

Remark: no increase in beta-galactosidase activity was observed; only abstract available; no further data.
Test substance: formaldehyde; no data on purity of the compound
Reliability: (3) invalid
02-FEB-1999 (720)

Type: other: in vitro DNA damage - prokaryotes (bacteria)
System of testing: Escherichia coli WP2 (repair-proficient), WP67 (uvrA- polA-), CM871 (uvrA- recA- lexA-)
Concentration: 0.004 or 0.008 mg
Metabolic activation: with and without
Result: positive

Method: other: DNA damage and repair assay
GLP: no data
Test substance: no data

Remark: Liquid micromethod procedure; reproducible induction of DNA damage in the presence and absence of S-9 mix prepared from liver homogenate of Aroclor pretreated rats was observed. According to the authors, the indicated doses were minimal inhibitory concentrations. No further data.
Reliability: 2 (reliable with restrictions)
Test substance: formaldehyde; no data on purity of the compound
18-JUN-1998 (179)

Type: other: in vitro DNA damage - prokaryotes (bacteria)
System of testing: Escherichia coli WP2 uvrA (repair-proficient), TM1080 (polA- lexA-)

```
Concentration:           10 ul
Metabolic activation:    without
Result:                  positive

Method:           other: DNA damage and repair assay
   GLP:           no data
Test substance:   no data


Remark:           A dose-dependent increase in diameters in the
                  repair-deficient tester strain was observed when compared
                  to the repair-proficient tester strain. According to the
                  authors, the indicated doses were minimal inhibitory
                  concentrations. No further data.
                  Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; no data on purity of the compound
18-JUN-1998                                                              (179)

Type:                    other: in vitro DNA damage - lower eukaryotes (yeast,
                         fungi)
System of testing:       Saccharomyces cerevisia D61.M
Concentration:           50 - 137 nl/ml
Metabolic activation:    without
Result:                  positive

Method:           other: DNA damage
   GLP:           no data
Test substance:   no data

Remark:           A dose-related induction of mitotic recombination was
                  observed at doses of 75-100 nl/ml.
                  Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-1998                                                              (732)

Type:                    other: in vitro DNA damage - lower eukaryotes (yeast,
                         fungi)
System of testing:       Saccharomyces cerevisia D3, D4
Concentration:           6 - 60 mM (ca. 180 - 1800 mg/l)
Metabolic activation:    without
Result:                  positive

Method:           other: DNA damage
   GLP:           no
Test substance:   no data

Remark:           Induction of intergenic recombinants was observed with
                  tester strain D3 at 60 mM. A dose-related increase in ADE+
                  and TRP+ intragenic recombinants was observed with tester
                  strain D4 at >=20 mM (ca. 600 mg/l). A decrease in survival
                  was found in both tester strains at concentrations >20 mM.
                  Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-1998                                                              (134)

Type:                    other: in vitro DNA damage - prokaryotes (bacteria)
System of testing:       Saccharomyces cerevisia N123 (wild type), rad1-3,
                         rad3-e5
Concentration:           8.2 - 66 mM (ca. 246 - 1980 mg/l)
Metabolic activation:    without
```

Result: positive

Method: other: DNA damage and repair assay
GLP: no data
Test substance: no data

Remark: A dose-related increase in single strand breaks (SSB) in DNA of exponential phase cells of the wild type strain was observed. Strains defective in excision-repair showed a reduced capacity to undergo SSB after treatment. Analysis was performed by the use of the alkaline sucrose gradients technique. According to the authors, the appearance of SSB might be a step in a repair process of formaldehyde lesions. Reliability: 2 (reliable with restrictions)
Test substance: formaldehyde; no data on purity of the compound
18-JUN-1998 (445)

Type: other: in vitro DNA damage - eukaryotes (mammalian cells/SCE)
System of testing: V79 cells
Concentration: 0.033 - 0.54 mM (ca. 1 - 16.2 mg/l)
Metabolic activation: with and without
Result: positive

Method: other: Sister chromatid exchange assay
GLP: no data
Test substance: no data

Remark: A dose- and exposure-dependent (1, 2, 3, or 28 h) frequency with a 3- to 4-fold increase was found at non-toxic doses without S-9 mix; S-9 mix (prepared from liver homogenate of Aroclor pretreated Wistar rats) as well as primary hepatocytes (prepared from Aroclor pretreated Wistar rats) reduced the SCE frequency to nearly control value. According to the authors, the decrease in genotoxicity was due to a rapid metabolism and not to an unspecific binding to the macromolecules of the S-9 mix or hepatocytes; toxicity was reduced after adding a metabolizing system. Reliability: 2 (reliable with restrictions)
Test substance: formaldehyde; no data on purity of the compound
13-MAY-1998 (49) (50)

Type: other: in vitro DNA damage - eukaryotes (mammalian cells/SCE)
System of testing: CHO cells
Concentration: 1 - 4 mg/l (-S-9), 0.5 - 3 mg/l (+S-9)
Metabolic activation: with and without
Result: positive

Method: other: Sister chromatid exchange assay
GLP: no data
Test substance: no data

Remark: Induction of SCE both with and without S-9 mix prepared

fromliver homogenate of Aroclor pretreated Wistar rats, but without any dose-related effect; S-9 activation lowered the minimum effective concentration for SCE induction. Reliability: 2 (reliable with restrictions)

```
Test substance:   formaldehyde; no data on purity of the compound
18-JUN-1998                                                          (111)

Type:                     other: in vitro DNA damage - eukaryotes (mammalian
                          cells/SCE)
System of testing:        CHO cells
Concentration:            no data
Metabolic activation:     with and without
Result:                   positive

Method:           other: Sister chromatid exchange assay
   GLP:           no data
Test substance:   no data

Remark:           dose-related increase with and without S-9 mix; only
                  abstract available, no further data
Test substance:   formaldehyde; no data on purity of the compound
Reliability:      (3)  invalid
18-JUN-1998                                                          (112)

Type:                     other: in vitro DNA damage - eukaryotes (mammalian
                          cells/SCE)
System of testing:        CHO cells
Concentration:            (a) 0.5-5.0 mg/l (-S-9); (b) 1.6-16 mg/l (+S-9); (c)
                          0.37-3.7 mg/l (-S-9); (d) 6.0-11.0 mg/l (-S-9); (e)
                          0.37-3.7 (+S-9); (f) 6.0-11.0 mg/l (+S-9)
Metabolic activation:     with and without
Result:                   positive

Method:           other: Sister chromatid exchange assay
   GLP:           no data
Test substance:   no data

Remark:           (a): negative result
                  (b), (e): positive result at only 1 dose
                  (c), (d), (f): positive result
                  S-9 prepared from liver homogenate of Aroclor pretreated
                  Wistar rats
                  The tests were performed by 2 different laboratories (lab.
                  1: protocols (a) and (b), Lab. 2: protocols (c) - (f)).
                  Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-1998                                                          (240)

Type:                     other: in vitro DNA damage - eukaryotes (mammalian
                          cells/SCE)
System of testing:        human lymphocytes
Concentration:            0.05 - 100 mg/l
Metabolic activation:     without
Result:                   positive

Method:           other: Sister chromatid exchange assay
   GLP:           no data
Test substance:   no data

Remark:           elevated SCE/cell at a dose range of 1 - 10 mg/l;
                  cytotoxicity (30% decrease in viability) at already 0.05
                  mg/l (Abstract, no further details)
```

```
                  Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; no data on purity of the compound
18-JUN-1998                                                          (246)

Type:                     other: in vitro DNA damage - eukaryotes (mammalian
                          cells/SCE)
System of testing:        human lymphocytes
Concentration:            0.1 - 15 mg/l
Metabolic activation:     no data
Result:                   positive

Method:           other: Sister chromatid exchange assay
   GLP:           no data
Test substance:   no data

Remark:           Increase in the number of SCE with a statistical
                  significance at doses >= 10 mg/l; Polish publication with
                  English abstract.
                  Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-1998                                                           (51)

Type:                     other: in vitro DNA damage - eukaryotes (mammalian
                          cells/SCE)
System of testing:        human lymphocytes
Concentration:            0.01 - 100 mg/l
Metabolic activation:     without
Result:                   positive

Method:           other: Sister chromatid exchange assay
   GLP:           no data
Test substance:   no data

Remark:           low SCE induction rate at doses > 5 mg/l; cytotoxicity
                  at all doses; significant SCE induction only at 80%
                  nonviable cells
                  Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; no data on purity of the compound
18-JUN-1998                                                          (405)

Type:                     other: in vitro DNA damage - eukaryotes (mammalian
                          cells/SCE)
System of testing:        CHO cells
Concentration:            0.003 - 0.024 ul/ml
Metabolic activation:     with and without
Result:                   positive

Method:           other: Sister chromatid exchange assay
   GLP:           no data
Test substance:   no data

Remark:           dose-related increase in the SCE frequency with and without
                  S-9 mix; slight reduction of SCE frequencies with S-9
                  Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; no data on purity of the compound

13-MAY-1998                                                          (503)
```

```
Type:                     other: in vitro DNA damage - eukaryotes (mammalian
                          cells/SCE)
System of testing:        CHO cells
Concentration:            0.0001 - 0.0004 %
Metabolic activation:     without
Result:                   positive

Method:            other: Sister chromatid exchange assay
   GLP:            no data
Test substance:    no data

Remark:            Reliability: 2 (reliable with restrictions)
                   Slight, but dose-dependent increase in the SCE frequency;
                   increase ca. 2-fold over background
Test substance:    formaldehyde; no data on purity of the compound
13-MAY-1998                                                              (520)

Type:                     other: in vitro DNA damage - eukaryotes (mammalian
                          cells/SCE)
System of testing:        human lymphocytes
Concentration:            0.0001 - 0.001 %
Metabolic activation:     without
Result:                   positive

Method:            other: Sister chromatid exchange assay
   GLP:            no data
Test substance:    no data

Remark:            Reliability: 2 (reliable with restrictions)
                   Slight, but dose-dependent increase in the SCE frequency;
                   increase ca. 4-fold over background
Test substance:    formaldehyde; no data on purity of the compound
13-MAY-1998                                                              (520)

Type:                     other: in vitro DNA damage - eukaryotes (mammalian
                          cells/SCE)
System of testing:        human lymphocytes
Concentration:            0.032 - 1.0 mM (ca. 1.0 - 30 mg/l)
Metabolic activation:     with and without
Result:                   positive

Method:            other: Sister chromatid exchange assay
   GLP:            no data
Test substance:    no data

Remark:            Dose-related increase in SCE frequencies with and without
                   S-9 mix prepared from liver homogenate of Clophen A50
                   induced Wistar rats at 0.125 - 0.25 (ca. 3.75 - 7.5 mg/l);
                   at 0.5 mM (ca. 15 mg/l) with S-9 mix, SCE frequency was
                   significantly reduced.
                   Reliability: 2 (reliable with restrictions)
Test substance:    formaldehyde; no data on purity of the compound
13-MAY-1998                                                              (590)

Type:                     other: in vitro DNA damage - eukaryotes (mammalian
                          cells/SCE)
System of testing:        V79 cells
Concentration:            0.5 - 20 mg/l
Metabolic activation:     with and without
Result:                   positive
```

```
Method:            other: Sister chromatid exchange assay
   GLP:            no data
Test substance:    no data

Remark:            - exposure for 4 h; dose-related increase at 0.5-5 mg/l
                     without S-9 (prepared from liver homogenate of Aroclor
                     pretreated Wistar rats) and at 2.5-15 mg/l with S-9;
                     toxicity was observed at doses >= 7.5 mg/l (-S-9) or at 20
                     mg/l (+S-9).
                   - exposure for 2x4 h: dose-related increase at 0.5-5 mg/l
                     (-S-9) and at 0.5-10 mg/l (+S-9); toxicity was observed at
                     >=7.5 mg/l (-S-9) and at >=15 mg/l (+S-9).
                   - exposure for 3x4 h: dose-related increase at 0.5-2.5 mg/l
                     (-S-9) and at 0.5-7.5 mg/l (+S-9); toxicity was observed
                     at >=5 mg/l (-S-9) and at >=10 mg/l (+S-9).
                   Reliability: 2 (reliable with restrictions)
Test substance:    formaldehyde; no data on purity of the compound
13-MAY-1998                                                                (483)

Type:                     other: in vitro DNA damage - eukaryotes (mammalian
                          cells/SCE)
System of testing:        rat nasal epithelial cells
Concentration:            0.5 - 20 mg/l
Metabolic activation:     with and without
Result:                   positive

Method:            other: Sister chromatid exchange assay
   GLP:            no data
Test substance:    no data

Remark:            - treatment for 4 h; dose-related increase in the SCE
                     frequency at 5-15 mg/l without S-9 (prepared from liver
                     homogenate of Aroclor pretreated Wistar rats); no
                     differential stained cells at 20 mg/l; weakly positive
                     reaction at 20 mg/l with S-9; significant reduction of MII
                     cells at >= 10 mg/l (-S-9); toxicity was reduced after
                     adding a metabolizing system.
                   - treatment for 2x4 h (with an interval of 24 h):
                     dose-related increase at 5-10 mg/l (-S-9) and at 15-20
                     mg/l (+S-9).
                   - treatment for 3x4 h (with an interval of 24 h):
                     dose-relatd increase at 1-10 mg/l (-S-9) and at 10-15
                     mg/l (+S-9).
                   Toxicity was observed at a dose >10 mg/l (-S-9) after 2 or
                   3 treatments and at 20 mg/l (+S-9) after 3 treatments.
                   Reliability: 2 (reliable with restrictions)
Test substance:    formaldehyde; no data on purity of the compound
13-MAY-1998                                                                (483)

Type:                     other: in vitro DNA damage - eukaryotes (mammalian
                          cells/UDS)
System of testing:        HeLa S3 cells
Concentration:            10E-6 - 10E-8 M (ca. 0.03 - 0.0003 mg/l)
Metabolic activation:     without
Result:                   positive

Method:            other: Unscheduled DNA synthesis
   GLP:            no data
Test substance:    no data
```

```
Remark:           induction of UDS; 56 dpm/ug DNA above background
                  Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-1998                                                        (464)

Type:                     other: in vitro DNA damage - eukaryotes (mammalian
                          cells/UDS)
System of testing:        CDF rat tracheal epithelial cells
Concentration:            1 - 1000 uM (ca. 0.03 - 30 mg/l)
Metabolic activation:     no data
Result:                   negative

Method:           other: Unscheduled DNA synthesis
   GLP:           no data
Test substance:   no data

Remark:           no induction of UDS; cytotoxicity at doses >100 uM
                  Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-1998                                                        (196)

Type:                     other: in vitro DNA damage - eukaryotes (mammalian
                          cells/UDS)
System of testing:        human bronchial epithelial cells
Concentration:            1 - 100 uM (ca. 0.03 - 3 mg/l), 1 - 100 mM (ca. 30 -
                          3000 mg/l)
Metabolic activation:     without
Result:                   negative

Method:           other: Unscheduled DNA synthesis
   GLP:           no data
Test substance:   no data

Remark:           no induction of UDS; DNA repair was assessed by
                  quantitative autoradiography; cell lethality at 1-100 mM
                  Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-1998                                                        (197)

Type:                     other: in vitro DNA damage - eukaryotes (mammalian
                          cells/UDS)
System of testing:        F-344 rat nasal epithelial cells (nasal- and maxillar
                          turbinates)
Concentration:            0.05 - 1.0 mM (ca. 1.5 - 30 mg/l)
Metabolic activation:     without
Result:                   positive

Method:           other: Unscheduled DNA synthesis
   GLP:           no data
Test substance:   no data

Remark:           Reliability: 2 (reliable with restrictions)
                  UDS (and scheduled DNA synthesis) was stimulated at
                  0.05-0.1 mM and inhibited at 0.1-1.0 mM; quantitative
                  differences were observed in the response of nasal- and
                  maxillar turbinates
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-1998                                                         (66)

Type:                     other: in vitro DNA damage - eukaryotes (mammalian
                          cells/UDS)
```

```
System of testing:       human bronchial fibroblasts
Concentration:           100 - 1000 uM (ca. 3 - 30 mg/l)
Metabolic activation:    without
Result:                  negative

Method:           other: Unscheduled DNA synthesis
   GLP:           no data
Test substance:   no data

Remark:           no significant increase in UDS; formaldehyde inhibited UDS
                  by UV irradiation
                  Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-1998                                                              (269)

Type:                    other: in vitro DNA damage - eukaryotes (mammalian
                         cells/UDS)
System of testing:       human fibroblasts
Concentration:           0.05 - 2 mM (ca. 1.5 - 60 mg/l)
Metabolic activation:    without
Result:                  negative

Method:           other: Unscheduled DNA synthesis
   GLP:           no data
Test substance:   no data

Remark:           no induction of UDS; formaldehyde treatment caused
                  alterations in deoxynuceloside uptake
                  Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-1998                                                              (615)

Type:                    other: in vitro DNA damage - eukaryotes (mammalian
                         cells/UDS)
System of testing:       F-344 rat hepatocytes
Concentration:           no data
Metabolic activation:    no data
Result:                  positive

Method:           other: Unscheduled DNA synthesis
   GLP:           no data
Test substance:   no data

Remark:           dose-related increase in net grain counts at least at 2
                  concentrations; according to the authors, the lowest
                  positive concentration used was 400 mM (12000 mg/l).
                  Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-1998                                                              (705)

Type:                    other: in vitro DNA damage - eukaryotes (mammalian
                         cells/DNA strand breaks)
System of testing:       F344 rat tracheal epithel cells
Concentration:           100 - 400 uM (ca. 3 - 12 mg/l)
Metabolic activation:    without
Result:                  positive

Method:           other: alkaline elution assay (DNA strand breaks)
   GLP:           no data
Test substance:   no data
```

```
Remark:           dose-related increase in single strand breaks (SSB) up to
                  400 uM; SSB were repaired within 2 h; rapid and complete
                  removal of SSB within 2 h
                  Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-2003                                                          (157)

Type:                     other: in vitro DNA damage - eukaryotes (mammalian
                          cells/DNA strand breaks)
System of testing:        mouse leukemia L1210 cells
Concentration:            up to 300 uM (ca. 9 mg/l)
Metabolic activation:     without
Result:                   positive

Method:           other: alkaline elution assay (DNA strand break)
   GLP:           no data
Test substance:   no data

Remark:           A small number of single strand breaks (SSB) occurred at
                  200 uM with an increase up to 300 uM. According to the
                  authors, DNA damage was accompanied by inhibition of DNA
                  synthesis. Extensive DNA-protein crosslinks (DPC) which were
                  repaired after removal of the test substance were observed.
                  Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-2003                                                          (565)

Type:                     other: in vitro DNA damage - eukaryotes (mammalian
                          cells/DNA strand breaks)
System of testing:        mouse lymphoma cells
Concentration:            no data
Metabolic activation:     without
Result:                   positive

Method:           other: alkaline unwinding assay (DNA strand breaks)
   GLP:           no data
Test substance:   no data

Remark:           Reliability: 2 (reliable with restrictions)
                  single strand breaks were observed; only abstract
                  available;no further data
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-2003                                                          (241)

Type:                     other: in vitro DNA damage - eukaryotes (mammalian
                          cells/DNA strand breaks)
System of testing:        mouse lymphoma cells
Concentration:            0.03 - 1.1 mmoles/l (ca. 0.9 - 33 mg/l)
Metabolic activation:     without
Result:                   negative

Method:           other: alkaline unwinding assay (DNA strand breaks)
   GLP:           no data
Test substance:   no data

Remark:           No induction of double and single strand breaks was
                  observed; only abstract available; no further data
Test substance:   formaldehyde; no data on purity of the compound
Reliability:      (2)  valid with restrictions
13-MAY-2003                                                          (239)
```

```
Type:                     other: in vitro DNA damage - eukaryotes (mammalian
                          cells/DNA strand breaks)
System of testing:        human fibroblasts
Concentration:            0.1, 1 mM (ca. 3, 30 mg/l)
Metabolic activation:     without
Result:                   positive

Method:            other: Nick translation assay (DNA strand breaks)
   GLP:            no data
Test substance:    no data

Remark:            induction of DNA damage (DNA strand breaks) as measured by
                   the incorporation of dCTP into the DNA; little or no
                   reduction of long-patch repair
                   Reliability: 2 (reliable with restrictions)
Test substance:    formaldehyde; no data on purity of the compound
13-MAY-2003                                                                (614)

Type:                     other: in vitro DNA damage - eukaryotes (mammalian
                          cells/DNA strand breaks)
System of testing:        human fibroblasts
Concentration:            100 - 500 uM (ca. 3 - 15 mg/l)
Metabolic activation:     without
Result:                   negative

Method:            other: alkaline sucrose sedimentation assay (DNA strand
                   breaks)
   GLP:            no data
Test substance:    no data

Remark:            no DNA strand breaks up to 250 uM (ca. 7.5 mg/l); doses
                   >=250 uM caused sedimentation anomalies
                   Reliability: 2 (reliable with restrictions)
Test substance:    formaldehyde; no data on purity of the compound
13-MAY-2003                                                                (615)

Type:                     other: in vitro DNA damage - eukaryotes (mammalian
                          cells/DNA strand breaks)
System of testing:        human fibroblasts
Concentration:            0.1 - 10 mM (ca. 3 - 300 mg/l)
Metabolic activation:     without
Result:                   positive

Method:            other: Nick translation assay (DNA strand breaks)other: in
                   vitro DNA damage - eukaryotes (mammalian cells/DNA strand
                   breaks)
   GLP:            no data
Test substance:    no data

Remark:            induction of DNA damage (DNA strand breaks) as measured by
                   the incorporation of dNTPs into the DNA; higher doses (>=
                   1mM) were inhibitory in this assay
                   Reliability: 2 (reliable with restrictions)
Test substance:    formaldehyde; no data on purity of the compound
13-MAY-2003                                                                (615)

Type:                     other: in vitro DNA damage - eukaryotes (mammalian
                          cells/DNA strand breaks)
System of testing:        human bronchial epithelial cells
Concentration:            0.1 mM (ca. 3 mg/l)
Metabolic activation:     without
```

```
Result:                  positive

Method:           other: alkaline elution assay (DNA strand break)
   GLP:           no data

Test substance:   no data

Remark:           induction of a significant level of single strand breaks
                  (SSB); according to the authors, formaldehyde caused
                  substantially higher levels of DNA-Protein cross links
                  (DPC) than SSB
                  Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; no data on purity of the compound

13-MAY-2003                                                          (580)

Type:                    other: in vitro DNA damage - eukaryotes (mammalian
                         cells/DNA strand breaks)
System of testing:       primary rat hepatocytes, SV-40 transformed CHO cells
                         CO631
Concentration:           no data
Metabolic activation:    without
Result:                  positive

Method:           other: alkaline elution assay (DNA strand break)
   GLP:           no data
Test substance:   no data

Remark:           Reliability: 2 (reliable with restrictions)
                  slight increase in single strand breaks (2-3-fold) in both
                  cell lines; induction of DNA amplification (SDA) in CHO
                  cells; no further data
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-2003                                                          (547)

Type:                    other: in vitro DNA damage - eukaryotes (mammalian
                         cells/DNA strand breaks)
System of testing:       Yoshida lymphosarcoma cells
Concentration:           250 uM (ca. 7.5 mg/l)
Metabolic activation:    without
Result:                  positive

Method:           other: alkaline elution assay (DNA strand break)
   GLP:           no data
Test substance:   no data

Remark:           induction of a small number of single strand breaks;
                  according to the authors, formaldehyde caused several-fold
                  higher levels of DNA-Protein Crosslinks
                  Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-2003                                                          (518)

Type:                    other: in vitro DNA damage - eukaryotes (mammalian
                         cells/DNA strand breaks)
System of testing:       primary rat tracheal cells, rat tracheal epithelial
                         cell line C18
Concentration:           200 uM (ca. 6 mg/l)
Metabolic activation:    without
Result:                  positive
```

```
Method:           other: alkaline elution assay (DNA strand break)
   GLP:           no data
Test substance:   no data

Remark:           induction of a few single strand breaks in both C18 and
                  primary cells; only abstract available; no further data
                  Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; no data on purity of the compound

13-MAY-2003                                                          (155)

Type:                     other: in vitro DNA damage - eukaryotes (mammalian
                          cells/DNA strand breaks)
System of testing:        primary rat tracheal cells

Concentration:            200 uM (ca. 6 mg/l)
Metabolic activation:     without
Result:                   positive

Method:           other: alkaline elution assay (DNA strand break)
   GLP:           no data
Test substance:   no data

Remark:           induction of single strand breaks (SSB), SSB were removed
                  within 2 h; only abstract available; no further data
                  Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-2003                                                          (158)

Type:                     other: in vitro DNA damage - eukaryotes (mammalian
                          cells/DNA strand breaks)
System of testing:        human cells: bronchial epithelial cells
Concentration:            100 uM (ca. 3 mg/l)
Metabolic activation:     without
Result:                   positive

Method:           other: alkaline elution assay (DNA strand break)
   GLP:           no data
Test substance:   no data

Remark:           induction of single strand breaks (SSB); according to the
                  authors, formaldehyde caused 7-fold higher levels of
                  DNA-Protein Crosslinks (DPC) than SSB.
                  Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-2003                                                          (297)

Type:                     other: in vitro DNA damage - eukaryotes (mammalian
                          cells/DNA strand breaks)
System of testing:        human cells: bronchial epithelial cells, bronchial
                          fibroblasts
Concentration:            0.8 mM (ca. 24 mg/l)
Metabolic activation:     without
Result:                   negative

Method:           other: alkaline elution assay (DNA strand break)
   GLP:           no data
Test substance:   no data
```

Remark: no increase in single strand breaks (SSB); according to the authors, a significant accumulation of SSB was observed after treatment with formaldehyde combined with polymerase inhibitors
Reliability: 2 (reliable with restrictions)
Test substance: formaldehyde; no data on purity of the compound

13-MAY-2003 (231)

Type: other: in vitro DNA damage - eukaryotes (mammalian cells/DNA strand breaks)
System of testing: human cells: bronchial epithelial cells, bronchial fibroblasts
Concentration: up to 500 uM (ca. 15 mg/l)
Metabolic activation: without
Result: positive

Method: other: alkaline elution assay (DNA strand break)
GLP: no data
Test substance: no data

Remark: dose-dependent increase in single strand breaks (SSB) in both cell types; according to the authors, formaldehyde inhibited DNA-repair (resealing of SSB and inhibition of UDS)
Reliability: 2 (reliable with restrictions)
Test substance: formaldehyde; no data on purity of the compound
13-MAY-2003 (269)

Type: other: in vitro DNA damage - eukaryotes (mammalian cells/DNA strand breaks)
System of testing: human cells: bronchial epithelial cells
Concentration: 0.1 mM (ca. 3000 mg/l)
Metabolic activation: without
Result: positive

Method: other: alkaline elution assay (DNA strand break)
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
slight increase in single strand breaks (SSB); according to the authors, formaldehyde caused several-fold higher levels of DNA-Protein Crosslinks (DPC); the effect occurred at moderate levels of cytotoxicity.
Test substance: formaldehyde; no data on purity of the compound
13-MAY-2003 (268)

Type: other: in vitro DNA damage - eukaryotes (mammalian cells/DNA strand breaks)
System of testing: human cells: bronchial epithelial cells
Concentration: 0.4 mM (ca. 12 mg/l)
Metabolic activation: without
Result: positive

Method: other: alkaline elution assay (DNA strand break)
GLP: no data
Test substance: no data

```
Remark:           Reliability: 2 (reliable with restrictions)
                  slight increase in single strand breaks (SSB); according to
                  the authors, formaldehyde dose that inhibited Colony-Forming
                  Efficiency (CFE) to 50% was used.
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-2003                                                              (272)

Type:                     other: in vitro DNA damage - eukaryotes (mammalian
                          cells/DNA strand breaks)

System of testing:        B6C3F1 mouse hepatocytes
Concentration:            0.25, 0.5 mM (ca. 7.5, 15 mg/l)
Metabolic activation:     without
Result:                   positive

Method:           other: alkaline elution assay (DNA strand break)
   GLP:           no data
Test substance:   no data

Remark:           Reliability: 2 (reliable with restrictions)
                  significant and dose-related increase in single strand
                  breaks (SSB) at doses >= 0.25 mM
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-2003                                                        (275) (276)

Type:                     other: in vitro DNA damage - eukaryotes (mammalian
                          cells/DNA strand breaks)
System of testing:        AP rat hepatocytes
Concentration:            1 - 5 mM (ca. 30 - 150 mg/l)
Metabolic activation:     without
Result:                   positive

Method:           other: alkaline elution assay (DNA strand break)
   GLP:           no data
Test substance:   no data

Remark:           Reliability: 2 (reliable with restrictions)
                  significant and dose-related increase in single strand
                  breaks (SSB) at doses >= 1 mM
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-2003                                                        (275) (276)

Type:                     other: in vitro DNA damage - eukaryotes (mammalian
                          cells/DNA strand breaks)
System of testing:        CHO cells
Concentration:            0.125 - 0.5 mM (ca. 3.75 - 15 mg/l) (-S-9); 2.0 - 4.0
                          mM (ca. 60 - 120 mg/l) (+S-9)
Metabolic activation:     with and without
Result:                   positive

Method:           other: alkaline elution assay (DNA strand break)
   GLP:           no data
Test substance:   no data

Remark:           Reliability: 2 (reliable with restrictions)
                  significant and dose-related increase in single strand
                  breaks (SSB) with and without mouse liver S-9; in the
                  presence of S-9, higher concentrations of the test substance
                  were needed to induce DNA damage
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Test substance: formaldehyde; no data on purity of the compound
13-MAY-2003 (275) (276)

Type: other: in vitro DNA damage - eukaryotes (mammalian cells/DNA strand breaks)
System of testing: F344 rat hepatocytes
Concentration: 0.5 - 4.0 mM (ca. 15 - 120 mg/l)
Metabolic activation: without
Result: positive

Method: other: alkaline elution assay (DNA strand break)
GLP: no data
Test substance: no data

Remark: dose-related induction of single strand breaks (SSB) at doses of 0.75-1.5 mM (ca. 22.5-45 mg/l); no induction of double strand breaks (DSB) was observed up to 4.0 mM; 2 mM formaldehyde decreased intracellular glutathione content (60% of control)
Reliability: 2 (reliable with restrictions)
Test substance: formaldehyde; no data on purity of the compound
13-MAY-2003 (184)

Type: other: in vitro DNA damage - eukaryotes (mammalian cells/DNA strand breaks)
System of testing: human cells: skin fibroblasts, bronchial fibroblasts, bronchial epithelial cells, XP skin fibroblasts
Concentration: 0.1 - 1.0 mM (ca. 3 - 30 mg/l)
Metabolic activation: without
Result: positive

Method: other: alkaline elution assay (DNA strand break)
GLP: no data
Test substance: no data

Remark: dose-related increase in single strand breaks (SSB) in all cell types; formaldehyde caused more SSB in normal cell types than in the xeroderma pigmentosum (XP) cells; formaldehyde was only moderately toxic to normal cells at DNA damaging concentrations.
Reliability: 2 (reliable with restrictions)
Test substance: formaldehyde; no data on purity of the compound
13-MAY-2003 (271)

Type: other: in vitro DNA damage - eukaryotes (mammalian cells/DNA strand breaks)
System of testing: human fibroblasts N1, N2, XP1, XP2
Concentration: 0.8 mM (ca. 24 mg/l)
Metabolic activation: without
Result: negative

Method: other: alkaline elution assay (DNA strand break)
GLP: no data
Test substance: no data

Remark: no appreciable level of single strand breaks (SSB); in the presence of a polymerase inhibitor, a signifcant level of SSB accumulated in normal cells (N1, N2) but not in excision-deficient xeroderma pigmentosum cells was found.
Reliability: 2 (reliable with restrictions)

Test substance: formaldehyde; no data on purity of the compound
13-MAY-2003 (232)

Type: other: in vitro DNA damage - eukaryotes (mammalian cells/DNA strand breaks)
System of testing: Sprague-Dawley rat hepatocytes; SV-40 transformed Chinese hamster embryo cells CO631, CO60
Concentration: 0.002- 0.016 umoles (ca. 6x10E-6 - 4.8x10E-4 mg)
Metabolic activation: with and without
Result: positive

Method: other: alkaline elution assay (DNA strand break)
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
The hepatocytes were testes without metabolic activation; the CHO cells were testes with and without metabolic activation. The test substance was a weak inducer of single strand breaks (SSB) in hepatocytes and in CO631 cells. DNA amplification (SDA) was not detected in CHO cells (C0631 and CO60).
Test substance: formaldehyde; no data on purity of the compound
13-MAY-2003 (234)

Type: other: in vitro DNA damage - eukaryotes (mammalian cells/DNA-protein crosslinks)
System of testing: F344 rat tracheal epithelial cells
Concentration: 0.05 - 0.4 mM (ca. 1.5 - 12 mg/l)
Metabolic activation: without
Result: positive

Method: other: alkaline elution assay (DNA-protein crosslinks)
GLP: no data
Test substance: no data

Remark: dose-dependent formation of DNA-Protein Crosslinks (DPC) up to 0.4 mM; after 16 h, most of the DPC were eliminated
Reliability: 2 (reliable with restrictions)

Test substance: formaldehyde; no data on purity of the compound
07-MAY-1998 (157)

Type: other: in vitro DNA damage - eukaryotes (mammalian cells/DNA-protein crosslinks)
System of testing: rat tracheal epithelial cell line, C18
Concentration: 0.1 - 0.4 mM (ca. 3 - 12 mg/l)
Metabolic activation: without
Result: positive

Method: other: alkaline elution assay (DNA-protein crosslinks)
GLP: no data
Test substance: no data

Remark: formation of DNA-Protein Crosslinks (DPC) linear up to 0.4 mM; treatment for 90 min reduced the Colony-Forming Efficiency (CFE) at 0.4 mM (25% of control)
Reliability: 2 (reliable with restrictions)
Test substance: formaldehyde; no data on purity of the compound
13-MAY-1998 (156)

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Type:                     other: in vitro DNA damage - eukaryotes (mammalian
                          cells/DNA-protein crosslinks)
System of testing:        primary rat tracheal cells
Concentration:            0.2 mM (ca. 6 mg/l)
Metabolic activation:     without
Result:                   positive

Method:            other: alkaline elution assay (DNA-protein crosslinks)
   GLP:            no data
Test substance:    no data

Remark:            formation of DNA-Protein Crosslinks (DPC); complete repair
                   of DPC took 24 h; only abstract available, no further data
Test substance:    formaldehyde; no data on purity of the compound
Reliability:       (2)  valid with restrictions
18-JUN-1998                                                              (158)

Type:                     other: in vitro DNA damage - eukaryotes (mammalian
                          cells/DNA-protein crosslinks)
System of testing:        primary rat tracheal cells, rat tracheal epithelial
                          cell line C18
Concentration:            200 uM (ca. 6 mg/l)
Metabolic activation:     without
Result:                   positive

Method:            other: alkaline elution assay (DNA-protein crosslinks)
   GLP:            no data
Test substance:    no data

Remark:            Reliability: 2 (reliable with restrictions)
                   significant production of DNA-Protein Crosslinks (DPC) in
                   both cell types; similar removal rates of DPC in both cell
                   lines; only abstract available; no further data
Test substance:    formaldehyde; no data on purity of the compound

13-MAY-1998                                                              (155)

Type:                     other: in vitro DNA damage - eukaryotes (mammalian
                          cells/DNA-protein crosslinks)
System of testing:        human cells: bronchial epithelial cells
Concentration:            0.4 mM (ca. 12 mg/l)
Metabolic activation:     without
Result:                   positive

Method:            other: alkaline elution assay (DNA-protein crosslinks)
   GLP:            no data
Test substance:    no data

Remark:            Reliability: 2 (reliable with restrictions)
                   significant production of DNA-Protein Croslinks (DPC); DPC
                   were formed at ca. 10-fold higher amounts than single strand
                   breaks (SSB) at doses that decreased Colony-Forming
                   Efficiency (CFE) to 50%.
Test substance:    formaldehyde; no data on purity of the compound
13-MAY-1998                                                              (272)

Type:                     other: in vitro DNA damage - eukaryotes (mammalian
                          cells/DNA-protein crosslinks)
System of testing:        human cells: bronchial epithelial cells, bronchial
                          fibroblasts
Concentration:            0.1 mM (ca. 3 mg/l)
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Metabolic activation:    without
Result:                  positive

Method:           other: alkaline elution assay (DNA-protein crosslinks)
   GLP:           no data
Test substance:   no data

Remark:           formation of DNA-Protein Crosslinks (DPC) to a similar
                  extent in both cells types; the half-time of removal was ca.
                  2 h for both cell types
                  Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-1998                                                              (269)

Type:                    other: in vitro DNA damage - eukaryotes (mammalian
                         cells/DNA-protein crosslinks)
System of testing:       human cells: bronchial epithelial cells
Concentration:           0.1 m uM (ca. 3 mg/l)
Metabolic activation:    without
Result:                  positive

Method:           other: alkaline elution assay (DNA-protein crosslinks)
   GLP:           no data
Test substance:   no data

Remark:           Reliability: 2 (reliable with restrictions)
                  significant production of DNA-Protein Crosslinks (DPC); the
                  effect occurred at moderate levels of cytotoxicity.
Test substance:   formaldehyde; no data on purity of the compound

13-MAY-1998                                                              (268)

Type:                    other: in vitro DNA damage - eukaryotes (mammalian
                         cells/DNA-protein crosslinks)
System of testing:       human cells: bronchial epithelial cells
Concentration:           100 mM (ca. 3000 mg/l)
Metabolic activation:    without
Result:                  positive

Method:           other: alkaline elution assay (DNA-protein crosslinks)
   GLP:           no data
Test substance:   no data

Remark:           Reliability: 2 (reliable with restrictions)
                  significant production of DNA-Protein Crosslinks (DPC) (ca.
                  7-fold higher than single strand break level)
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-1998                                                              (297)

Type:                    other: in vitro DNA damage - eukaryotes (mammalian
                         cells/DNA-protein crosslinks)
System of testing:       Yoshida lymphosarcoma cells
Concentration:           250 uM (ca. 7.5 mg/l)
Metabolic activation:    without
Result:                  positive

Method:           other: alkaline elution assay (DNA-protein crosslinks)
   GLP:           no data
Test substance:   no data
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Remark:           production of DNA-Protein Crosslinks; the concentration
                  caused 50% inhibition of cell growth
                  Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-1998                                                          (518)

Type:                     other: in vitro DNA damage - eukaryotes (mammalian
                          cells/DNA-protein crosslinks)
System of testing:        mouse leukemia L1210 cells
Concentration:            0.01 - 0.3 mM (ca. 0.3 - 9 mg/l)
Metabolic activation:     without
Result:                   positive

Method:           other: alkaline elution assay (DNA-protein crosslinks)
   GLP:           no data
Test substance:   no data

Remark:           Reliability: 2 (reliable with restrictions)
                  significant production of DNA-Protein Crosslinks (DPC); DPC
                  formation occurred at relatively nontoxic doses (i.e. <0.2
                  mM); DPC were repaired after removal of the test substance
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-1998                                                          (565)

Type:                     other: in vitro DNA damage - eukaryotes (mammalian
                          cells/DNA-protein crosslinks)
System of testing:        human bronchial epithelial cells
Concentration:            0.1 mM (ca. 3 mg/l)
Metabolic activation:     without
Result:                   positive

Method:           other: alkaline elution assay (DNA-protein crosslinks)
   GLP:           no data
Test substance:   no data

Remark:           Reliability: 2 (reliable with restrictions)
                  significant production of DNA-Protein cross links (DPC);
                  reduction of cell growth rate to 50% at 0.21 mM (6.3 mg/l)
Test substance:   formaldehyde; no data on purity of the compound
18-JUN-1998                                                          (580)

Type:                     other: in vitro DNA damage - eukaryotes (mammalian
                          cells/DNA-protein crosslinks)
System of testing:        F344 rat nasal epithelial cells (nasal- and maxillar
                          turbinates)
Concentration:            up to 1.0 mM (ca. 30 mg/l)
Metabolic activation:     without
Result:                   positive

Method:           other: alkaline elution assay (DNA-protein crosslinks)
   GLP:           no data
Test substance:   no data

Remark:           DNA-Protein cross links (DPC) were found at 0.5 and 1.0 mM;
                  only abstract available, no further data
Test substance:   formaldehyde; no data on purity of the compound
Reliability:      (2)  valid with restrictions
18-JUN-1998                                                           (66)
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Type:                     other: in vitro DNA damage - eukaryotes (mammalian
                          cells/DNA-protein crosslinks)
System of testing:        human cells: bronchial epithelial cells, bronchial
                          fibroblasts
Concentration:            0.8 mM (ca. 24 mg/l)
Metabolic activation:     without
Result:                   positive

Method:            other: alkaline elution assay (DNA-protein crosslinks)
   GLP:            no data
Test substance:    no data

Remark:            formation of DNA-Protein Crosslinks (DPC); DPC were rapidly
                   removed in both cell types
                   Reliability: 2 (reliable with restrictions)
Test substance:    formaldehyde; no data on purity of the compound
13-MAY-1998                                                              (232)

Type:                     other: in vitro DNA damage - eukaryotes (mammalian
                          cells/DNA-protein crosslinks)
System of testing:        human lymphocytes
Concentration:            0.015 - 0.6 mM (ca. 0.45 - 18 mg/l)
Metabolic activation:     without
Result:                   positive

Method:            other: alkaline elution assay (DNA-protein crosslinks)
   GLP:            no data
Test substance:    no data

Remark:            dose-related production of DNA-Protein Crosslinks (DPC) at
                   0.05-0.6 mM; rapid removal of DPC; only abstract available;
                   no further data.
Test substance:    formaldehyde; no data on purity of the compound
Reliability:       (2)  valid with restrictions
18-JUN-1998                                                               (65)

Type:                     other: in vitro DNA damage - eukaryotes (mammalian
                          cells/DNA-protein crosslinks)
System of testing:        Yoshida sarcoma cells

Concentration:            0.25 mM (ca. 7.5 mg/l)
Metabolic activation:     without
Result:                   positive

Method:            other: alkaline elution assay (DNA-protein crosslinks)
   GLP:            no data
Test substance:    no data

Remark:            formation of DNA-Protein Crosslinks (DPC); removal of the
                   DPC revealed the presence of a small amount of single
                   strand breaks
                   Reliability: 2 (reliable with restrictions)
Test substance:    formaldehyde; no data on purity of the compound
13-MAY-1998                                                               (58)

Type:                     other: in vitro DNA damage - eukaryotes (mammalian
                          cells)
System of testing:        CHO cells AA8 (wild type), EM9, UV4, UV5
                          (repair-deficient)
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Concentration:           5.6 mg/l
Metabolic activation:    without
Result:                  positive

Method:           other: differential cell killing (DNA damage)
   GLP:           no data
Test substance:   no data

Remark:           Differential cytotoxicity was observed with the mutant
                  cells UV4 and UV5 compared to the wild-type; differential
                  cell killing (based on colony-forming ability) was
                  interpreted as a measure of lethal, potentially repairable
                  damage to DNA
                  Reliability: 2 (reliable with restrictions)
Test substance:   formaldehyde; no data on purity of the compound

26-NOV-1997                                                            (342)

Type:                    other: ex vivo (in vitro/in vivo) DNA damage -
                         prokaryotes (bacteria)
System of testing:       other: male NMRI mice and Escherichia coli K-12/343/636
                         (uvrB+/recA+), K-12/343/591 (uvrB-/recA-)
Concentration:           (a) 17, 50 mg/kg (oral); (b) 10, 30 mg/kg (i.v.)
Metabolic activation:    with
Result:                  positive

Method:           other: host-mediated assay
   GLP:           no data
Test substance:   no data

Remark:           Reliability: 2 (reliable with restrictions)
Result:           Seven male NMRI mice per dose were used. The bacterial mix
                  was injected in the lateral vein. The lowest effective dose
                  was 17 mg/kg after oral administration and 10 mg/kg after
                  intravenous administration of formaldehyde. Preferential
                  reduction of DNA repair deficient strain was observed in
                  blood and lungs.
Test substance:   formaldehyde; no data on purity of the compound
13-MAY-1998                                                      (310) (311)

Type:                    other: in vitro DNA damage - lower eukaryotes (yeast,
                         fungi)
System of testing:       Saccharomyces cerevisia N123 (wild type)
Concentration:           8.2 - 66 mM
Metabolic activation:    without
Result:                  positive

Method:           other: DNA damage
   GLP:           no data
Test substance:   no data

Result:           Dose-related increase in single-strand breaks (SSB) in DNA
                  of exponential phase cells of the wild type strain. Strains
                  defective in excision-repair showed a reduced capacity to
                  undergo SSB after FA treatment.
                  Analysis was done by the alkaline sucrose gradients
                  technique. It is discussed, that the appearance of SSB may
                  be a step in a repair process of FA-induced lesions.
Reliability:      (2)  valid with restrictions
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18-JUN-1998 (445)

Type: other: Induction of double strand breaks (DSB)
System of testing: in human lung epithelial cell line A549

Method: other
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Method: Concentration 10, 100, 300 and 1000 µM.
Result: DSB induced only if viability of cells was reduced to less than about 60% of control. Exposure time dependent increase of cytotoxicity and DSB. Authors conclude that DSB by formaldehyde are induced by a cytotoxic and not genotoxic pathway
Reliability: (2) valid with restrictions
no guideline

23-AUG-2001 (685)

Type: Unscheduled DNA synthesis
System of testing: Syrian Hamster Embryo (SHE) cells
Metabolic activation: without

Method: other
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Method: as described by Tsutsui T. et al.: Mut. Res. 129, 111-117 (1984)
Result: Survival rate decreased to 27.7 % at 3 µg/ml.
UDS tested and positive at 3 to 30 µg/ml (cytotoxic concentrations)
Reliability: (2) valid with restrictions
no guideline

23-AUG-2001 (290)

Type: other: in vitro gene mutation - prokaryotes (bacteria)
System of testing: Salmonella typhimurium TA98, TA100, TA102, TA1535, TA1537, TA1538
Concentration: up to 0.2 mg/plate
Metabolic activation: without
Result: positive

Method: other: Maron and Ames, 1983, Mutation Research, 113, 173-215
Year: 1983
GLP: no data
Test substance: other TS: formaldehyde; no data on purity of the compound

Method: Standard Plate Test and Preincubation Test without external metabolic activation
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint

24-JUL-2002 (519)

Type: other: in vitro gene mutation - prokaryotes (bacteria)
System of testing: Salmonella typhimurium TA100
Concentration: up to 1.5 mM (ca. 45 mg/l)
Metabolic activation: with and without
Result: positive

Method: other:Ames et al., 1975, Mutation Research, 31, 347-364; Yahagi et al., 1975, Cancer Letters, 1, 91-96
Year: 1975
GLP: no data
Test substance: other TS: formaldehyde; no data on purity of the compound

Test condition: Standard Plate Test (SPT) concentration up to 1.5 mM (ca. 45 mg/l) and Preincubation Test (PIT); concentration up to 0.3 mM (ca. 9 mg/l) with and without metabolic activation with S-9 mix prepared from liver homogenate of Clophen A50 pretreated Wistar rats. Increase over background by a factor of 1.3 (-S-9) or 1.7 (+S-9) in SPT and by a factor of 1.6 (-S-9) or 2.7 (+S-9) in PIT.
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
24-JUL-2002 (590)

Type: other: in vitro gene mutation - prokaryotes (bacteria)
System of testing: Salmonella typhimurium TA97, TA98, TA100, TA102, TA104
Concentration: up to 1 mg/plate
Metabolic activation: without
Result: positive

Method: other: Maron and Ames, 1983, Mutation Research, 113, 173-215
Year: 1983
GLP: no data
Test substance: other TS: formaldehyde; no data on purity of the compound

Test condition: Preincubation Test without metabolic activation; clearly positive and dose-related mutagenic effect at doses up to 1.25 umoles (37.5 ug) in tester strain TA104 and up to 2.0 umoles (60 ug) in tester strain TA102; only weak response in tester strains TA97, TA98, and TA100
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
24-JUL-2002 (457)

Type: other: in vitro gene mutations - eukaryotes (mammalian cells)
System of testing: human lymphoblasts TK6 (TK+/-)
Concentration: (a) 0.015-0.15 mM (ca. 0.45-4.5 mg/l); (b) 3x0.05 mM (ca. 1.5 mg/l); (c) 5x0.03 mM (ca. 0.9 mg/l); (d) 10x0.015 mM (ca. 0.45 mg/l)
Metabolic activation: without
Result: positive

GLP: no data
Test substance: other TS: formaldehyde; no data on purity of the compound

Method: TK6 human lymphoblastoid cell line (originally H2BT) was used.
Cultures at a cell density of 4 x 10E5 cells/ml were exposed to HCHO for 2 h. HCHO was added directly to the culture media at a final concentration of 15, 30, 50, 125 or 150 µM. Multiple treatments were given every 2 - 4 days with a total of 10 exposures at 15 µM, 5 exposures at 30 µM, and 3 exposures at 50 µM. As positive controls, 25-ml cultures (4 x 10E5 cells/ml) were treated with 0.2 mM EMS or MNNG for 2 h.

After regaining control growth rate, cells were grown for a minimum of 3 days with daily dilutions to 4 x 10E5 cells/ml to ensure phenotypic expression. Cells were cloned in 96-well microtiter dishes to measure colony-forming ability and at 4 x 10E4 cells/well in the same medium plus selective agent to determine mutant fraction. Selective agents used were 1 µg/ml trifluorothymidine. Two microtiter dishes were seeded to determine colony-forming ability for each treatment. To determine mutant fraction using trifluorothymidine selection, 10 dishes were seeded for each treated culture except for the 150 µM formaldehyde- and EMS-treated cultures, for which 4 dishes were seeded. The dishes were kept for 10 - 14 days. The efficiency of colony formation was calculated by dividing the negative natural log of the fraction of negative wells by the number of cells per well. The mutant fraction was calculated by dividing the colony-forming efficiency observed with selective agent. The statistical significance of the various treatments was determined by the Wilcoxon signed rank test.

Result: According to protocol (a), a nonlinear increase in induced F3TdR-resistant mutants with increasing slope above 125 uM (ca. 3.75 mg/l) was observed (mutant fraction: 4.8x10E-6). Significant response was obtained at doses of 30 uM (ca. 0.9 mg/l) and more. 125 and 150 uM resulted in ca. 30% and 20% survival, respectively. Increases of F3TdR-resistant mutants were 2.1x10E-6, 2.2x10E-6, and 3.0x10E-6 after application according to protocol (b), (c), and (d), respectively. According to the authors, combined effect of multiple treatments was less than single treatment with an equivalent concentration (0.15 mM).

Reliability: (2) valid with restrictions

Flag: Critical study for SIDS endpoint

24-JUL-2002 (161) (162)

Type: other: in vitro gene mutations - eukaryotes (mammalian cells)

System of testing: mouse lymphoma cells L5178Y (TK+/-)

Concentration: (a) 0.008-0.020 ul/ml (-S-9, -FDA); (b) 0.008-0.024 ul/ml (-S-9, +FDA); (c) 0.04-0.065 ul/ml (+S-9, +-FDA)

Metabolic activation: with and without

Result: positive

GLP: no data

Test substance: other TS: formaldehyde; no data on purity of the compound

Method: The Mouse Lymphoma L5178Y TK+/- Mutagenesis Assay was performed according to the standard protocol by Clive et al. (1979) and Turner et al. (1984). Liver S-9 from Aroclor 1254-induced male Sprague-Dawley rats was used for external metabolic activation. FDH and NAD+ were added to the cultures during dosing at concentrations of 0.09 units/ml and 8.1 mM, respectively in the presence and absence of metabolic activation from rat liver S-9. A chemical was designated as mutagenic when it induced a mutant frequency of 2-fold or greater over the control value.

Remark: - About 30-fold increase in mutation frequency in the absence of both S-9 and formaldehyde dehydrogenase (FDA) and its co-factor NAD+. Parallel to the increasing mutant frequency, total cell growth declined to zero (protocol (a)).

- Negative response in mutation frequency in the absence of S-9 and presence of FDA / NAD+. No change in cell growth was observed (protocol (b)).
- About 10 fold increase in mutation frequency in the presence of S-9 (prepared from liver homogenate of Aroclor pretreated rats) and absence of FDA / NAD+; parallel to the increasing mutant frequency, total cell growth declined 10%. Negative response in the presence of both S-9 and FDA / NAD+; no change in cell growth was observed (protocol (c)).

Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
24-JUL-2002 (79)

Type: other: in vitro gene mutations - eukaryotes (mammalian cells)
System of testing: human lymphoblasts TK6 (hprt locus)
Concentration: 8 x 150 uM (ca. 4.5 mg/l)
Metabolic activation: without
Result: positive

GLP: no data
Test substance: other TS: formaldehyde; no data on purity of the compound

Method: Induction of 6-thioguanine-resistant (6-TGr) mutants following treatment with formaldehyde was observed. Mutants were characterized by Northern blot analysis and DNA sequence analysis.

Northern blot analyses:
Isolation of total RNA was performed. Gel electrophoresis of

RNA samples was in 1.3% agarose gels in MOPS with 2.2 M formaldehyde. Transfer conditions were those described by Maniatis et al. (1982). Prehybridizations were overnight at 37°C. Hybridization for 48 - 72 h were in an identical mixture. After hybridization with the hprt probe, the filters were stripped and rehybridized with an actin probe. This served as a control for amount of RNA and suggested that comparable levels of RNA were present in each lane. herefore, the relative levels of hprt message were estimated directly from the autoradiograms.

DNA sequence anlysis of induced mutants:
Total cellular RNA was isolated from mutants and then reverse transcriptase was utilized to synthesize the first strands of cDNAs. The polymerase chain reaction was then employed, with primers specific for hprt, to amplify only hprt cDNA; the amplified DNA was cloned into an m13 vector and analyzed. All 654 base pairs which code for the 218 amino acids in hprt were included in the region analyzed.

Result: According to the authors, 6/30 mutants had completely lost the hprt gene, 8/30 had partial deletions, and 16/30 had been described as point mutations
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
24-JUL-2002 (428)

Type: other: in vitro gene mutations - eukaryotes (mammalian

cells)
System of testing: Chinese hamster V79 cells
Concentration: 0.1 - 1.0 mM (ca. 3 - 30 mg/l)
Metabolic activation: without
Result: positive

GLP: no data
Test substance: other TS: formaldehyde; no data on purity of the compound

Remark: A dose-related increase in the frequency of 6-thioguanine resistance in the HPRT gene locus was observed at doses of 0.3 to 1.0 mM. Accordding to the authors, 0.1 and 1.0 mM decreased the colony-forming ability.
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
24-JUL-2002 (267)

Type: other: in vitro chromosomal aberrations - eukaryotes (mammalian cells)
System of testing: CHO cells
Concentration: (a) 1.6-16 mg/l -S-9; (b) 1.6-50 mg/l +S-9; (c) 1.1-11 mg/l -S-9; (d) 1.1-11 mg/l + S-9; (e) 15-25 mg/ml + S-9
Metabolic activation: with and without
Result: positive

GLP: no data
Test substance: other TS: formaldehyde; no data on purity of the compound

Result: positive response at protocols (a), (b), and (e); protocol (a) at only 1 dose level; negative response at protocols (c)and (d).
With S-9 mix (prepared from liver homogenate of Aroclor pretreated Sprague-Dawley rats), high level of damage at toxic doses with marked mitotic suppression was observed.
The tests were performed by 2 laboratories (lab. 1: protocols (a) and (b), lab. 2: protocols (c) - (e)).
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
24-JUL-2002 (240)

Type: other: in vitro chromosomal aberrations - eukaryotes (mammalian cells)
System of testing: human fibroblasts
Concentration: 2 - 8 mM (ca. 60 - 240 mg/l)
Metabolic activation: without
Result: positive

GLP: no data
Test substance: other TS: formaldehyde; no data on purity of the compound

Method: A skin fibroblast cell line (Ja) was obtained from a biopsy of an 11-year old normal male donor. The experiments were performed at pasages 10 - 13.
PBS containing 2, 4 or 8 mM FA. The cells were incubated at 37°C for 15 min.
After treatments, the cultures were scanned for the appearance of the first post-treatment mitoses. 24 h after cells treatment, colcemid was added at a final concentration of 0.1 µg/ml. The were transfered to prewarmed hypotonic solution and fixed twice in methanol:glacial acetic acid.
The slides were stained with Giemsa.

The chromosome number and aberration number distributions were determined on 50 - 100 mitoses in controls and treated cells. The aberration were classified according to the nomenclature of Savage and Evans.
Result: dose-related increase in the number of aberrations (chromatid- and chromosome-type) including and excluding gaps
Reliability: (2) valid with restrictions
24-JUL-2002 (425)

Type: other: in vitro DNA damage - eukaryotes (mammalian cells/DNA strand breaks)
System of testing: F344 rat tracheal epithel cell line, C18
Concentration: 100 - 400 uM (ca. 3 - 12 mg/l)
Metabolic activation: without
Result: positive

Method: other: alkaline elution assay (DNA strand break)
GLP: no data
Test substance: other TS: formaldehyde; no data on purity of the compound

Method: Kohn, 1985, Assessment of DNA Damage by Filter Elution Assay, in Simic et al. (eds.), Plenum Press, New York, USA, p. 101
Remark: dose-related increase in single strand breaks (SSB) up to 400 uM; SSB were repaired within 2 h; treatment for 90 min. reduced the Colony-Forming Efficiency (CFE) at 400 uM (25% of control)
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
13-MAY-2003 (156)

Type: other: in vitro DNA damage - eukaryotes (mammalian cells/DNA-protein crosslinks)
System of testing: human cells: skin fibroblasts, bronchial fibroblasts, bronchial epithelial cells, XP skin fibroblasts
Concentration: 0.2 - 0.8 mM (ca. 6 - 24 mg/l)
Metabolic activation: without
Result: positive

Method: other: alkaline elution assay (DNA-protein crosslinks)
GLP: no data
Test substance: other TS: formaldehyde; no data on purity of the compound

Method: Kohn, 1985, Assessment of DNA Damage by Filter Elution Assay, in Simic et al. (eds.), Plenum Press, New York, USA, p. 101
Remark: Test substance-related formation of DNA-Protein Crosslinks (DPC) at similar levels in all cell types; the half-life of DPC was ca. 2-3 h in all cell types
Reliability: (2) valid with restrictions
25-APR-2003 (271)

Type: other: in vitro DNA damage - eukaryotes (mammalian cells/DNA-protein crosslinks)
System of testing: CHO cells
Concentration: 0.125 - 0.5 mM (ca. 3.75 - 15 mg/l) (-S-9); 2.0 - 4.0 mM (ca. 60 - 120 mg/l) (+S-9)
Metabolic activation: with and without
Result: positive

```
Method:           other: alkaline elution assay (DNA-protein crosslinks)
   GLP:           no data
Test substance:   no data

Method:           Kohn, 1985, Assessment of DNA Damage by Filter Elution
                  Assay, in Simic et al. (eds.), Plenum Press, New York, USA,
                  p. 101
Remark:           Dose-dependent formation of DNA-Protein Crosslinks (DPC)
                  with and without mouse liver S-9; in the presence of S-9,
                  higher concentrations of the test substance were needed to
                  induce DNA damage
Reliability:      (2)  valid with restrictions
13-MAY-2003                                                        (275) (276)

Type:                     other: in vitro DNA damage - eukaryotes (mammalian
                          cells/DNA-protein crosslinks)
System of testing:        human lymphoblasts
Concentration:            up to 0.6 mM (ca. 18 mg/l)
Metabolic activation:     without
Result:                   positive

Method:           other: alkaline elution assay (DNA-protein crosslinks)
   GLP:           no data
Test substance:   other TS: formaldehyde; no data on purity of the compound

Method:           Kohn, 1985, Assessment of DNA Damage by Filter Elution
                  Assay, in Simic et al. (eds.), Plenum Press, New York, USA,
                  p. 101
Remark:           Significant nonlinear increase in DNA-Protein Crosslinks
                  (DPC) at 0.05-0.6 mM for 2 h; holding the culture for 24 h
                  resulted in complete removal of DPC
Reliability:      (2)  valid with restrictions
13-MAY-2003                                                            (163)

Type:                     other: in vitro DNA damage - eukaryotes (mammalian
                          cells/DNA-protein crosslinks)
System of testing:        CHO cells
Concentration:            up to 13 mM (ca. 39 mg/l)
Metabolic activation:     without
Result:                   positive

Method:           other: two-dimensional gel electrophoresis, immunoblotting
                  (DNA-protein crosslinks)

   GLP:           no data
Test substance:   other TS: formaldehyde; no data on purity of the compound

Remark:           Formation of DNA-Protein Crosslinks (DPC); exposure to 1.45
                  mM for 90 min. resulted in a 50% reduction in colonies; at 3
                  mM, histone DNA crosslinks were observed.
Reliability:      (2)  valid with restrictions
13-MAY-2003                                                 (159) (480) (481)

Type:                     other: in vitro DNA damage - eukaryotes (mammalian
                          cells/DNA-protein crosslinks)
System of testing:        CHO cells
Concentration:            0.02 - 2.0 mM (ca. 0.6 - 60 mg/l)
Metabolic activation:     without
Result:                   positive
```

Method: other: K-SDS precipitation assay (DNA-protein crosslinks)
GLP: no data
Test substance: other TS: formaldehyde; no data on purity of the compound

Remark: dose-dependent formation of DNA-Protein Crosslinks (DPC); exposure to 0.02 mM resulted in a 10-fold increase of DPC
Reliability: (2) valid with restrictions
24-JUL-2002 (725)

5.6 Genetic Toxicity 'in Vivo'

Type: Cytogenetic assay
Species: rat Sex: no data
Strain: Wistar
Route of admin.: inhalation
Exposure period: 5 d, 6 h/d
Doses: 0.1 - 20 ppm (ca. 0.0001 - 0.025 mg/l)

Method: other: ex vivo (in vitro/in vivo) chromosomal aberrations - eukaryotes (mammalian cells)
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: positive

Chromosome analysis of nasal epithelial cells nasal-, maxillar- and ethmoturbinates) was performed. Application of the test substance via inhalation route resulted in an increase in the number of aberrant metaphases only at a dose level of 20 ppm; additionally, a 30% reduction of the mitotic index was observed at this dose level. Positive reaction was observed in nasal- and maxillar-, but not in ethmoturbinates.
Test substance: formaldehyde; no data on purity of the compound
18-JUN-1998 (483)

Type: Cytogenetic assay
Species: mouse Sex: female
Strain: ICR
Route of admin.: i.v.
Exposure period: no data
Doses: 1.5, 3.0 mg

Method: other: ex vivo (in vitro/in vivo) chromosomal aberrations - eukaryotes (mammalian cells)
GLP: no data
Test substance: no data

Remark: Reliability: 3 (not reliable)
Result: positive

Injection of the test substance into the tail vein of pregnant mice resulted in induction of chromosomal aberrations (gaps, breaks, and exchanges) in fetal liver cells. No further data; interpretation of the results is not possible.
Test substance: formaldehyde; no data on purity of the compound

14-JUL-1997 (525)

Type: Cytogenetic assay
Species: Drosophila melanogaster Sex: no data
Strain: no data
Route of admin.: unspecified
Exposure period: no data
Doses: no data

Method: other: in vivo chromosomal aberrations - eukaryotes (non-mammalian/Drosophila)
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: positive

ADH system; deletions were recognized by the absence of salivary chromosome bands; 14 out of 18 induced lesions were found to be deletions, 4 mutants exhibited no detectable loss of genetic material.
Test substance: formaldehyde; no data on purity of the compound

08-DEC-1997 (544)

Type: Cytogenetic assay
Species: rat Sex: female
Strain: other: no data
Route of admin.: inhalation
Exposure period: no data
Doses: 0.0005, 0.0015 mg/l

Method: other: in vivo chromosomal aberrations - mammals (bone marrow cells and embryos)
GLP: no data
Test substance: no data

Method: Forty female rats were exposed to dynamic atmospheres 4 hours per day for 4 months. After exposure the animals were mated with untreated males. Two to three days after the mating embryos were washed out of the oviducts and bone marrow was gathered for cytogenetic examination.
Remark: No details are given on exposure technique and test groups. It is described that the exposure concentration was determined gravimetrically, which probably means that the nominal concentration was calculated from test substance consumption and air flow used and no direct analysis of the formaldehyde concentration in the exposure atmospheres was performed.
There are no details on number of animals or number of metaphases per animal evaluated. Essential details necessary for the evaluation of the genotoxic response, e.g. specification of the various forms of aberrations, are lacking. Examination of chromosomal changes 48-72 hours after cessation of exposure is unusually late (normally a 24-h interval is used).
In the light of the toxicokinetic behaviour of formaldehyde at the tested concentration the described effects are neither plausible nor convincing.

Result: 0.5 mg/m³: no effects were observed in the embryos; mitotic activity of the bone marrow cells was decreased; number of chromatid aberrations and aneuploid cells increased
1.5 mg/m³: increased number of morphologically degenerated embryos but no clastogenic effect in embryo cells; mitotic activity of the bone marrow decreased; number of chromatid and chromosomal aberrations and aneuploid cells increased
Test substance: formaldehyde; no data on purity of the compound
Reliability: (3) invalid
25-OCT-2002 (394)

Type: Cytogenetic assay
Species: mouse Sex: male
Strain: other: Q-strain
Route of admin.: i.p.
Exposure period: single dose
Doses: 50 mg/kg

Method: other: in vivo chromosomal aberrations - mammals (germ cells)
GLP: no data
Test substance: other TS

Result: negative

After a single i.p. injection of the test substance, 2 males/day were analyszed (scoring of a total of 400 spermatocytes for spermatocyte I chromosome analysis): no increase in chromosomal lesions were observed on days 8-15 after treatment, i.e. during diakinese-metaphase 1.
Test substance: formaldehyde; 35% Merck
Reliability: (2) valid with restrictions
25-OCT-2002 (230)

Type: Cytogenetic assay
Species: rat Sex: no data
Strain: Sprague-Dawley
Route of admin.: inhalation
Exposure period: 1 week, 2, 4, 6 months; 5 d/w, 6 h/d
Doses: 0.5 - 15 ppm (ca. 0.0006 - 0.019 mg/l)

Method: other: in vivo chromosomal aberrations - mammals (somatic cells)
GLP: no data
Test substance: no data

Result: negative in bone marrow;
positive in pulmonary alveolar macrophage

Four to 5 animals per group were sacrificed after 1 week, 2, 4, and 6 months of treatment; 50 cells/animal were scored for bone marrow and pulmonary alveoar macrophage chromosome analysis. After 1 week and after 2 months, no increase in chromosomal aberrations was observed in bone marrow but a 2-fold increase in chromosomal aberrations (mostly chromatid-type) over background was found in pulmonary alveolar macrophages. After 4 and 6 months of treatment, there were not enough cell available for scoring. Only abstract available; no further data.

Test substance: formaldehyde; no data on purity of the compound
Reliability: (3) invalid
08-DEC-1997 (595)

Type: Cytogenetic assay
Species: mouse Sex: male/female
Strain: CBA
Route of admin.: i.p.
Exposure period: 2 injections
Doses: 6.25 - 25 mg/kg

Method: other: in vivo chromosomal aberrations - mammals (somatic cells)
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: negative

The test substance was administered to 3-5 mice/sex/group by 2 intraperitoneal injections with an interval of 24 h. Cells of bone marrow and spleen were sampled for chromosome analysis 16 an 40 h after the 2nd injection. No induction of chromosomal aberration was observed.
Test substance: formaldehyde; no data on purity of the compound
08-DEC-1997 (503)

Type: Cytogenetic assay
Species: rat Sex: no data
Strain: other: no data
Route of admin.: inhalation
Exposure period: 4 months
Doses: 0.0005, 0.0015 mg/l

Method: other: in vivo chromosomal aberrations - mammals (somatic cells)
GLP: no data
Test substance: no data

Remark: Reliability: 3 (not reliable)
Result: positive

Bone marrow chromosome analysis; an increase in the number of chromosomal aberrations and aneuploid cells was observed. Russian publication with English abstract.
Test substance: formaldehyde; no data on purity of the compound
08-DEC-1997 (393)

Type: Cytogenetic assay
Species: mouse Sex: no data
Strain: CD-1
Route of admin.: inhalation
Exposure period: 4 or 5 days, 6 h/d
Doses: 6 and 12 ppm (ca. 0.007 and 0.015 mg/l) for 5 days or 25 ppm (ca. 0.03 mg/l) for 4 days

Method: other: in vivo chromosomal aberrations - mammals (somatic cells)
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: negative

Preliminary results of bone marrow chromosome analysis; no increase in the number of chromosomal aberrations.
Test substance: formaldehyde; no data on purity of the compound
07-MAY-1998 (111)

Type: Cytogenetic assay
Species: mouse Sex: no data
Strain: other: no data
Route of admin.: i.p.
Exposure period: 3 daily doses
Doses: 15 - 60 mg/kg

Method: other: in vivo chromosomal aberrations - mammals (somatic cells)
GLP: no data
Test substance: no data

Remark: Reliability: 3 (not reliable)
Result: positive

Bone marrow chromosome analysis; dose-related response of structural aberrations, especially of centric fusions; 3 daily doses. Only abstract available; no further data.
Test substance: formaldehyde; no data on purity of the compound
14-JUL-1997 (138)

Type: Cytogenetic assay
Species: mouse Sex: female
Strain: other: no data
Route of admin.: oral unspecified
Exposure period: no data
Doses: 100 mg/kg

Method: other: in vivo chromosomal aberrations - mammals (somatic cells)
GLP: no data
Test substance: no data

Remark: Reliability: 3 (not reliable)
Result: positive

A bone marrow chromosome analysis revealed an increase in the incidence of chromosomal aberrations, particularly aneuploidy and exchanges. Only abstract available; no further data.
Test substance: formaldehyde; no data on purity of the compound
16-AUG-2001 (541)

Type: Cytogenetic assay
Species: rat Sex: male/female
Strain: Fischer 344
Route of admin.: inhalation
Exposure period: 5 days, 6 h/d
Doses: 15 ppm (ca. 0.019 mg/l)
Result: negative

Method: other: in vivo chromosomal aberrations - mammals (somatic cells)
GLP: no data
Test substance: other TS: formaldehyde; no data on purity of the compound

Method: The inhalation exposure was performed under the same controlled conditions as the chronic inhalation study published by Kerns et al. 1983.
Lymphocytes chromosome analysis was carried out in 3 animals/sex/dose group. Fifty first-division metaphases per animal were scored.
Result: No significant effects on mitotic activity and no increase in chromosomal aberrations were observed.
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
23-OCT-2002 (397)

Type: Cytogenetic assay
Species: rat Sex: male
Strain: Sprague-Dawley
Route of admin.: inhalation
Exposure period: 1 or 8 weeks; 5 d/w, 6 h/d
Doses: 0.5, 3 and 15 ppm (ca. 0.0006, 0.0036 and 0.19 mg/l)

Method: other: in vivo chromosomal aberrations - mammals (somatic cells)
GLP: no data
Test substance: other TS: formaldehyde; no data on the purity of the compound

Method: Exposure to controlled dynamic atmospheres. Fifty metaphases of bone marrow cells and lung macrophages obtained by lavage per animal from 4-5 animals per concentration were examined for chromosomal aberrations. Mitotic arrest of the cells in metaphase was induced by i.p. colchicine treatment 2 hours before cell sampling.
Result: No increase of chromosomal aberrations was observed in bone marrow cells.
A slight, but statistically significant increase of chromosomal abnormalities in macrophages was seen at the high concentration. No clear concentration response relationship was present
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
23-OCT-2002 (169)

Type: Dominant lethal assay
Species: mouse Sex: male
Strain: other: ICR/Ha Swiss
Route of admin.: i.p.
Exposure period: single dose
Doses: (a) 32-40 mg/kg, 3 weeks of mating; (b) 16-20 mg/kg, 3 weeks of mating; (c) 16-20 mg/kg, 8 weeks of mating
Result: negative

Method: other: in vivo chromosomal aberrations - mammals (germ cells)
GLP: no
Test substance: no data

Method: The doses used approximated LD 25. Five to 9 males per dose were treated. Each male was caged with 3 untreated females which were replaced weekly for 3 or 8 consecutive weeks. The females were necropsied from mid-week of mating.
Remark: Test was developed by this group and this paper summarizes the results obtained with a multitude of substances.
Result: Mortality was observed in all dose groups.
16 mg/kg 3/12
20 mg/kg 2/16
32 mg/kg 2/5
40 mg/kg 5/5
Formaldehyde was allocated to the group of substances which produced early fetal death and preimplantation losses within control limits.

Test substance: formaldehyde; no data on purity of the compound
Reliability: (2) valid with restrictions
25-APR-2003 (217)

Type: Dominant lethal assay
Species: mouse Sex: male
Strain: CD-1
Route of admin.: i.p.
Exposure period: no data
Doses: 20 mg/kg
Result: negative

Method: other: in vivo chromosomal aberrations - mammals (germ cells)
GLP: no
Test substance: no data

Method: Intraperitoneal injection of 0.1 ml substance preparation in tricaprylin. Dose administered was LD5. Each treated male was caged with 3 untreated females which were replaced weekly for 8 consecutive weeks. The females were necropsied 13 days from mid-week of mating.
Remark: Test was developed by this group
Result: Nineteen of 24 animals pregnant. 12.3 implants per mouse. Fertility parameters comparable to control levels No induction of dominant lethal effects were observed
Test substance: formaldehyde; no data on purity of the compound
Reliability: (3) invalid
From the results it is obvious that only 1 animal was used. Study is interpreted as preliminary to the examinations reported by Epstein et al. 1972
25-OCT-2002 (216)

Type: Dominant lethal assay
Species: mouse Sex: no data
Strain: other: no data
Route of admin.: oral unspecified
Exposure period: no data
Doses: 70 mg/kg

Method: other: in vivo chromosomal aberrations - mammals (germ cells)
GLP: no data
Test substance: no data

Remark: Reliability: 3 (not reliable)
Result: negative

No induction of dominant lethal efffect was observed after oral administration of the test substance. Japanese publication with English abstract.
Test substance: formaldehyde; no data on purity of the compound
14-JUL-1997 (640)

Type: Dominant lethal assay
Species: mouse Sex: male
Strain: other: Q-strain
Route of admin.: i.p.
Exposure period: single dose
Doses: 50 mg/kg
Result: ambiguous

Method: other: in vivo chromosomal aberrations - mammals (germ cells)
GLP: no data
Test substance: other TS

Method: After treatment each of ten males was caged with 2 virgin females (3 in the first week) for a maximum of 1 week. Females were renewed each week for 7 weeks. The were sacrificed 14 days after detection of sperm plug.
Remark: No details on controls. Values reported might be historical controls
Result: No lethality occurred. No effects on the incidence of pregnancy were observed. Embryonic lethality was statistically significantly increased in the first week due to pre- and post-implantation deaths (2.6% versus 1.2% in controls) and in the third week due to pre-implantation deaths (2.1% versus 1,2%).
The author discusses the results in the light of those published by Epstein et al. 1968 and 1972. No conclusion concerning a dominant lethal effect is presented in the publication.
Test substance: formaldehyde 35% (Merck)
Reliability: (2) valid with restrictions
25-OCT-2002 (230)

Type: Dominant lethal assay
Species: rat Sex: male
Strain: other: albino (own breed)
Route of admin.: i.p.
Exposure period: 5 consecutive days
Doses: 0.125, 0.25 and 0.6 mg/kg

GLP: no data
Test substance: other TS

Method: 12 males per dose and 5 for vehicle control (distilled water), weekly mating with two females per male for 3 weeks, examination of females 13 days after the mid of the week of mating
Remark: The doses used were based on a previously determined LD50 of 2 mg/kg (no details), which is very low in comparison to the values found in other acute parenteral toxicity studies. This raises questions concerning the test substance preparation and administration procedures.
Compromised evaluation of dominant lethal effect due to

small numbers of pregnant females (reduction of fertile matings).
and inadequate reporting of some methods and results.

Result: Dose dependent decrease in fertile matings in week 1 and 2 after treatment of males.
Increased dominant lethal mutation index mainly in females mated 1 and 2 weeks after treatment of males.
Test substance: Formaldehyde 37% solution stabilized with 10% methanol
Reliability: (3) invalid
25-OCT-2002 (523)

Type: Drosophila SLRL test
Species: Drosophila melanogaster Sex: male
Strain: other: no data
Route of admin.: oral feed
Exposure period: no data
Doses: 1100, 2600 ppm

Method: other: in vivo gene mutations - eukaryotes (non-mammalian/Drosophila)
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: positive

Treated males (larvae) were mated only twice and left with 3 BASC-females for 1 dayonly. During the treatment period, spermatogonia were the only germ cells present. Mutagenicity was observed (total number of lethals per number tested was 37/5833 and 69/2445 in the 1100 and 2600 ppm group, respectively).
Test substance: formaldehyde; no data on purity of the compound
14-JUL-1997 (677)

Type: Drosophila SLRL test
Species: Drosophila melanogaster Sex: male
Strain: other: no data
Route of admin.: oral feed
Exposure period: during first instar larval stage
Doses: 0.25 % (ca. 2.5 mg/g)

Method: other: in vivo gene mutations - eukaryotes (non-mammalian/Drosophila)
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: positive

Raising of first-instar larvae on formaldehyde-containing medium resulted in an induction of lethal mutations.
Test substance: formaldehyde; no data on purity of the compound
14-JUL-1997 (213)

```
Type:              Drosophila SLRL test
Species:           Drosophila melanogaster          Sex: male
Strain:            other: no data
Route of admin.:   oral feed
Exposure period:   3 days
Doses:             12000 ppm (ca. 12 mg/g)

Method:            other: in vivo gene mutations - eukaryotes
                   (non-mammalian/Drosophila)
   GLP:            no data
Test substance:    no data

Remark:            Reliability: 2 (reliable with restrictions)
Result:            negative

                   Feeding of the test substance for 3 days did not induce
                   sex-linked recessive lethal mutations.
Test substance:    formaldehyde; no data on purity of the compound
14-JUL-1997                                                          (711)

Type:              Drosophila SLRL test
Species:           Drosophila melanogaster          Sex: male
Strain:            other: no data
Route of admin.:   other: injection
Exposure period:   no data
Doses:             2000 ppm

Method:            other: in vivo gene mutations - eukaryotes
                   (non-mammalian/Drosophila)
   GLP:            no data
Test substance:    no data

Remark:            Reliability: 2 (reliable with restrictions)
Result:            positive

                   Injection of the test substance resulted in an induction of
                   sex-linked recessive lethal mutations but not in an
                   induction of reciprocal translocations.
Test substance:    formaldehyde; no data on purity of the compound
14-JUL-1997                                                          (711)

Type:              Drosophila SLRL test
Species:           Drosophila melanogaster          Sex: male
Strain:            other: no data
Route of admin.:   oral feed
Exposure period:   no data
Doses:             1000 ppm

Method:            other: in vivo gene mutations - eukaryotes
                   (non-mammalian/Drosophila)
   GLP:            no data
Test substance:    no data

Remark:            Reliability: 2 (reliable with restrictions)
Result:            positive

                   Larval feeding of the test substance resulted in a 6-fold
                   increase of the mutation frequency.
Test substance:    formaldehyde; no data on purity of the compound
14-JUL-1997                                                            (1)
```

```
Type:              Drosophila SLRL test
Species:           Drosophila melanogaster           Sex: male
Strain:            other: no data
Route of admin.:   oral feed
Exposure period:   no data
Doses:             according to the authors, a concentration which allowed 50% of
                   the larvae to develop to the adult stage

Method:            other: in vivo gene mutations - eukaryotes
                   (non-mammalian/Drosophila)
   GLP:            no data
Test substance:    no data

Remark:            Reliability: 2 (reliable with restrictions)
Result:            positive

                   Larval feeding of the test substance resulted in an
                   induction of lethal mutations; no induction of lethal
                   mutations was observed after feeding of adults. The
                   mutagenic effect of the treatment on the male germ-line
                   cells was tested by the M-5 technique.
Test substance:    formaldehyde; no data on purity of the compound
08-DEC-1997                                                                (635)

Type:              Drosophila SLRL test
Species:           Drosophila melanogaster           Sex: male
Strain:            other: no data
Route of admin.:   oral feed
Exposure period:   no data
Doses:             20 mM (ca. 600 mg/l)

Method:            other: in vivo gene mutations - eukaryotes
                   (non-mammalian/Drosophila)
   GLP:            no data
Test substance:    no data

Remark:            Reliability: 2 (reliable with restrictions)
Result:            positive

                   Significant effects on the induction of sex-linked recessive
                   lethals was observed.
Test substance:    formaldehyde; no data on purity of the compound
14-JUL-1997                                                                 (14)

Type:              Drosophila SLRL test
Species:           Drosophila melanogaster           Sex: male
Strain:            other: no data
Route of admin.:   other: injection
Exposure period:   no data
Doses:             25, 50 mM (ca. 750, 1500 mg/l)

Method:            other: in vivo gene mutations - eukaryotes
                   (non-mammalian/Drosophila)
   GLP:            no data
Test substance:    no data

Remark:            Reliability: 2 (reliable with restrictions)
Result:            positive
```

A dose-related increase in mutagenicity was observed: raising the concentration from 25 to 50 mM resulted in an 8-fold increase of sex-linked recessive lethals.
Test substance: formaldehyde; no data on purity of the compound
14-JUL-1997 (728)

Type: Micronucleus assay
Species: rat Sex: no data
Strain: Wistar
Route of admin.: inhalation
Exposure period: 5 days or 4 weeks (5 d/wk); 6 h/d
Doses: (a) 20 ppm (ca. 0.025 mg/l) for 4 weeks; (b) 0.1-20 ppm (ca. 0.0001-0.025 mg/l) for 5 days; (c) 0.5-1.0 ppm (ca. 0.0006-0.0012 mg/l) for 4 weeks

Method: other: ex vivo (in vitro/in vivo) chromosomal aberrations - eukaryotes (mammalian cells)
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: positive

Chromosome analysis of nasal epithelial cells (nasal- and maxillarturbinates in all experiments; ethmoturbinates only in experiment (a)) was performed. Application of the test substance via inhalation route resulted in an increase in the number of micronucleated cells; positive reaction was observed in nasal- and maxillar-, but not in ethmoturbinates. The effects were more pronounced in nasal- than in maxillar turbinates (experiment (a)). In experinment(b) and (c), an increase in micronucleated cells was observed only at the highest dose levels.
Test substance: formaldehyde; no data on purity of the compound
14-JUL-1997 (483)

Type: Micronucleus assay
Species: other: Pleurodeles waltl (newt) Sex: no data
Strain: no data
Route of admin.: unspecified
Exposure period: 8 days
Doses: 5 ppm

Method: other: in vivo chromosomal aberrations - eukaryotes (non-mammalian)
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: negative

The micronuclei were analyzed in blood smears after larval treatment (scoring of >1000 cells). According to the authors, the dose corresponded to half the concentration which did not induce toxicity. No clastogenic effects were observed.
Test substance: formaldehyde; no data on purity of the compound
08-DEC-1997 (224)

```
Type:              Micronucleus assay
Species:           other: Pleurodeles waltl (newt)   Sex: no data
Strain:            no data
Route of admin.:   unspecified
Exposure period:   12 days
Doses:             5 ug/ml

Method:            other: in vivo chromosomal aberrations - eukaryotes
                   (non-mammalian)
   GLP:            no data
Test substance:    no data

Remark:            Reliability: 2 (reliable with restrictions)
Result:            negative

                   The micronuclei were analyzed in peripheral blood
                   erythrocytes after larval treatment (scoring of 1000
                   cells).No clastogenic effects were observed.
Test substance:    formaldehyde; no data on purity of the compound
07-MAY-1998                                                          (418)

Type:              Micronucleus assay
Species:           other: Pleurodeles waltl (newt)   Sex: no data
Strain:            no data
Route of admin.:   unspecified
Exposure period:   1 week
Doses:             5 ppm

Method:            other: in vivo chromosomal aberrations - eukaryotes
                   (non-mammalian)
   GLP:            no data
Test substance:    no data

Result:            negative

                   After larval treatment, red blood cells were scored. No
                   clastogenic effects were observed. Only abstract available;
                   no further data.
Test substance:    formaldehyde; no data on purity of the compound
Reliability:       (3)  invalid
08-DEC-1997                                                          (359)

Type:              Micronucleus assay
Species:           other: Pleurodeles waltl (newt)   Sex: no data
Strain:            no data
Route of admin.:   unspecified
Exposure period:   1 week
Doses:             5 ppm

Method:            other: in vivo chromosomal aberrations - eukaryotes
                   (non-mammalian)
   GLP:            no data
Test substance:    no data

Remark:            Reliability: 2 (reliable with restrictions)
Result:            negative

                   After larval treatment, red blood cells were scored. No
                   clastogenic effects were observed. Doses >5 ppm were toxic.
Test substance:    formaldehyde; no data on purity of the compound
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14-JUL-1997 (604)

Type: Micronucleus assay
Species: mouse Sex: male/female
Strain: NMRI
Route of admin.: i.p.
Exposure period: 2 injections
Doses: 10 - 30 mg/kg

Method: other: in vivo chromosomal aberrations - mammals (somatic cells)
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: negative

The test substance was applied 6 and 30 h prior to sacrifice of 2 animals/sex/dose group. Bone marrow was prepared, 1000 polychromatic erythrocytes per animal were analyzed. No increase in the number of micronuclei in polychromatic erythrocytes were observed.
Test substance: formaldehyde; no data on purity of the compound

14-JUL-1997 (253)

Type: Micronucleus assay
Species: mouse Sex: male/female
Strain: CBA
Route of admin.: i.p.
Exposure period: 2 injections
Doses: 6.25 - 25 mg/kg

Method: other: in vivo chromosomal aberrations - mammals (somatic cells)
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: negative

The test substance was administered to 3-5 mice/sex/group by 2 intraperitoneal injections with an interval of 24 h. Bone marrow was prepared 16 an 40 h after the 2nd injection.No increase in the number of micronucleated polychromatic erythrocytes obtained from the bone marrow was observed.
Test substance: formaldehyde; no data on purity of the compound

14-JUL-1997 (503)

Type: Micronucleus assay
Species: mouse Sex: male/female
Strain: CD-1
Route of admin.: i.p.
Exposure period: 15 or 30 days
Doses: 5, 10 mg/kg

Method: other: in vivo chromosomal aberrations - mammals (somatic cells)
GLP: no data
Test substance: no data

Result: ambiguous

Intraperitoneal injection of the test substance to 5 mice/sex/group resulted in increase of the micronucleus frequency in peripheral erythrocytes only in males treated with 5 mg/kg for 15 days (2-fold of control value). Only abstract available; no further data.
Test substance: formaldehyde; no data on purity of the compound
Reliability: (3) invalid
08-DEC-1997 (645)

Type: Micronucleus assay
Species: mouse Sex: no data
Strain: other: CD-7, C57/BL, HSD-ICR
Route of admin.: unspecified
Exposure period: chronic; no data specified
Doses: no data

Method: other: in vivo chromosomal aberrations - mammals (somatic cells)
GLP: no data
Test substance: no data

Remark: Reliability: 3 (not reliable)
Result: positive

A peripheral erythrocyte micronucleus test resulted in positive response (2-3-fold of control) after a relatively long duration of exposure with a non linear dose-effect correlation. Only abstract available; no further data.
Test substance: formaldehyde; no data on purity of the compound
08-DEC-1997 (438)

Type: Micronucleus assay
Species: mouse Sex: male/female
Strain: other: CD-7
Route of admin.: i.p.
Exposure period: biweekly for 3 months
Doses: 5 - 15 mg/kg

Method: other: in vivo chromosomal aberrations - mammals (somatic cells)
GLP: no data
Test substance: no data

Result: positive

The test substance was administered to 5 mice/sex/group; 10000 peripheral erythrocytes per animal were scored. In alldose groups, significantly higher frequencies of micronuclei(ca. 0.4%) compared to controls (ca. 0.2%) were observed; however, this increase was found only in blood samples of the first month of treatment. Only abstract available; no further data.
Test substance: formaldehyde; no data on purity of the compound
Reliability: (3) invalid
02-FEB-1999 (433)

Type: Micronucleus assay
Species: mouse Sex: male/female
Strain: other: no data
Route of admin.: inhalation
Exposure period: 2 hours
Doses: 281 - 299 ppm (ca. 0.35 - 0.37 mg/l; males), 253 - 273 ppm (ca. 0.31 - 0.34 mg/l; females)

Method: other: in vivo chromosomal aberrations - mammals (somatic cells)
GLP: no data
Test substance: no data

Remark: Reliability: 3 (not reliable)
Result: negative

No formation of micronuclei was observed (bone marrow micronucleus test). Korean publication with English abstract.
Test substance: formaldehyde; no data on purity of the compound
14-JUL-1997 (390)

Type: Micronucleus assay
Species: mouse Sex: no data
Strain: other: LACA
Route of admin.: inhalation
Exposure period: 14 or 30 days
Doses: up to 133 ppm (ca. 0.17 mg/l)

Method: other: in vivo chromosomal aberrations - mammals (somatic cells)
GLP: no data
Test substance: no data

Remark: Reliability: 3 (not reliable)
Result: negative

No increase in of micronucleated cells was observed (bone marrow micronucleus test). Chinese publication with English abstract.
Test substance: formaldehyde; no data on purity of the compound
02-FEB-1999 (721)

Type: Micronucleus assay
Species: mouse Sex: no data
Strain: other: no data
Route of admin.: oral unspecified
Exposure period: no data
Doses: 100 mg/kg

Method: other: in vivo chromosomal aberrations - mammals (somatic cells)
GLP: no data
Test substance: no data

Remark: Reliability: 3 (not reliable)
Result: positive

A bone marrow micronucleus test revealed an increase in the incidence of micronuclei in polychromatic erythrocytes.

Only abstract available; no further data.
Test substance: formaldehyde; no data on purity of the compound
18-JUN-1998 (541)

Type: Micronucleus assay
Species: rat Sex: male
Strain: Sprague-Dawley
Route of admin.: gavage
Exposure period: single dose
Doses: 200 mg/kg
Result: positive

GLP: no data
Test substance: other TS: formaldehyde; no data on purity of the compound

Method: Micronucleus test was performed by histology in cells of the gastro-intestinal epithelium (stomach, duodenum, ileum, and colon). The test substance was administered to groups of 5 animals 16, 24, and 30 h prior to sacrifice and after sacrifice, 3000 cells for each tissue per animal were scored. An increase in the number of micronucleated cells was observed in the stomach at each time point, in the duodenum after 24 h and in the cells of both ileum and colon after 30 h.
Result: According to the authors, the observed effects were clearly correlated with severe local irritation. Nuclear anomalies were increased in all tissues.
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
24-OCT-2002 (478)

Type: Mouse spot test
Species: mouse Sex: female
Strain: other: see result
Route of admin.: inhalation
Exposure period: on days 8, 9, and 10 of pregnancy, 6 h/d
Doses: 0.006-0.0061 or 0.0175-0.0181 mg/l

Method: other: in vivo gene mutations - mammals (somatic cells)
GLP: no data
Test substance: no data

Result: negative

Female C57BL/6J Han and male T-stock mice were used (exposure of mated females to formaldehyde gas). No increase in recessive spots in the offspring of the exposed mice was observed. Only abstract available; no further data.
Test substance: formaldehyde; no data on purity of the compound
Reliability: (3) invalid
06-MAY-1998 (361)

Type: Mouse spot test
Species: mouse Sex: female
Strain: other: no data
Route of admin.: inhalation
Exposure period: days 9-11 of pregnancy, 6 h/d
Doses: no data

Method: other: in vivo gene mutations - mammals (somatic cells)
GLP: no data

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Test substance:   no data

Result:           negative

                  No incidence of coat color spots was observed after
                  inhalation exposure of the mice for the test substance.
Test substance:   formaldehyde; no data on purity of the compound
Reliability:      (3)  invalid
08-DEC-1997                                                          (111)

Type:             Sister chromatid exchange assay
Species:          rat                              Sex: no data
Strain:           Wistar
Route of admin.:  inhalation
Exposure period:  5 days or 4 weeks (5 d/wk); 6 h/d
Doses:            0.1 - 20 ppm (ca. 0.0001 - 0.025 mg/l)

Method:           other: ex vivo (in vitro/in vivo) DNA damage - eukaryotes
                  (mammalian cells/SCE)
   GLP:           no data
Test substance:   no data

Remark:           Reliability: 2 (reliable with restrictions)
Result:           positive

                  Nasal epithelial cells were examined for sister chromatid
                  exchange (SCE). After exposure for 5 days, an increase in
                  the SCE frequency was observed at 20 ppm (ca. 0.025 mg/l)
                  in 2/2 experiments and a slight increase was found at 1 ppm
                  (ca. 0.0012 mg/l) in 1/2 experiments. After exposure for 4
                  weeks, a clear and concentration-related increase in SCE
                  frequencies was observed at doses >= 1.0 ppm (ca. 0.0012
                  mg/l).
Test substance:   formaldehyde; no data on purity of the compound
08-DEC-1997                                                          (483)

Type:             Sister chromatid exchange assay
Species:          rat                              Sex: male/female
Strain:           Fischer 344
Route of admin.:  inhalation
Exposure period:  5 days, 6 h/d
Doses:            0.5 - 15 ppm (ca. 0.006 - 0.019 mg/l)

Method:           other: in vivo DNA damage - mammals (somatic cells)
   GLP:           no data
Test substance:   no data

Remark:           Reliability: 2 (reliable with restrictions)
Result:           negative

                  Three rats/sex/dose group were used. No increase in sister
                  chromatid exchange (SCE) frequency in lymphocytes was found;
                  20 second-divison metaphases/animal were scored; no
                  significant dose-related effect on mitotic activity was

                  observed.
Test substance:   formaldehyde; no data on purity of the compound
14-MAY-1998                                                          (397)
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Type:              Sister chromatid exchange assay
Species:           rat                                Sex: no data
Strain:            Fischer 344
Route of admin.:   inhalation
Exposure period:   5 days, 6 h/d
Doses:             0.5, 6.0 ppm (ca. 0.0006, 0.0075 mg/l)

Method:            other: in vivo DNA damage - mammals (somatic cells)
   GLP:            no data
Test substance:    no data

Result:            negative

                   no increase in sister chromatid exchange in lymphocytes only
                   abstract available; no further data
Test substance:    formaldehyde; no data on purity of the compound
Reliability:       (3)  invalid
08-DEC-1997                                                                (396)

Type:              Sister chromatid exchange assay
Species:           mouse                              Sex: male/female
Strain:            CD-1
Route of admin.:   inhalation
Exposure period:   4 or 5 days, 6 h/d
Doses:             6, 12 ppm (ca. 0.007, 0.015 mg/l) for 5 days or 25 ppm (ca.
                   0.03 mg/l) for 4 days

Method:            other: in vivo DNA damage - mammals (somatic cells)
   GLP:            no data
Test substance:    no data

Result:            positive

                   elevated levels of sister chromatid exchange in bone marrow
                   cells at 12 and 25 ppm (ca. 0.015 and 0.03 mg/l) in females,
                   only; preliminary results, no further data
Test substance:    formaldehyde; no data on purity of the compound
Reliability:       (3)  invalid
07-MAY-1998                                                                (111)

Type:              Unscheduled DNA synthesis
Species:           rat                                Sex: no data
Strain:            other: CDF
Route of admin.:   inhalation
Exposure period:   1, 3, 5 days, 6 h/d
Doses:             0.5 - 15 ppm (ca. 0.0006 - 0.019 mg/l)

Method:            other: ex vivo (in vitro/in vivo) DNA damage - eukaryotes
                   (mammalian cells/UDS)
   GLP:            no data
Test substance:    no data

Remark:            Reliability: 2 (reliable with restrictions)
Result:            negative

                   Tracheal epithelium, no DNA repair; no increase of cells in
                   S-phase
Test substance:    formaldehyde; no data on purity of the compound
08-DEC-1997                                                                (196)
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Type: other: DNA damage - (DNA-protein crosslinks)
Species: rat Sex: no data
Strain: Fischer 344
Route of admin.: inhalation
Exposure period: 6 hours
Doses: ca. 0.0004 - 0.0124 mg/l (0.3 - 10 ppm 14C HCHO) and 6 ppm (3H HCHO)
Result: positive

Method: other: in vivo DNA damage - mammals (somatic cells/DNA-protein crosslinks)
GLP: no data
Test substance: other TS: formaldehyde; no data on purity of the compound

Result: Formation of DNA-protein crosslinks (DPC) in nasal mucosa cells at all concentrations; the slope of the fitted concentration-response curve at 10 ppm was 7.3-fold greater than at 0.3 ppm.
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
26-OCT-2000 (120)

Type: other: DNA damage - (DNA-protein crosslinks)
Species: monkey Sex: no data
Strain: other: Rhesus
Route of admin.: inhalation
Exposure period: 6 hours
Doses: ca. 0.0009 - 0.0075 mg/l (0.7 - 6.0 ppm)

Result: positive

GLP: no data
Test substance: other TS: formaldehyde; no data on purity of the compound

Method: Examination of formation of DNA-protein crosslinks (DPC) in middle turbinates, anterior lateral walls/septum, nasopharynx, maxillary sinuses, larynx/trachea/carina, major intrapulmonary airways, and lungs.
Result: Highest DPC concentrations in the mucosa of the middle turbinate at >=0.7 ppm (ca. 0.0009 mg/l); lower DPC concentrations in the larynx/trachea/carina and in the proximal portions of the major bronchi at >=2.0 ppm (ca. 0.0025 mg/l); no DPC in the maxillary sinuses or lung parenchyma.
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
26-OCT-2000 (121)

Type: other: DNA damage - (DNA-protein crosslinks)
Species: rat Sex: no data
Strain: Fischer 344
Route of admin.: inhalation
Exposure period: 11 weeks + 4 days
Doses: ca. 0.0009 - 0.0187 mg/l (0.7 - 15 ppm)
Result: positive

GLP: no data
Test substance: other TS: formaldehyde; no data on purity of the compound

Method: Examinations of nasal mucosal tissue, from low and high tumor sites for DNA-protein crosslinks (DPC) after subchronic (whole body) preexposure to 0 ppm (N rats) or 0.7-15 ppm formaldehyde (PE) rats for 11 weeks + 4 days (5 d/w, 6 h/d) followed by acute (nose-only) exposure of N and PE rats to 0.7-15 ppm of H14CHO or unlabeled substance for 3 h on the 5th day of the 12th week were carried out.
Result: Acute DPC yields measured with labeled formaldehyde at the high tumor site were ca. 6-fold higher than at the low tumor site. At 0.7 and 2.0 ppm (ca. 0.0009 and 0.0025 mg/l, respectively), no differences between PE and N rats were detected in either tissue. At 6 and 15 ppm (ca. 0.0075 and 0.0187 mg/l, respectively), acute DPC yields in the high tumor site of PE rats were approximately half those of N rats, but no differenes were detected in the low tumor site. With non-labelled formaldehyde (Interfacial DNA (IF) method) a concentration-dependent increase in DPC was observed in both groups, with yields smaller in PE than in N rats. According to the authors, these result suggested that no accumulation of DPC occurred in PE rats.

Cell proliferation was induced in PE rats at 6 ppm (high tumor site) and at 15 ppm (all sites).
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
26-OCT-2000 (122)

Type: other: DNA-Damage
Species: rat Sex: no data
Strain: other: Fischer 344 tracheal implant model
Route of admin.: other: instillation
Exposure period: no data
Doses: 0.0005 - 0.2% (single dose) 0.2% (3 time twice weekly)

Method: other: in vivo DNA damage - mammals (somatic cells/DNA-protein crosslinks, Alkaline filter elution assay)
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: positive

DNA-protein crosslinks (DPC) were examined in tracheal implants (OETI = Open-Ended Tracheal Implant). Formaldehyde-Phosphate Buffered Saline solutions were introduced into the OETI. A dose-dependent increase in DPC from 0.005% onward with a maximum response at 0.2% was observed. Nearly complete removal of DPC induced by either single of multiple exposure after 72 hours was recorded.
Test substance: formaldehyde; no data on purity of the compound
18-JUN-1998 (157)

Type: other: ex vivo (in vitro/in vivo) gene mutations - eukaryotes (mammalian cells)
Species: rat Sex: no data
Strain: Wistar
Route of admin.: inhalation
Exposure period: 5 days or 4 weeks (5 d/wk); 6 h/d

Doses: (a) 20 ppm (ca. 0.025 mg/l) for 5 days; (b) 0.1-1.0 ppm (ca. 0.0001-0.0012 mg/l) for 5 days; (c) 1.0 ppm (ca. 0.0012 mg/l) for 4 weeks

Method: other: gene mutation (HPRT)
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: positive

Nasal epithelial cells (nasal- and maxillar turbinates) were investigated. Induction of mutation at the hprt locus was observed only after exposure to 20 ppm (ca. 0.025 mg/l) for 5 days (experiment (a)).
Test substance: formaldehyde; no data on purity of the compound

10-AUG-1999 (483)

Type: other: ex vivo (in vitro/in vivo) gene mutations - eukaryotes (non-mammalian)
Species: other: Caenorhabditis elegans (nematode) Sex: no data
Strain: other: N2S (various strains)
Route of admin.: unspecified
Exposure period: no data
Doses: 0.01 - 1.0% (ca. 0.1 - 10.0 mg/ml)

GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: positive

Mutations were observed in the unc-22 region of linkage group IV at dose levels of 0.07 and 0.1%. At 0.07%, 22 pointmutations and 11 deficiencies (forward mutation frequency was 2x10E-4) were observed; at 0.1%, 4 point mutations and 3deficiencies (forward mutations frequency was 3x10E-5) were observed. A dose level of 1.0% was lethal to the worms.
Test substance: formaldehyde; no data on purity of the compound

18-JUN-1998 (485)

Type: other: ex vivo (in vitro/in vivo) gene mutations - eukaryotes (non-mammalian)
Species: other: Caenorhabditis elegans (nematode) Sex: no data
Strain: no data
Route of admin.: unspecified
Exposure period: no data
Doses: 0.07 - 0.175% (ca. 0.7 - 1.75 mg/ml)

GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: positive

Exposure to the test substance resulted in induction of small deficiencies. Lethality rates were 0.3% and 1.6% at dose levels of 0.07% and 0.105-0.175% formaldehyde, respectively.
Test substance: formaldehyde; no data on purity of the compound
18-JUN-1998 (365)

Type: other: ex vivo (in vitro/in vivo) gene mutations - eukaryotes (non-mammalian)
Species: other: Caenorhabditis elegans (nematode) Sex: no data
Strain: other: BC2200
Route of admin.: unspecified
Exposure period: no data
Doses: 0.07 - 0.18% (ca. 0.7 - 1.8 mg/ml)

GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: positive

The induction of recessive lethal mutations by formaldehyde was studied. The test substance induced putative point mutations, deficiencies, and more complex lesions. Accordingto the authors, the best mutation induction was found after 4-h treatment with 0.1% formaldehyde.
Test substance: formaldehyde; no data on purity of the compound
18-JUN-1998 (366)

Type: other: ex vivo (in vitro/in vivo) gene mutations - eukaryotes (non-mammalian/Drosphila)
Species: Drosophila melanogaster Sex: male
Strain: other: no data
Route of admin.: unspecified
Exposure period: no data specified
Doses: 0.1% (ca. 1 mg/ml)

GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: positive

Eggs and first instar larvae were exposed to the test substance. Adult males that emerged after treatment were crossed. The Adh gene from 4 formaldehyde-generated ADH-negative mutants had been cloned and sequenced. According to the authors, formaldehyde engendered both large and small deletions at the Adh locus.
Test substance: formaldehyde; no data on purity of the compound
18-JUN-1998 (62)

Type: other: gene mutation (P53)
Species: rat Sex: male
Strain: Fischer 344
Route of admin.: inhalation
Exposure period: 6 h/d, 5 d/w
Doses: ca. 0.019 mg/l

Method: other: no data
GLP: no data
Test substance: other TS

Remark: No detailed data were given on method, number of animals, duration of exposure. According to the authors, the exposure was carried out as decribed by Chang et al., 1983.
Result: The aim of the study was to investigate the role of mutations of the tumor supressor gene p53 in rat nasal tumors induced by repeated inhalation exposure to formaldehyde (study of Monticello et al.). Male Fischer 344 rats were whole-body exposed to 15 ppm (ca. 0.019 mg/l) formaldehyde gas (6 h/d, 5 d/w). According to the authors, the rats were exposed until macroscopic or behavioural changes suggesting a nasal mass were observed; thereafter the rats were sacrificed. The nasal passages were dissected; sections containing tumors or other substance-related lesions were collected. Cell lines derived from rat nasal tumors induced by the test substance were investigated immunohistochemically to localize the p53 tumor suppressor gene (p53), proliferating cell nuclear antigen (PCNA), and transforming growth factor-alpha proteins (TGF-alpha proteins).
According to the authors, 5 tumors that had p53 mutations were mutant for p53 protein by immunohistochemistry and 3/6 tumors with no detected p53 mutations were immunoreactive for p53 protein, too. The presence, pattern, and distribution of p53 staining in tissue sections were found to be dependent on the morphology of the lesion. PCNA immunoreaction was strikingly similar in pattern and distribution to p53 immunoreactivity. The pattern and distribution of immunoreactivity for TGF-alpha did not correlate with the other markers.
According to the authors, this study demonstrated that immunohistochemistry might be a useful tool to identify the sites within a tumor that might have p53 mutations.
The results suggest that mutation of the p53 tumor suppressor gene might be an important step of formaldehyde-induced nasal carcinogenesis in the rat.
However it is not clear if FA exposure is causally related to p53 mutation induction.
Test substance: formaldehyde; no data on purity of the compound
Reliability: (2) valid with restrictions
30-JUN-1998 (557)

Type: other: in vivo DNA damage - eukaryotes (non-mammalian/Drosphila)
Species: Drosophila melanogaster Sex: no data
Strain: no data
Route of admin.: oral unspecified
Exposure period: no data specified
Doses: 12.5 mM (ca. 375 mg/l)

Method: other: SMART = Somatic mutation and recombination test
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: positive

Chronic exposure of larvae; positive effect,i.e. twin (TS) and single light (LS) mosaic spots in adult flies of both sexes; formaldehyde caused high yields of small eye spots inthird larval instar. According to the authors, ca. 95% of all TS and LS induced appeared to be a result of recombinogenic activity between the 2 homologous X-chromosomes.
Test substance: formaldehyde; no data on purity of the compound
30-JUN-1998 (687)

Type: other: in vivo DNA damage - eukaryotes (non-mammalian/Drosphila)
Species: Drosophila melanogaster Sex: no data
Strain: no data
Route of admin.: oral unspecified
Exposure period: no data specified
Doses: 12.5 mM (ca. 375 mg/l)

Method: other: eye mosaic assay
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)

Result: positive

Chronic exposure of larvae; induction of mosaic spots with a majority of small spots: According to the authors, the events were predominantly caused by interchromosomal mitotic recombination.
Test substance: formaldehyde; no data on purity of the compound
18-JUN-1998 (686)

Type: other: in vivo DNA damage - mammals (somatic cells/DNA-protein crosslinks)
Species: rat Sex: no data
Strain: Fischer 344
Route of admin.: inhalation
Exposure period: 3 hours

Doses: ca. 0.0012 - 0.0075 mg/l (1 - 6 ppm)

Method: other: Alkaline filter elution assay
GLP: no data
Test substance: no data

Result: positive

DNA-protein crosslinks (DPC) were examined in nasoturbinates and maxilloturbinates after 3-hours nose-only exposure. A dose-dependent increase of DPC from 2 ppm (ca. 0.0025 mg/l) onward was observed in both locations; DPC were readily reversible. Only abstract available; no further data.
Test substance: formaldehyde; no data on purity of the compound
Reliability: (3) invalid
19-JUN-1998 (67)

Type: other: in vivo gene mutations - eukaryotes (non-mammalian Drosophila)
Species: Drosophila melanogaster Sex: male

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Strain:            other: no data
Route of admin.:   other: abdominal injection
Exposure period:   no data
Doses:             25 mM (ca. 750 mg/l)

Method:            other: SLRL test and Ring-X loss test
   GLP:            no data
Test substance:    no data

Remark:            Reliability: 2 (reliable with restrictions)
Result:            positive

                   Injection of the test substance resulted in induction of
                   both sex-linked recessive lethals and ring-X loss in male
                   adults. According to the authors, the low ratio sex-linked
                   recessive lethals : ring-X loss indicated the involvement of
                   cross-links in genotoxic action.
Test substance:    formaldehyde; no data on purity of the compound
18-JUN-1998                                                                (729)

Type:              other: in vivo gene mutations - eukaryotes
                   (non-mammalian/Drosophila)
Species:           Drosophila melanogaster          Sex: no data
Strain:            other: no data
Route of admin.:   oral feed
Exposure period:   no data
Doses:             20 mM (ca. 600 mg/l)

Method:            other: Visible mutation test
   GLP:            no data
Test substance:    no data

Remark:            Reliability: 2 (reliable with restrictions)
Result:            negative

                   No induction of visible mutations at several selected loci
                   were observed.
Test substance:    formaldehyde; no data on purity of the compound
30-JUN-1998                                                                 (14)

Type:              other: in vivo gene mutations - eukaryotes
                   (non-mammalian/Drosophila)
Species:           Drosophila melanogaster          Sex: no data
Strain:            other: no data
Route of admin.:   oral feed
Exposure period:   48 or 72 h
Doses:             10, 50 mM (ca. 300, 1500 mg/l)

Method:            other: Wing SMART = Wing Somatic Mutation and Recombination
                   Test
   GLP:            no data
Test substance:    no data

Remark:            Reliability: 2 (reliable with restrictions)
Result:            positive

                   Negative or inconclusive results in the repair proficient
                   genotype but positive ones in the excision repair defective
                   genotype,  i.e. high frequency of total spots (single and
                   twin spots) in excision repair defective wings were
                   obtained after chronic larval feeding. Single spots were
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                    produced by pount mutation, chromosome breakage, and
                    mitotic recombination. Twin spots were produced by mitotic
                    recombination, exclusively. According to the authors, 72h
                    treatment with 10 mM was less efficient than the 48h
                    treatment with 50 mM.
Test substance:     formaldehyde; no data on purity of the compound
30-JUN-1998                                                                (266)

Type:               other: in vivo gene mutations - eukaryotes
                    (non-mammalian/Drosophila)
Species:            Drosophila melanogaster           Sex: male/female
Strain:             other: no data
Route of admin.:    other
Exposure period:    during larval stage
Doses:              according to the authors, a concentration which allowed 50% of
                    the larvae to develop to the adult stage

Method:             other: mosaic test
   GLP:             no data
Test substance:     no data

Remark:             Reliability: 2 (reliable with restrictions)
Result:             positive

                    Larval feeding (second instar larvae) with formaldehyde-
                    containing food for 3-4 days until pupation resulted in an
                    increase in the frequency of mosaic spots (eye mosaicism).
                    Fewer clones were induced in males than in females (ca. 59%
                    were twin spot females). Highly significant elevations in
                    wing-clone frequency (wing mosaicism) was observed. Accoring
                    to the authors, there was no indication of female germ-line
                    mosaicism.
Test substance:     formaldehyde; no data on purity of the compound
30-JUN-1998                                                                (635)

Type:               other: in vivo gene mutations - eukaryotes
                    (non-mammalian/Drosophila)
Species:            Drosophila melanogaster           Sex: male
Strain:             other: no data
Route of admin.:    oral feed
Exposure period:    during the entire larval and pupal development stages
Doses:              30 - 70 mM (ca. 900 - 2100 mg/l)

Method:             other: unstable zeste-white test
   GLP:             no data
Test substance:     no data

Remark:             Reliability: 2 (reliable with restrictions)
Result:             positive

                    Exposure to the test substance resulted in a dose-related
                    increase of somatic mutations (aberrantly pigmented spots
                    in the eyes) in adult males.
Test substance:     formaldehyde; no data on purity of the compound
02-FEB-1999                                                                (556)

Type:               other: in vivo gene mutations - eukaryotes
                    (non-mammalian/Drosophila)
Species:            Drosophila melanogaster           Sex: male
Strain:             other: no data
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Route of admin.: oral feed
Exposure period: during larval stage
Doses: 50 mM (ca. 1500 mg/l)

Method: other: unstable zeste-white test
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: negative

Exposure of males (P fathers) to the test substance did not induce any germ cell mutations i.e. no mutations in F1 males were observed after treatment of P fathers.
Test substance: formaldehyde; no data on purity of the compound
02-FEB-1999 (556)

Type: other: in vivo gene mutations - eukaryotes (non-mammalian/Drosophila)
Species: Drosophila melanogaster Sex: male
Strain: other: no data
Route of admin.: oral feed
Exposure period: no data specified
Doses: 50, 160 mM (ca. 1500, 4800 mg/l)

Method: other: unstable zeste-white test
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: positive in somatic mutation;
negative in germinal mutation

An increase in delayed somatic mutations but no increase in the frequency of germinal mutations was observed in the male offspring after adult feeding. According to the authors, formaldehyde was not totally hampered from reaching the male gonads even after adult feeding, since it was capable of causing premutational DNA lesions in sperm, as revealed by the occurrance of delayed somatic spots.
Test substance: formaldehyde; no data on purity of the compound
02-FEB-1999 (556)

5.7 Carcinogenicity

Species: mouse Sex: male/female
Strain: other: hairless (hr/hr, Oslo)
Route of administration: dermal
Exposure period: 60 weeks
Frequency of treatment: twice a week
Post exposure period: none
Doses: ca. 2, 20 mg/animal (200 ul of a 1 and 10% aqueous solution, respectively)
Control Group: no data specified

Method: other: carcinogenicity study
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: The tumorigenic effect of dermally applied formaldehyde was studied in 16 mice/sex/group. Two hundred microlitres ofa 1% and 10% aqueous solution was applied. Examinations on general health, autopsy, and histopathology of brain, nasal mucosa, lungs, skin tumors and other tumors were performed. According to the authors, no skin tumors were observed. In a few animals of the high dose group, slight hyperplasia of the epidermis and skin ulcers were found. These results were part of an initiation-promotion study.
Test substance: formaldehyde; no data on purity of the compound
18-JUN-1998 (355)

Species: mouse Sex: male/female
Strain: other: hairless (hr/hr, Oslo)
Route of administration: dermal
Exposure period: up to 60 weeks
Frequency of treatment: twice a week
Post exposure period: none
Doses: ca. 20 mg/animal (200 ul of a 10% aqueous solution)
Control Group: no data specified

Method: other: initiation-promotion study
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: The tumorigenic effect of dermally applied formaldehyde was studied. All groups were treated once with 51.2 ug dimethyl benz(a)anthracene (DMBA in acetone; initiation). Thereafter the animals were treated with 200 ul 10% aqueous solution of formaldehyde (FA) or 17 nmoles of 12-O-tetradecanoylphorbol-13acetate (TPA) twice a week for 60 or 46 weeks; these groups consisted of 16 mice/sex. Hundred and seventy-six animals remained untreated for 80 weeks after the initiation. Examinations on general health, autopsy, and histopathology of brain, nasal mucosa, lungs, and skin and other tumors were performed.

In the group treated with DMBA + FA, skin tumors were observed in 11/32 (34%) mice, 3 squamous cell carcinomas and 22 papillomas were recorded (first tumors at week 10). In the group treated with DMBA + TPA, increased mortality was observed. Incidence of skin tumors was 100% at week 20; all animals had papillomas. In the group treated with DMBA alone, skin tumors were present in 85/176 (48%) mice, 6 squamous cell carcinomas and 219 papillomas were found. The first tumors were observed after ca. 22 weeks.

In FA treated mice, the incidence of lung adenomas was low and not statistically significantly different from historical control. Thus, according to the authors, the presence of a weak promoting activity of 10% FA due to the shortening of the latency time for tumor formation was concluded.
Test substance: formaldehyde; no data on purity of the compound
28-NOV-1997 (355)

Species: mouse Sex: female
Strain: Sencar
Route of administration: dermal

Exposure period: 48 weeks
Frequency of treatment: once or twice a week
Post exposure period: none
Doses: 3.7 - 4% solution; no further data
Control Group: yes

Method: other: initiation-promotion study
GLP: no data
Test substance: other TS: formaldehyde; no data on purity of the compound

Method: The aim of the study was to evaluate the role of formaldehyde in carcinogenesis (as a complete carcinogen, initiator, or promotor). Groups of 30 mice were treated with formaldehyde solutions (FA; 3.7-4% in acetone), dimethylbenz(a)anthracene (DMBA; 20 ug/dose in acetone), 12-O-tetradecanoylphorbol-13-acetate (TPA; 1.25 ug/dose in acetone), acetone, or with combinations of two compounds. Aninitiator was applied once; thereafter, a promotor was applied once or twice a week for 48 weeks. The incidence of skin papilloma was recorded.
Result: No papilloma formation was observed in mice treated with FA as both initiator and promotor; with DMBA as initiator and acetone as promotor; with FA as initiator and acetone as promotor, and in mice treated with acetone only. Few papillomas were observed in the groups applied DMBA as initiator and FA as promotor; and acetone as initiator and FA as promotor. Some papillomas were found in mice treated with FA as initiator and TPA as promotor; and with acetone as initiator and TPA as promotor. The combination of DMBA asinitiator and TPA as promotor resulted in the formation of many papillomas.

According to the authors, these results suggest that formaldehyde was probably not a complete carcinogen or an initiator; the data obtained on promotion effects were inconclusive. According to the authors, it was concluded that the test stubstance problably might be a very weak promotor.
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
18-DEC-2002 (617)

Species: mouse Sex: female
Strain: CD-1
Route of administration: dermal
Exposure period: 26 weeks
Frequency of treatment: 3 times a week
Post exposure period: 26 weeks
Doses: up to 10%
Control Group: yes

Method: other: initiation-promotion study
GLP: no data
Test substance: other TS: formaldehyde; no data on purity of the compound

Method: The aim of the study was to evaluate the role of formaldehyde in carcinogenesis (as an initiator or as a promotor). Groups of 30 mice were treated with combinations of formaldehyde solutions (FA; in acetone/water 1:1) at different concentrations, benzo(a)pyrene (BaP; 159 ug/dose in acetone), 12-O-tetradecanoylphorbol-13-acetate (TPA; 2.5 ug/dose in acetone), or acetone. The initiator was applied once (50 ul); thereafter, 100 ul of the promotor was applied 3 times a week for 26 weeks. Data on general health and the incidence of skin nodules were recorded.

Remark: Slightly higher numbers of animals at risk reported in the abstract.

Result: No tumors (0/28) were observed in both the groups exposed to FA (initiator) plus acetone (promotor), or 10% FA (initiator) plus 1% FA (promotor). Tumor incidences in groups initiated with BaP and treated with FA as promotor were 1/25 (4%), 2/28 (7%), and 7/27 (26%) at FA concentrations of 1%, 0.5%, and 0.1%, respectively. Initiation with BaP followed by promotion with acetone as well as initiation with acetone and promotion with TPA resulted in tumor incidences of 3/27 (11%) in both cases. Five of 28 mice (18%) treated with FA (initiator) and TPA (promotor) had skin nodules. The highest tumor incidence (28/29; 97%) was observed in the group initiated with BaP and treated with TPA as promotor. The average time to the first nodule was ca. 110 days for mice treated with BaP plus TPA and ca. 350 days in all other groups.

Most of the nodules were benign tumors (keratocanthomas or papillomas; malignant tumors were histopathologically diagnosed in the BaP+TPA group, only (ca. 30% squamous cell carcinomas). No statistically significant differences were observed between the treated groups and appropriate controlsin groups exposed to formaldehyde.

According to the authors, these results suggest that formaldehyde did not initiate or promote skin tumorigenesis in minimally irritating concentrations (in a preliminary test, a concentration of 10% FA was determined as moderately irritating, 1% caused mild irritation, 0.5% was slightly irritating; see chapter 5.4).

Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
26-OCT-2000 (406) (407)

Species: rat Sex: male/female
Strain: Wistar
Route of administration: drinking water
Exposure period: 104 weeks
Frequency of treatment: continuously in the drinking water
Post exposure period: none
Doses: ca. 10, 50, 300 mg/kg/d (200, 1000, 5000 ppm in the drinking water)
Control Group: yes, concurrent no treatment

Method: other: carcinogenicity study
GLP: no data
Test substance: no data

Result: The tumorigenic effect of orally administered formaldehyde was studied in 4 groups of 20 rats/sex (3 treated groups, 1 control group). Interim sacrifices were carried out with 6 animals/sex/group after 12 and 18 months. Examinations on general health, clinical pathology, autopsy, and histopathology of several organs were performed. The daily doses were calculated from body weight and liquid consumption: 10, 50, 300 mg/kg (200, 1000, 5000 ppm, respectively).

According to the authors, no evidence of substance induced tumors was observed. The stomach was presumed to be the target organ, since there were observed severe non-neoplastic lesions in the high dose group (squamous and basal cell hyperplasia, erosions/ulcers, and submucosal cell infiltration; see chapter 5.4).
Test substance: formaldehyde; no data on purity of the compound
Reliability: (2) valid with restrictions
More details are reported in the study by Til et al. 1989 and the outcome is comparable.
Flag: Critical study for SIDS endpoint
13-MAY-2003 (655)

Species: rat Sex: male/female
Strain: Sprague-Dawley
Route of administration: drinking water
Exposure period: 104 weeks
Frequency of treatment: continuously in the drinking water
Post exposure period: up to natural death
Doses: ca. 10, 50, 100, 500, 1000, 1500 mg/l in the drinking water
Control Group: yes

Method: other: carcinogenicity study
GLP: no data
Test substance: no data

Result: The tumorigenic effect of orally administered formaldehyde was studied. Groups of 50 rats/sex were treated with the test substance at several doses, another 50 rats/sex were given 15 mg/l of methanol, and 100 rats/sex remained untreated. Examinations on general health, autopsy, and histopathology of ca. 50 tissues were performed. At the beginning of the studies, the rats were 7 weeks old.

No substance related effects on survival and body weight gain were observed. According to the authors, increased incidences in leukemias (lymphoblastic leukemias and lymphosarcomas, immunoblastic lymphosarcomas and others) and gastro-intestinal tumors (stomach adenomas, adenocarcinomas and leiomyosarcomas as well as intestinal adeno(carcinomas) and leiomyo(sarcomas) were observed without clear dose response relationship. They concluded that formaldehyde was a multipotential carcinogen.
Test substance: formaldehyde; no data on purity of the compound
Reliability: (3) invalid
The study (Soffritti et al., 1989) was challenged by Feron et al. (1990) because of the following reasons:
- leukemia incidence was not statistically significantly different from methanol controls and was within the range

of historical control data
- there was a lack of dose response relation for gastro-intrestinal tumors
- heterogeneity of tumor types in both leukemias and gastro-intestinal tumors
- non-neoplastic lesions were not reported
- the results were not found in other oral long term studies.

13-MAY-2003 (226) (616)

Species: rat Sex: male/female
Strain: Sprague-Dawley
Route of administration: drinking water
Exposure period: 104 weeks
Frequency of treatment: continuously in the drinking water
Post exposure period: up to natural death

Doses: ca. 2500 mg/l in the drinking water
Control Group: yes, concurrent no treatment

Method: other: carcinogenicity study
GLP: no data
Test substance: no data

Result: The tumorigenic effect of orally administered formaldehyde was studied in 25 weeks old breeding rats. A group of 18 males and 18 mated females was exposed to the test substancefrom days 12 of gestation for 104 weeks and observed up to natural death. Another group of 20 males and 20 mated females remained untreated (control). Examinations on general health, autopsy, and histopathology of ca. 50 tissues were performed.

Totally, 59 male and 49 female offsprings were recorded in the control group; 36 male and 37 female offsprings were recorded in the exposed group. No substance related effects on survival and body weight gain was observed in the breeders, however, depression of body weight gain was observed in the offsprings. According to the authors, increased incidences in leukemia and gastro-intestinal tumors were observed. According to the authors, these findings allowed to conclude that formaldehyde was a multipotential carcinogen.

Test substance: formaldehyde; no data on purity of the compound
Reliability: (3) invalid
The study (Soffritti et al., 1989) was challenged by Feron et al. (1990) because of the following reasons:
- leukemia incidence was not statistically significantly different from methanol controls and was within the range of historical control data
- there was a lack of dose response relation for gastro-intrestinal tumors
- heterogeneity of tumor types in both leukemias and gastro-intestinal tumors
- non-neoplastic lesions were not reported
- the results were not found in other oral long term studies.

13-MAY-2003 (226) (616)

Species: rat Sex: male
Strain: Wistar
Route of administration: drinking water
Exposure period: 32 weeks
Frequency of treatment: continuously in the drinking water
Post exposure period: none
Doses: ca. 450 mg/kg/d (calculated from 5000 ppm in the drinking water)
Control Group: no data specified

Method: other: initiation-promotion study
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: The tumor promoting effect of formaldehyde (FA) was studied. Initiation was carried out with 100 mg/l N-methyl-N'-nitroso-N-nitroguanidine (MNNG) in the drinking water plus 10% sodium chloride (NaCl) in the diet for 8 weeks; promotion was carried out with 5000 ppm FA in the drinking water for 32 weeks. Ten rats remained untreated (control), 10 rats were given FA only (promotor only), 30 rats were given MNNG only (initiator only), and 17 rats weregiven MNNG + FA (initiator + promotor). Examinations on general health, autopsy, and histopathology of stomach and duodenum were performed.
Papillomas were observed in 80% of the animals treated with FA alone. In animals treated with MNNG + FA, papillomas of the forestomach (88%) and increased incidence of adenomatous hyperplasia of the fundus (88%), preneoplastic hyperplasia of pylorus (41%), and adenocarcinomas of the pylorus (23.5%) were observed; as compared to the values of initiation alone(0, 23.3 and 3.3%). No increased incidence of duodenal tumors was recorded. Non-neoplastic lesions were diffuse proliferative changes in the superficial epithelium of the glandular stomach, and erosions and ulcers along the limiting ridge of fundic mucosa (see chapter 5.4).
According to the authors, gastric irritation and damage to the mucosa and corresponding proliferation stimuli was discussed as mechanism for promotion.
Test substance: formaldehyde; no data on purity of the compound
01-DEC-1997 (639)

Species: rat Sex: male/female
Strain: Wistar
Route of administration: drinking water
Exposure period: 104 weeks
Frequency of treatment: continuously in the drinking water
Post exposure period: none
Doses: ca. 1.2, 15, 82 mg/kg/d (males); 1.8, 21, 109 mg/kg/d (females)
Control Group: yes, concurrent no treatment

Method: other: carcinogenicity study
GLP: no data
Test substance: other TS: formaldehyde; no data on purity of the compound

Method: The tumorigenic effect of orally administered formaldehyde was studied in 70 rats/sex/group (3 treated groups and 1 control group of each sex). Interim sacrifices were carried out with 10 animals/sex/group after 12 and 18 months. Examinations on general health, clinical pathology, autopsy,and histopathology of ca. 50 organs and tissues were performed. The concentrations of the test substance in the drinking water were adjusted for body weight and liquid consumption up to week 52; the average concentrations were 20, 260, and 1900 mg/l in the low, mid, and high dose groups, respectively.
Result: According to the authors, no evidence of substance induced tumors was observed. The stomach and the kidneys were presumed to be the target organs, since there were observed severe non-neoplastic lesions in the high dose groups (papillary epithelial hyperplasia in the forestomach, chronic atrophic gastritis in the glandular stomach, renal papillary necrosis; see chapter 5.4).
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
26-OCT-2000 (651)

Species: rat Sex: male
Strain: Fischer 344
Route of administration: gavage
Exposure period: single dose
Frequency of treatment: single dose
Post exposure period: none
Doses: 11 - 110 mg/kg (1 ml of 0.185 - 1.85% solution)
Control Group: yes, concurrent vehicle

Method: other: S-phase-response
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: The effect of a single dose of formaldehyde on ornithine decarboxylase and DNA synthesis (in vitro) induction in pyloric mucosa was studied. A concentration (dose) dependentinduction of both decarboxylase and DNA synthesis was observed. Maxima were reached at 16 h post application of ca. 100 or 49 fold of control, respectively; the effects reversed after 48-72 h.
According to the authors, these results allowed to conclude that the test substance had tumor promoting activity.
Test substance: formaldehyde; no data on purity of the compound
11-DEC-1997 (238)

Species: rat Sex: male
Strain: Wistar
Route of administration: inhalation
Exposure period: 4, 8, and 13 weeks
Frequency of treatment: 5 d/w, 6 h/d
Post exposure period: none or up to study week 131
Doses: ca. 0.0124, 0.0245 mg/l (10, 20 ppm)
Control Group: yes, concurrent no treatment

Method: other: carcinogenicity study
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: The incidence of tumors due to exposure to the test substance was investigated in groups of 50-55 rats. The rats were treated with formaldehyde for 4, 8, or 13 weeks with sacrifices immediately after cessation of exposure (5-10 animals per group) or with observation up to study week 131. Data on general health were recorded, autopsy and histopathological examination of the nose was performed.

Nasal tumors were observed in 2/134, 2/132, and 10/132 rats of the control, low dose, and high dose group, respectively. Tumors originating from tissue prone to formaldehyde toxicity and - according to the authors - therefore considered to be associated with exposure to the test substance were only found in 6/132 animals of the high dose group. Particularly, 3 squamous cell carcinomas and 1 carcinoma in situ were observed in animals exposed to 20 ppm for 13 weeks; 2 polyploid adenomas were observed in animals exposed to the high dose level for 4 or 8 weeks. According to the authors, a concentration and exposure time dependent occurrence of non-neoplastic lesions were found (see chapter 5.4)
Test substance: formaldehyde; no data on purity of the compound
10-AUG-1999 (225)

Species: rat Sex: male
Strain: Sprague-Dawley
Route of administration: inhalation
Exposure period: lifetime
Frequency of treatment: 5 d/w, 6 h/d
Post exposure period: none
Doses: premix of ca. 0.018 mg/l of formaldehyde (FA) + ca. 0.016 mg/l of hydrogen cloride (HCl) (14.7 ppm FA + 10.6 ppm HCl)
Control Group: yes

Method: other: carcinogenicity study
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: The incidence of tumors due to exposure to the test substance (FA) in combination with hydrogen chloride (HCl) was investigated. Two control groups of 50 male rats each were sham exposed or remained untreated; 99 rats were exposed to a premix of 14.7 ppm of FA and 10.6 ppm of HCl. After sacrifice, examinations on general health,autopsy, and histopathology of nose, larynx, trachea, lung, liver, bladder, kidneys, and spleen were performed.

The incidence of squamous cell carcinomas and squamous papillomas were 25/99 (25%) and 3/99 (3%), respectively, in rats exposed to the premix (the first tumor was detected after 223 days); no tumors (0/50) were observed in colony controls; the tumor incidence in sham treated controls was not reported. No increase in extranasal tumorincidence was recorded. In the exposed group, increased mortality and reduced body weight gain was observed. Non-neoplastic lesions of the upper respiratory tract (epithelial hyperplasia and squamous metaplasia) were observed (see

chapter 5.4).
Test substance: formaldehyde; no data on purity of the compound
07-JUL-1997 (10)

Species: rat Sex: male
Strain: Sprague-Dawley
Route of administration: inhalation
Exposure period: lifetime
Frequency of treatment: 5 d/w, 6 h/d
Post exposure period: none
Doses: ca. 0.018 mg/l (14.8 - 15.2 ppm) alone or in combination with ca. 0.015 mg/l (9.7 - 10.0 ppm) of hydrogen cloride (HCl)
Control Group: yes

Method: other: carcinogenicity study
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: The incidence of tumors due to exposure to the test substance (FA) in combination with hydrogen chloride (HCl) was investigated in groups of 100 male rats. Groups were exposed to a premix of 15.2 ppm FA + 9.9 ppm HCl, a non-premix of 14.9 ppm FA + 9.7 ppm HCL, 14.8 ppm FA alone, 10.0 ppm HCL alone, air, or remained unexposed. After sacrifice, examinations on general health, autopsy, and histopathology of nose, larynx, trachea, lung, liver, bladder, kidneys, and testes were performed.

The incidence of squamous cell carcinomas and polyps or papillomas were 38/100 and 10/100 in the groups exposed to FA alone, 45/100 and 13/100 in the groups exposed to the premix, 27/100 and 11/100 in the groups exposed to the non-premix, and 0/99 in the HCl group, air control, and unexposed group, respectively. The average latency periods ranged from 603 to 645 days. According to the authors, tumors were originating from naso-maxillary turbinates and nasal septum. No increase in extranasal tumor incidence was recorded. In groups exposed to FA, increased mortality and reduced body weight gain was observed. Non-neoplastic lesions of the upper respiratory tract (epithelial hyperplasia and squamous metaplasia) were observed (see chapter 5.4).
Test substance: formaldehyde; no data on purity of the compound
18-JUN-1998 (10) (597) (598)

Species: rat Sex: female
Strain: Sprague-Dawley
Route of administration: inhalation
Exposure period: no data specified
Frequency of treatment: no data specified
Post exposure period: no data
Doses: ca. 0.016 mg/l (12.4 - 12.7 ppm) alone or in combination with ca. 25 mg/m3 of wood dust
Control Group: yes

Method: other: carcinogenicity study
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: The incidence of tumors due to exposure to the test substance in combination with wood dust was investigated. Groups of 15-16 rats were exposed to 12.4 ppm formaldehyde alone, 12.7 ppm formaldehyde combined with 25 mg/m3 of wood dust, 25 mg/m3 wood dust alone, or remained untreated. Examinations on general health and histopathology of nose and lungs were performed.
According to the authors, tumor incidence was 1/16 (6%) in the group exposed to 12.4 ppm of formaldehyde. No nasal tumors were observed in the animals coexposed to formaldehyde and wood dust, although more severe non-neoplastic lesions (e.g. squamous metaplasia and dysplasia) were present (see chapter 5.4).
Test substance: formaldehyde; no data on purity of the compound
01-DEC-1997 (331)

Species: rat Sex: male
Strain: Fischer 344
Route of administration: inhalation
Exposure period: 28 months
Frequency of treatment: 5 d/w, 6 h/d
Post exposure period: none
Doses: ca. 0.0004, 0.0027, 0.0185 mg/l (0.3, 2.2, 14.9 ppm)
Control Group: yes, concurrent no treatment

Method: other: carcinogenicity study
GLP: no data
Test substance: other TS: formaldehyde; no data on purity of the compound

Method: Male F-344 rats were exposed by inhalation to gaseous formaldehyde at 0.3, 2, and 15 ppm 6 h/day, 5 days/week for 28 months.
All animals were observed and recorded for clinical signs once a day during the study. Body weights and food consumption were recorded weekly. Five animals per group were randomly selected at the end of the 12th, 18th, and 24th month, and surviving animals at 28 months were sacrificed for hematological, biochemical, and pathological examinations. Blood samples were collected via the jugular vein under anesthesia.

Autopsies were performed and the wet weights of the brain, heart, lungs, liver, kidneys, spleen, testis, and adrenal gland of each rat were measured. Histopathological examinations were performed on the pituitary, thyroid, nasal region, trachea, esophagus, stomach, small and large intestine, prostate gland, urinary bladder, muscle, femur, sciatic nerve, spinal cord, mesenteric lymph nodes, and any other gross lesions.
Mortaltiy and histopathological incidences were statistically evaluated by the Fisher's exact test. The hematology, clinical chemistry and organ weight data were statistically evaluated using Bartlett's test for heterogeneity of variance. If the variance was not heterogenous, standard one-way ANOVA was used. If there were significant differences among the means, Dunnett's or Scheffés tests were applied to determine which group was significantly different from the controls.

Result: In the high dose group, neoplastic nasal lesions were observed for the first time after ca. 420 days of treatment. The incidence of squamous cell carcinomas of the nasal cavity was 14/32 (44%); the incidence of squamous cell papillomas was 5/32 (16%). According to the authors, because of the interim sacrifice of 5 animals/group after 12 months, the population of risk (exposure for >= 18 months) would be 27 animals/group; thus, the tumor incidence raised to 52 and 19% for carcinomas and papillomas, respectively. Non-neoplasic lesions observed in the high dose group were squamous metaplasia, epithelial cell hyperplasia, epithelial cell hyperkeratosis, and papillary hyperplasia. At 2.2 and 0.3 ppm, only non-neoplastic lesions (squamous metaplasia and epithelial cell hyperplasia) were observed from months 24 onwards. However, according to the authors, the lesions detected at these dose levels could not be attributed clearly to formaldehyde exposure because there did not exist a clear concentration response relation (see chapter 5.4).
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
18-DEC-2000 (375) (655) (666)

Species: rat Sex: male/female
Strain: Fischer 344
Route of administration: inhalation
Exposure period: up to 24 months
Frequency of treatment: 5 d/w, 6 h/d
Post exposure period: up to 6 months
Doses: ca. 0.0025, 0.0070, 0.0178 mg/l (2.0, 5.6, 14.3 ppm)
Control Group: yes, concurrent no treatment

Method: other: no data
GLP: no data
Test substance: no data

Method: Groups of approximately 120 male and 120 female Fischer-344 rats were exposed by inhalation to 0, 2.0, 5.6, and 14.3 ppm of formaldehyde gas 6 hr/day, 5 days/week, for 24 months. This exposure period was followed by up to 6 months of non-exposure. Interim sacrifice were conducted at 6, 12, 18, 24, 27, and 30 months. Seven-week-old Fischer-344 rats were used.
There were 119 to 121 animals of each sex of the exposure and control groups.
Hematology, serum chemistry, and urinalysis determinations were made from animals selected randomly (10/sex/group) at each scheduled sacrifice. Neurofunction and ophthalmoscopic examinations were also done at selected intervals in the study.
Gross-pathological examinations were performed on all animals that died or were sacrificed at the 6-, 12-, 18-, 24-, 27-, and 30-month scheduled intervals during the course of the study (22). All major tissues on each organ system (appoximately 50 tissues/animal) in the control and high exposure groups were evaluated histologically.
Multiple sections of nasal turbinates were evaluated as target tissues in all rats and mice.
Data were tested for homogeneity of variances using

Bartlett's test (4), and, when not statistically different (p > 0.05), ANOVA3 to test for equality of exposure group means was done. When significant differences in means were observed (ANOVA), exposure level versus control comparisons were made by Dunnett's test.
X2 tests for homogeneity were done on clinical, ophthalmological, and neurobehavioral data.
Histomorphological lesions were analyzed using the actuarial life table method and the National Cancer Institute's bioassay analysis program.

Result: In the high dose group rats, neoplastic nasal lesions were observed for the first time after ca. 12 months of treatment. The incidence of squamous cell carcinomas of the nasal cavity was 51/117 (44%) in males and 52/115 (45%) in females; according to Kaplan-Meier life table analysis, the adjusted cumulative incidence rate was 67% in males and 87% in females. In the mid dose group, the incidence of squamous cell carcinomas of the nasal cavity was 1/119 (0.8%) and 1/116 (0.9%) in males and females, respectively. However, these incidences were not statistically significant.

According to the authors, severe damage of nasal epithelium was observed in the high and mid dose group rats, anterior nasal lesions were present in the low dose group. The incidence of polyploid adenomas was increased in males without showing concentration response; thus, according to the authors, this finding was judged to be incidental.

Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
20-DEC-2002 (384) (632)

Species: rat Sex: male
Strain: Fischer 344
Route of administration: inhalation
Exposure period: up to 24 months
Frequency of treatment: 5 d/w, 6 h/d
Post exposure period: none
Doses: ca. 0.0008, 0.0026, 0.0075, 0.0123, 0.0187 mg/l (0.69, 2.1, 6.0, 9.9, 14.9 ppm)
Control Group: yes, concurrent no treatment

Method: other: no data
GLP: no data
Test substance: other TS: formaldehyde; no data on purity of the compound

Method: General health, histopathology of the nasal cavity, mapping of nasal tumours and cell proliferation measurements were performed. No explanation concerning total number of animals at risk (90 animals per group seem to comprise animals for early interim sacrifices (personal communication with CIIT scienctists)).

Result: Incidence of squamous cell carcinomas:
0 ppm: 0%
0.69 ppm: 0%
2.1 ppm: 0%
6.0 ppm: 2%
9.9 ppm: 38%
14.9 ppm: 67%
Incidence of polypiod adenomas:
0 ppm: 0%

0.69 ppm: 0%
2.1 ppm: 0%
6.0 ppm: 2%
9.9 ppm: 9%
14.9 ppm: 14%
Increased early mortality at 15 ppm; concentration dependent time to tumours: first tumour observed at about 12 month with 15 ppm, at 18 month with 9.9 ppm and at 20 month with 6 ppm; tumours mostly localised at sites of "high doses": lateral meatus, mid septum; correlation of tumour incidence with population weighted cell proliferation (chapter 5.4).

Reliability: (2) valid with restrictions

Flag: Critical study for SIDS endpoint

18-DEC-2000 (493) (494) (495)

Species: rat Sex: male
Strain: Wistar
Route of administration: inhalation
Exposure period: 28 months
Frequency of treatment: 5 d/w, 6 h/d
Post exposure period: none
Doses: ca. 0.0001, 0.0012, 0.0115 mg/l (0.1, 1.0, 9.2 ppm)
Control Group: yes, concurrent no treatment

Method: other: carcinogenicity study
GLP: no data
Test substance: other TS: formaldehyde; no data on purity of the compound

Method: The formation of nasal tumors after severe nasal injury to the mucosa (due to electrocoagulation) and prolonged exposure to the test substance was investigated. Sixty rats with damaged nose and 30 rats with undamaged nose were used per treated group; controls consisted of 60 rats with undamaged nasal tissue and 120 rats with damaged nasal tissue. After termination of exposure, histopathological examinations of the nose were performed.

Result: After 28 months, the pooled incidence of nasal tumors in controls were 0/52 and 1/111 (0.9%) in rats without and with damaged nasal tissue, respectively. In rats with undamaged nasal tissue, 1/26-1/28 (4%) squamous cell carcinoma was observed in each concentration group. Seventeen out of 58 (29%) rats with damaged nasal tissue exposed to 9.2 ppm had nasal tumors, 15 of which (26%) were squamous cell carcinomas. At 1.0 and 0.1 ppm, tumor incidence was 0 and 1/56-58, respectively.

Non-neoplastic lesions comprised degenerative and inflammatory changes of nasal mucosa were observed at 9.2 ppm in animals with undamaged nasal tissue and at each concentration level in animals with damaged nasal tissue. According to the authors, these changes were independent of exposure regimen (see chapter 5.4).

Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint

26-OCT-2000 (714)

Species: rat Sex: male
Strain: Wistar
Route of administration: inhalation
Exposure period: 3 months
Frequency of treatment: 5 d/w, 6 h/d
Post exposure period: 25 months
Doses: ca. 0.0001, 0.0012, 0.0122 mg/l (0.1, 1.0, 9.8 ppm)
Control Group: yes, concurrent no treatment

Method: other: carcinogenicity study
GLP: no data
Test substance: other TS: formaldehyde; no data on purity of the compound

Method: The formation of nasal tumors after severe nasal injury to the mucosa (due to electrocoagulation) and prolonged exposure to the test substance was investigated. Sixty rats with damaged nose and 30 rats with undamaged nose were used per treated group; controls consisted of 60 rats with undamaged nasal tissue and 120 rats with damaged nasal tissue. After termination of exposure, histopathological examinations of the nose were performed.
Result: After 3 months of exposure and 25 months of observation, the pooled incidence of nasal tumors in controls were 0/52 and 1/111 (0.9%) in rats without and with damaged nasal tussue, respectively. In rats with undamaged nasal tissue and treated with 9.8 ppm, 2/26 (8%) nasal tumors were observed, 1 of which (4%) was squamous cell carcinoma. Among the rats with damaged nasal tissue, 2/53-57 (4%) nasal tumors were observed in each concentration group; most of these tumors were squamous cell carcinomas.
Non-neoplastic lesions comprised degenerative and inflammatory changes of nasal mucosa were observed at 9.8 ppm in animals with undamaged nasal tissue and at each concentration level in animals with damaged nasal tissue. According to the authors, these changes were independent of exposure regimen (see chapter 5.4).
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
26-OCT-2000 (714)

Species: mouse Sex: no data
Strain: C3H
Route of administration: inhalation
Exposure period: up to 68 weeks
Frequency of treatment: 1 h/d, 3 d/w
Doses: 0, 42, 83, 167 ppm (0. 50, 100, 200 mg/m3) or 42 ppm (50 mg/m3) or 125 ppm (150 mg/m3)
Control Group: no data specified

Method: other: no data
GLP: no
Test substance: no data

Result: Route/Dosage:
Inhalation (whole body) 0, 42, 83, 167 ppm (0, 50, 100, 200, mg/m3) 1h/d, 3d/w for up to 35 weeks or 42 ppm (50 mg/m3) 1h/d, 3d/w for 35 weeks and 125 ppm (150 mg/m3) 1h/d, 3d/w from week 36-68.

Examination:
General health, histopathology of trachea and lungs

Findings:
No increase in tracheobronchial or pulmonary tumors

Exposure to 167 ppm terminated during week 4. No changes in tumour incidence produced by coal tar aerosols with or without pretreatment with FA.

Test substance: formaldehyde; no data on purity of the compound
Reliability: (2) valid with restrictions
02-FEB-1999 (337)

Species: mouse Sex: male/female
Strain: B6C3F1
Route of administration: inhalation
Exposure period: 24 months
Frequency of treatment: 5 d/w, 6 h/d
Post exposure period: up to 6 months
Doses: ca. 0.0025, 0.007, 0.018 mg/l (2.0, 5.6, 14.3 ppm)
Control Group: yes, concurrent no treatment

Method: other: carcinogenicity study
GLP: no data
Test substance: other TS: formaldehyde; no data on purity of the compound

Method: The incidence of tumors due to exposure to formaldehyde was investigated in groups of 120 mice/sex. The age of the animals at start of exposure was about 6 weeks. Some animals per group were sacrificed after 6, 12, 18, 24, 27, and 30 months. Autopsy and histopathology of ca. 50 different tissues was performed (see also rat study of same authors).
Result: According to the authors, squamous cell carcinomas were found only in 2 males of the high doses group, however, this incidence was not statistically significant (no incidence table presented). Non-neoplastic lesions were found in the high dose group (epithelial dysplasia and squamous metaplasia) and in the mid dose group (epithelial dysplysia). An exposure dependent increase in mortality due to infections of the genitourinary tract was observed in males.
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
20-DEC-2002 (384)

Species: Syrian hamster Sex: male
Strain: other: no data
Route of administration: inhalation
Exposure period: lifetime
Frequency of treatment: 1 d/w, 5 h/d
Post exposure period: none
Doses: ca. 0.037 mg/l (30 ppm)
Control Group: yes

Method: other: initiation-promotion study
GLP: no data
Test substance: no data

Result: The tumorigenic effects of formaldehyde on the respiratory tract were studied. A group of 50 animals was initiated with diethylnitrosamine (DEN; subcutaneous injection of 0.5 mg once a week for 10 weeks) and then exposed to FA for 5 h/d once a week for lifetime. Another group of 50 hamsters was treated in the same manner; additionally, these animals were exposed to FA for 5 h 48 h prior to each DEN injection. Hundred hamsters were given the s.c.injection of DEN only and 50 control animals remained untreated. An evaluation of the respiratory tract for tumorsusing a special subgross (stereomicroscopical) method and histopathology of selected tumors were performed.

A treatment related reduction of survival time was observed;this reduction was more pronounced in the groups exposed to FA. The incidence of adenomas of the respiratory tract was ca. 80% and was independent from treatment. Tumors were found mainly in lower regions of the respiratory tract. Low tumor incidence (ca. 2%) arising from nasal epithelium was observed. According to the authors, a substantial number

of hamsters was lost due to an exposure accident at 48 weeks. An increased number of tumors/tumor bearing animal was observed in the trachea but not in the larynx or lungs of animals exposed to FA prior to DEN injection. According to the authors, this finding was interpreted as enhancement of DEN's effect by FA. The analytical concentration of the test substance was not reported.
Test substance: formaldehyde; no data on purity of the compound
Reliability: (2) valid with restrictions
30-JUN-1998 (168)

Species: Syrian hamster Sex: male
Strain: other: no data
Route of administration: inhalation
Exposure period: lifetime
Frequency of treatment: 5 d/w (10 ppm) or 1 d/w (30 ppm), 5 h/d
Post exposure period: none
Doses: ca. 0.012 or 0.037 mg/l (10 or 30 ppm, respectively)
Control Group: yes, concurrent no treatment

Method: other: carcinogenicity study
GLP: no data
Test substance: other TS: formaldehyde; no data on purity of the compound

Method: Two groups of hamsters were included in this study: 132 untreated controls and 88 hamsters exposed to 10 ppm H2CO 5 times/week for life-time. At necropsy all major tissues (no further data) were preserved in buffered formalin. Tissues from the respiratory tract were embedded in paraffin, sectioned, and stained with hematoxylin and eosin. The tissues examined were 2 transverse sections of the nasal turbinates, longitudinal sections of larynx and trachea, and all lung lobes cut along the bronchus prior to embedding. An evaluation of the respiratory tract for tumors using a special subgross (stereomicroscopical) method was performed.
Result: A treatment related reduced survival time and a slight increase in incidence of nasal epithelial hyperplasia of 50 control animals and metaplasia was recorded. However, no increased tumor incidence was observed in any group.

The analytical concentration of the test substance was not reported.
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
24-NOV-2000 (168)

Route of administration: other: in vitro assay
Doses: 0.5 - 2.5 mg/l

Method: other: cell transformation assay
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: Cell transformation assay without metabolic activation in Balb/c3T3 cells. Concentration dependent increase of transformation rate; concentrations refering to paraformaldehyde; no detailed description of the method
Test substance: formaldehyde; no data on purity of the compound
18-JUN-1998 (111)

Route of administration: other: in vitro assay
Doses: 0.1 - 2.5 mg/l

Method: other: cell transformation assay
GLP: no data
Test substance: no data

Remark: Cell transformation assay with C3H/10T1/2 cells; no data on metabolic activation. 24 h exposure, 6 weeks maintainance, both in the presence and absence of 12-O- tetradodecanoyl-phorbol-13-acetate (TPA); no transformation without TPA, concentration dependent transforming effect with TPA; LD50 concentration between 0.5 and 1 mg/l
Reliability: 2 (reliable with restrictions)
Test substance: formaldehyde; no data on purity of the compound
18-JUN-1998 (2) (85)

Route of administration: other: in vitro assay
Doses: 0.16, 0.8, 4, 20, 100 mg/l (0.0053, 0.0266, 0.1333, 0.6666. 3.3333 mM)

Method: other: cell transformation assay
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: Cell transformation assay with BHK-21/cl.13 baby hamster kidney cells; no data on metabolic activation. 3 h exposure, 3 weeks maintainance; concentration dependent increase of transformation between 0.8 and 2 mg/l; cytotoxicity: 0 and ca. 90% survival at 100 and 20 mg/l, respectively
Test substance: formaldehyde; no data on purity of the compound
18-JUN-1998 (545)

Species: rat Sex: male
Strain: Fischer 344
Route of administration: other: instillation into heterotopic bladder
Exposure period: 34 weeks
Frequency of treatment: 15 applications (every 2 weeks)
Post exposure period: no data

Doses: 0.3%
Control Group: yes

Method: other: initiation-promotion study
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: The tumor promoting effects of formaldehyde (FA) was studied in 35 rats per group with heterotopically transplanted urinary bladders. Initiation was performed by single dose of 0.25 mg MNU (negative control with saline); thereafter, 15 instillations of 0.3% FA, NaCl solutions, and urine were performed in different patterns every 2 weeks (total study duration 34 weeks). Histopathology of heterotopic urinary bladder was performed and cell proliferation was measured in some non-initiated bladders by 3H-thymidine labelling. Induction of epithelial hyperplasia was observed (40-50% in initiated bladders, 8% in non initiated bladders). Induction of fibrosis of the lamina propria (incidence 19-31%) was recorded. Labelling indices were increased. No significant differences in nodulo-papillary hyperplasia and carcinoma formation was observed in initiated bladders treated with saline of FA.

Acute instillation of 0.3% FA resulted in multiple erosions and focal ulcers. The authors discussed several possibilities for the missing promoting action of FA.
Test substance: formaldehyde; no data on purity of the compound
18-JUN-1998 (335)

5.8.1 Toxicity to Fertility

Type: Fertility
Species: mouse
Sex: male
Strain: B6C3F1
Route of administration: gavage
Exposure Period: 5 days
Frequency of treatment: daily
Premating Exposure Period
male: no mating
female: no mating
Duration of test: until 5 weeks after the last dosing
Doses: 100 mg/kg
Control Group: yes, concurrent vehicle

Method: other: no data
GLP: no data
Test substance: other TS: formalin; 37% formaldehyde; no data on purity

Method: The effects on sperm morphology of formalin (37% formaldehyde, 10% methanol in water) was determined. The test substance was administered to 10 mice for 5 consecutive days; 5 control mice were given distilled water. Five weeks after treatment, the mice were sacrificed; the cauda epididymides were dissected and flushed for recovery of the spermatozoa. For sperm counting, 7 treated and all control mice were used, 500 spermatozoa/mouse were examined.

Result: According to the authors, the overall results indicated a small increase in the number of abnormal cells; however, this was not statistically significant.

According to the authors, application by gavage of 250 and 500 mg/kg/d for 5 consecutive days or intraperitoneal injection of 5 daily doses of 100 mg/kg/d to groups of 10 mice were lethal to all animals treated.
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint

26-OCT-2000 (351) (694)

Type: other
Species: rat
Sex: male/female
Strain: Sprague-Dawley
Route of administration: drinking water
Exposure Period: 104 weeks beginning at day 12 of pregnancy
Frequency of treatment: continuously in the drinking water
Premating Exposure Period
male: none
female: none
Duration of test: lifetime
Doses: 2500 mg/l in the drinking water
Control Group: yes, concurrent no treatment

Method: other: no data
GLP: no data
Test substance: no data

Result: The effects of orally administered formaldehyde was studied in 25 weeks old breeding rats. A group of 18 males and 18 mated females was exposed to the test substancefrom day 12 of gestation for 104 weeks and observed up to natural death. Another group of 20 males and 20 mated females remained untreated (control). Examinations on general health, autopsy, and histopathology of ca. 50 tissues were performed.

Totally, 59 male and 49 female offsprings were recorded in the control group; 36 male and 37 female offsprings were recorded in the exposed group. No substance related effects on survival and body weight gain was observed in the breeders, however, depression of body weight gain was observed in the offsprings. These results were part of a 2-year carcinogenicity study.
Test substance: formaldehyde; no data on purity of the compound
Reliability: (4) not assignable
Results concerning carcinogenicity not reliable.
18-DEC-2002 (616)

Type: other
Species: rat
Sex: no data
Strain: other: Lew.1A
Route of administration: i.p.
Exposure Period: days 6 - 15 post coitum
Frequency of treatment: daily

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Doses:                      1, .5, 5, 7.5 and 10 mg (not clear if absulute or /kg
                            b.w.)
Control Group:              other: saline

Method:            other
   GLP:            no data
Test substance:    other TS

Method:            Pregnant rats were treated as described above. The following
                   parameters were examined in the pups after natural delivery:
Remark:            Post exposure: up to day 20 post partum
Result:            Reduction in litter size
Test substance:    Formaldehyde (no details)
Reliability:       (3)  invalid
                   non-physiological parenteral exposure route, dosage not
                   clear, no information on dose response for several
                   paprameters
10-SEP-2001                                                                (454)

Species:                    rat
Sex:                        male
Strain:                     other: Albino (own breed)
Route of administration:    i.p.
Exposure Period:            5 consecutive days
Frequency of treatment:     single injection
Doses:                      0.125, 0.25 and 0.5 or 0.6 mg/kg
Control Group:              other: yes (distilled water)

Method:            other
   GLP:            no data
Test substance:    other TS

Method:            Sperm analysis and dominant lethal study
Remark:            The doses used were based on a determined LD50 of 2 mg/kg
                   (no details), which is low in comparison to the values found
                   in other acute parenteral toxicity studies.
                   Post exposure: 3 weeks
Result:            Dose dependent decrease in sperm concentration and increase
                   in sperm head abnormalities.
Test substance:    Formaldehyde (37% solution stabilized with 10% methanol)
Reliability:       (3)  invalid
                   unphysiological route of administration with high local
                   toxicity
10-SEP-2001                                                                (523)

Species:                    mouse
Sex:                        male
Route of administration:    i.p.
Exposure Period:            5 days
Frequency of treatment:     successive
Doses:                      4, 10, 30 mg/kg


Result:            Decreased sperm quantity at 10 and 30 mg/kg. Changes in
                   activity and deformation ratio at all doses tested.
Reliability:       (4)  not assignable
                   Paper in Chinese (2 pages) with English abstract.
                   unphysiological route of administration
18-DEC-2002                                                                (719)
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Species: other: Mink (Mustela vison)
Sex: female
Route of administration: oral feed
Exposure Period: from 1 month before mating until its were 6-7 weeks ode (about 140 days) or until pelting (about 220 days for kits and 320 days for mothers)
Doses: 0, 550 and 1100 ppm
Control Group: yes

Method: other
GLP: no
Test substance: other TS

Method: Females mated to non-treated males.
Examination of reproductive performance, body weight development of adults and kits, clinical pahology (numerous parameters after 140 d), weights and histopathology of several organs.
Remark: Formaldehyde was tested as antimicrobial agent in mink feed, Post exposure: no
Result: Analyzed formaldehyde levels in feed: 17, 291 and 662 ppm.
High dose: reduction of body weights in male but not female kits; reduction of fur quality, reduction in red blood cell parameters

Low dose: increase of body weight development in kits mainly during the first few weeks after delivery, some increase in splenic and kidney weights in male kids, probably due to higher body weights
No effects on reproductive performance, blood chemistry and histopathology
Test substance: Formaldehyde 37% solution
Reliability: (2) valid with restrictions
18-DEC-2002 (427)

5.8.2 Developmental Toxicity/Teratogenicity

Species: rat Sex: female
Strain: other: albino
Route of administration: inhalation
Frequency of treatment: continuously
Duration of test: until delivery
Doses: ca. 0.000012, 0.001 mg/l (0.012, 1 mg/m3)
Control Group: yes, concurrent no treatment

Method: other: no data
GLP: no
Test substance: no data

Result: Inhalation, whole-body, 24h/d, male 6-10 days and female 10-14 days before mating until end of pregnancy.
Examinations: Clinical symtoms, visible malformations, selected biochemical parameters.
Findings: Prolongation of pregnancy
Pups/liter: control: 11.3
low : 9.8
high : 8.6
No visible malformations. Changes in organ weights of dams and pups. Morphological changes in some organs. Changes in ascorbic acid, DNA and RNA content in maternal and fetal tissues.

Partly in Russian limited examinations and documentation internal contradictions described by Bruehl and Einbrodt.
Test substance: formaldehyde; no data on purity of the compound
Reliability: (3) invalid
30-JUN-1998 (109) (255) (256) (257) (258) (351) (552) (553)

Species: rat Sex: female
Strain: other: no data
Route of administration: inhalation
Exposure period: days 1 - 19 of gestation
Frequency of treatment: 4 h/d
Doses: 0.0005, 0.005 mg/l
Control Group: no data specified

Method: other: no data
GLP: no
Test substance: no data

Result: Groups of 15 animals were used. Some of the rats were sacrificed on day 20 of pregnancy, fetuses were removed and examined. The remaining rats were allowed to litter naturally. In the groups sacrificed after exposure, increased preimplantation deaths were observed; no gross malformations were recorded. In the groups which were allowed to litter, reduced body lenght and reduced mobility of female offsprings were observed; males were unaffected.
Test substance: formaldehyde; no data on purity of the compound
Reliability: (2) valid with restrictions
02-FEB-1999 (109) (351) (603)

Species: rat Sex: female
Strain: other: no data
Route of administration: inhalation
Exposure period: 20 days
Frequency of treatment: 4 h/d
Doses: ca. 0.0004, 0.006 mg/l
Control Group: no data specified

Method: other: no data
GLP: no
Test substance: no data

Result: Some maternal toxicity at 5 ppm, no effect on pregnancy. No details. In Russian, contradictory evaluations by WHO 1989 and Bruehl and Einbrodt.
Test substance: formaldehyde; no data on purity of the compound
Reliability: (3) invalid
20-MAY-1999 (109) (583)

Species: rat Sex: female
Strain: Sprague-Dawley
Route of administration: inhalation
Exposure period: days 6 - 20 of gestation
Frequency of treatment: 6 h/d
Duration of test: until day 21 of gestation
Doses: 0.006, 0.012, 0.025, 0.05 mg/l (5, 10, 20, 40 ppm)
Control Group: yes, concurrent no treatment
NOAEL Maternal Toxity: 20 ppm
NOAEL Teratogenicity: 40 ppm

Method: other: no data
GLP: no data
Test substance: no data

Method: Groups of 25 mated felae rats werd whole body exposed.
The atmosphere concentrations were sampled periodically and samples were analyzed spectrophotometrically after derivatization with chromotropic acid.

Maternal toxicity was evaluated by clinical examination and body weight determination. Implantation and resoprtion sites were determined in the uteri.
Fetal examination comprised differntiation of live and dead fetuses, fetal weights and sex, external malformation and skeletal and soft tissue malformations after appropriate fixation.
Remark: From the data on repeated dose inhalation toxicity it is inferred, that at the concentrations of 10 and 20 ppm maternal toxicity was present in form of nasal irritation and epithelial damage, which impose considerable stress on the animals and represent maternal toxicity in addition to the observed retarded body weight development.

Thus the slight fetotoxicity found at 20 ppm is considered to be related to maternal toxicity.
Result: Maternal toxicity was indicated by a significantly reduced body weight gain at the highest dose level (0.05 mg/l (40 ppm)).
The pregnancy rate was at least 21/25 (84%)
No substance-related effect on lethality of embryo or fetus was recorded. No significant external, visceral, or skeletal anomalies were observed in fetuses of any groups. At the high and high intermedate concentration reduction of fetal body weight was observed (ca. 5% in males at 0.025 mg/l (20 ppm) and 20% at 0.05 mg/l (40 ppm)) as compared to air control. According to the authors, these results suggest that the test substance had a slightly fetotoxic effect at concentrations of 20 ppm and more. Neither embryolethal nor teratogenic effects were observed.
Test substance: 37% aqueous solution formaldehyde, containing 10% methanol; no data on purity of the compound
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
18-DEC-2002 (346) (578)

Species: rat Sex: female
Strain: other: no data
Route of administration: inhalation
Exposure period: no data specified
Frequency of treatment: no data
Duration of test: no data
Doses: 0.0005 mg/l
Control Group: no data specified

Method: other: no data
GLP: no data
Test substance: no data

Result: The embryotoxic effects of the test substance were studied. Exposure of pregnant rats to concentrations at the maximum permissible level in the working zone (0.5 mg/m3) increased anomalies of internal organs, retarded the skeletal development, affected the fetal acid-base equilibrium, and affected the behaviour responses of juvenile and adult rats. Only abstract available; no further data.
Test substance: formaldehyde; no data on purity of the compound
Reliability: (3) invalid
10-DEC-1997 (600)

Species: rat Sex: female
Strain: Sprague-Dawley
Route of administration: inhalation
Exposure period: days 6 to 15 of gestation
Frequency of treatment: 6 h/d
Doses: ca. 0.002, 0.006, 0.012 mg/l (2, 5, 10 ppm)
Control Group: yes
NOAEL Maternal Toxity: .006 mg/l
NOAEL Teratogenicity: .012 mg/l

Method: other: no data
GLP: no data
Test substance: other TS: formaldehyde; no data on purity of the compound

Method: The study consisted of exposing groups of 25 mated Sprague-Dawley rats by the whole-body exposure technique for 6 h/day, with formaldehyde at dosages of 2, 5, or 10 ppm from day 6 to day 15 of gestation, inclusive. Two control groups were included in the study; one was handled in an identical manner to the formaldehyde-treated groups except that it was treated with air, and the other was maintained in the animal room throughout the study. The females used for the study were 13 weeks of age and weighed between 221 and 277 g.
The group mean + SD live liter size, corporus luteum count, number of implants, and number of resorptions were calculated. The individual and group litter mean + SD for the preimplantation and postimplantation losses were calculated. The litter sex ratio was calculated for statistical analysis and the group sex ratio presented. Statistical analysis of these parameters was performed using the Man-Whitney U test.
The teratogenic effects of whole-body inhalation exposure to formaldehyde was studied in groups of 25 rats. Three groups were exposed to the test substance at concentrations of 2, 5, 10 ppm; one group was handled in an identical manner to the formaldehyde-treated groups except that it was treated with air (air-control); one group was maintained in the animal room throughout the study (room-control). The measured concentrations of the test substance were 0.01, 1.88,4.88, and 9.45 ppm in the air-control, 2, 5, and 10 ppm group, respectively.
Result: The pregnancy rate in all groups was at least 80%. In the highest dose group, a significant decrease in maternal food consumption and body weight gain was observed. Pregnancy parameters (numbers of corpora lutea, implantation sites, live fetuses, dead fetuses and resorptions, preimplantation and postimplantation losses, fetal weights, sex ratios) were unaffected. No evidence of maternal toxicity was found

in the other groups.
The overall incidences of litters and fetuses with major malformations, minor external and visceral anomalies, and minor skeletal anomalies were similar. At the 10 and 5 ppm levels, an apparently significant dose-related decrease in ossification was detected in the bones of the pelvic girdle. However, this alteration was only significant when compared with air-controls, but not when compared with room-controls. Thus, according to the authors, this finding was associated with larger litter sizes being accompanied by decreased fetal weights. According to the authors, neither this finding nor other parameters assessed demonstrated any adverse effect on the conceptus due to formaldehyde expusure under the conditions used in this study.

Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
27-OCT-2000 (346) (465)

Species: mouse Sex: female
Strain: CD-1
Route of administration: gavage
Exposure period: days 6 - 15 of gestation
Frequency of treatment: daily
Duration of test: until day 18 of gestation
Doses: 74, 148, 185 mg/kg/d
Control Group: yes, concurrent no treatment

Method: other: no data
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: The influence of formaldehyde on embryo and fetal development was studied. The test substance was applied as different amounts of a 1% solution. The control, low, mid and high dose group consisted of 76, 29, 35, and 34 mice, respectively. The surviving mice were sacrificed on day 18 of gestation; their reproductive status was determined. The high dose was clearly toxic; 22/34 females died before the day of sacrifice. According to the authors, methanol could have contributed to this toxicity; the original solution of the test substance contained 12-15% methanol as a preservative. In the mid dose group, mortality was 1/35. No deaths occurred in the low dose and control groups. Pregnancy rates were 69/76, 26/29, 28/35, and 8/34 in the control, low, mid, and high dose group, respectively.No malformations were found in any of the groups. According to the authors, these results suggested that formaldehyde solution containing 12-15% methanol did not produce statistically significantly teratogenic effects in mice at the doses tested although the high dose of the test

substance was toxic to the dams.
Test substance: aqueous solution formaldehyde, containing 12-15% methanol; no data on purity of the compound
14-MAY-1998 (109) (346) (351) (456)

Species: dog Sex: female
Strain: Beagle
Route of administration: oral feed
Exposure period: days 4 to 56 of gestation
Frequency of treatment: continuously in the diet
Duration of test: until weaning
Doses: 3.1, 9.4 mg/kg/d (125, 375 ppm in the diet)
Control Group: yes, concurrent no treatment

Method: other: no data
GLP: no
Test substance: other TS: formaldehyde; 40% solution; no data on purity

Method: The effects of formaldehyde on reproduction was studied in 32 female beagles. The dogs were fed normal diet (control, 11 bitches mated, 9 pregnant bitches) or diet containing formaldehyde (11 bitches mated and 10 pregnant bitches in the low dose group; 10 bitches mated and 9 pregnant bitches in the high dose group) on days 4 to 56 of pregnancy. On day 56, the dogs were transferred into a whelping room and were allowed to litter.
Result: The treatment did not affect the pregnancy rate, the weight gain of the pregnant dogs, the length of gestation or the size of the 28 litters (9, 10, and 9 litters in the control,low dose, and high dose group, respectively). Mean length of gestation was 65.8, 63.6, and 64.7 days in the untreated,low dose, and high dose group, respectively. No malformations (either external of skeletal) were observed in the 170 live-born and 8 still-born pups (56, 50, and 64 live-born in the control, low dose, and high dose group, respectively; 4 still-born pups in both control and low dose group).
Flag: Critical study for SIDS endpoint
26-OCT-2000 (109) (345) (351)

Species: Syrian hamster Sex: female
Strain: other: Lak:LVG(SYR) Syrian Golden Hamster
Route of administration: dermal
Exposure period: on day 8, 9, 10, or 11 of gestation
Frequency of treatment: single dose
Duration of test: 2 hours
Doses: 0.5 ml of a 37% solution
Control Group: yes, concurrent vehicle

Method: other: no data
GLP: no data
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)
Result: The possible embryotoxic effects of formaldehyde after percutaneous exposure was studied in 26 Syrian Golden hamsters (4 control animals; 6, 6, 5, and 5 anmials treated on day 8, 9, 10, or 11 of gestation, respectively). The 37% test substance was applied directly onto the clipped dorsal skin of the anesthetized hamsters by syringe; controls were given water. After 2 h, the skin was washed with water to remove any remaining test substance, and the animals were returned to their cages. Fetuses were recovered by laparatomy under ether anesthesia at the 15th day of gestation and examined for teratogenic effects.

The test substance did not significantly affect litter size and weight or length of the fetuses. A subcutaneous hemorrhage was observed in the dorsal cervical region of 1 normally sized fetus from a dam treated on day 10 of pregnancy; however this was not clearly attributable to the test substance. No skeletal or other malformations were found. According to the authors, it was concluded that fetal risk due to maternal topical exposure to formaldehyde was minimal in this model.
Test substance: formaldehyde, 37% aqueous solution; no data on purity of the compound

19-JUN-1998 (346) (351) (530)

Species: mouse Sex: female
Strain: other: DDP/Idr and Slc:ICR
Route of administration: i.p.
Exposure period: on day 7 - 14 of gestation
Frequency of treatment: daily
Duration of test: until day 18 of gestation
Doses: 30, 40, 50 mg/kg/d
Control Group: yes

Method: other: no data
GLP: no data
Test substance: no data

Remark: unphysiological route of exposure
Result: The study was designed to evaluate the teratogenic effects of intraperitoneally admininstered formaldehyde solution on developing mouse embryos using 2 strains. On day 18 of gestation, the mice were sacrificed; implantations and prenatal deaths were recorded. Mean body weights of exposed fetuses was lower than that of controls. The incidence of prenatal death was slightly increased in the treated groups. The incidence of fetal anomalies was significantly increased in treated mice. The major malformations observed were cleft palates and malformations of the limbs.
Test substance: formaldehyde solution; no data on purity of the compound
Reliability: (4) not assignable
No details, abstract only

18-DEC-2002 (351) (717)

Species: rat Sex: male
Strain: other: no data
Route of administration: other: combination of drinking water (d.w.) and inhalation (inh.)
Exposure period: 6 months
Frequency of treatment: continuously in the drinking water for 5 d/w; inhalation 5 d/w, 4 h/d
Duration of test: ca. 8 months; no data specified
Doses: 0.005 mg/l d.w. + 0.00012 mg/l (0.1 ppm) inh., 0.01 mg/l d.w. + 0.00025 mg/l (0.2 ppm) inh., 0.1 mg/l d.w. + 0.0005 mg/l (0.4 ppm) inh.
Control Group: yes, concurrent no treatment

Method: other: no data
GLP: no
Test substance: no data

Remark: Reliability: 2 (reliable with restrictions)

Result: After termination of exposure, each treated male was mated with 2 females. Gonadotropic effects in treated males were evaluated by determination of testicular nucleic acid contents and the reaction of the genital tract of females after s.c. injection of homogenates of hypophyses of test animals. On the 20th day of gestation, some of the dams were sacrificed; the remaining dams were allowed to litter naturally. Fetuses and newborn pups were examined macroscopically; the newborn rats were observed for 1 month with special regard on their developmental stages (opening of the eyes, development of the fur, and other parameters). These examinations were carried out with the offsprings of the low and high dose groups.

According to the author, no differences in fertility of the treated males were observed. All females became pregnant. Number and weight of fetuses or newborn pups were not significantly different from control. No damage or anomalies in development due to treatment of the fathers were observed in the offsprings during the 1-month observation period. However, the evaluation of testicular nucleic acid content revealed a significant decrease in the testes of males exposed to the high and the mid dose group.

Thus, according to the author, the gonadotropic effects of the test substance after simultaneous uptake via air and water are of a certain importance, although no adverse effect on the gonadotropic reaction or on fertiltity of the males was observed.

Test substance: formaldehyde; no data on purity of the compound

19-JUN-1998 (287) (351)

Species: rat Sex: female
Strain: Sprague-Dawley
Route of administration: other: intrauterine
Exposure period: on day 3 or 7 of gestation
Frequency of treatment: single dose
Duration of test: until day 15 of gestation
Doses: 0.005 ml of 0.005, 0.05, 0.5, 2.0, 3.5, 7, 10, or 40% (v/v) solution
Control Group: yes
NOAEL Maternal Toxity: = 7 %

Method: other: no data
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Reliability: 2 (reliable with restrictions)
Result: The efficacy of locally applied formaldehyde as a contragestional agent was studied in 2 groups of pregnant rats. The dams were treated either on day 3 (preimplantation) or on day 7 (postimplantation) of pregnancy. 0.05 ml of the test substance was injected directly into the lumen of one uterine horn funder laparotomy; 0.9% saline was injected into the other uterine horn (control). On day 15 of gestation, the rats were sacrificed; corpora lutea, viable conceptuses, and resorption sites were counted. According to the authors, formaldeyde was highly effective in terminating pregnancy when administered on day 3; the number of surviving embryos was statistically significantly decreased at concentrations

of 0.5% and more. Treatment on day 7 resulted on a decrease of the number of suviving embryos at concentrations of 2% and more; however, this reduction was not significant. Doses of 10 and 40% produced maternal toxicity and death.
Test substance: formaldehyde solution, 40% (v/v); reagent quality
10-AUG-1999 (109) (151)

Species: rat Sex: female
Strain: other: no data
Route of administration: s.c.
Exposure period: during gestation
Frequency of treatment: no data
Duration of test: during gestation
Doses: 0.25 ml * 2
Control Group: no data specified

Method: other: no data
GLP: no
Test substance: no data

Result: Pregnant rats were subcutaneously treated with 6% formalin (0.25 ml * 2) during the entire period of pregnancy. According to the autors, atrophy of the thymus and enlargement of the adrenal gland was observed in the dams. No malformations were observed in the pups, however, the median body weights of the pups was increased at delivery and the weights of the adrenals were reduced. Only secondary literature; no further data.
Test substance: formaldehyde; no data on purity of the compound
Reliability: (3) invalid
19-JUN-1998 (554)

Species: rat Sex: no data
Strain: other: no data
Route of administration: s.c.
Exposure period: on day 18, 19, 20, or 21 of gestation
Frequency of treatment: single dose
Doses: 6 ml/kg of a 2% solution (ca. 120 mg/kg)
Control Group: no data specified

Method: other: no data
GLP: no
Test substance: no data

Result: The effects of formaldehyde on adrenal ascorbic acid content of fetal rats were studied. Pups gained by Cesarean section on days 18, 19, 20, or 21 of gestation were injected subcutaneously with 6 ul/g of a 2% formaldehyde solution. In the pups treated on the 20th day of gestation, a decrease of the adrenal acsorbic acid content was observed; the pups treated at other points of time were unaffected. Cited from secondary literature; no further data.
Test substance: formaldehyde; no data on purity of the compound
Reliability: (3) invalid
19-JUN-1998 (145)

5.8.3 Toxicity to Reproduction, Other Studies

5.9 Specific Investigations

5.10 Exposure Experience

Remark: Review; assessment of data on the effects of FA on humans. Reviews
Reliability: (4) not assignable
4.2; review
19-OCT-2000 (206)

Remark: Review of mutagenic and carcinogenic potential.
Reliability: (4) not assignable
4.2; review
10-MAR-1998 (207)

Remark: Review; up-date of report 1 and 2.
Reliability: (4) not assignable
4.2; review
06-FEB-1998 (208)

Remark: Review of mutagenicity and carcinogenicity.
Reliability: (4) not assignable
4.2; review
02-OCT-2002 (222)

Remark: Review; evaluation of the carcinogenic risk
Reliability: (4) not assignable
4.2; review
10-MAR-1998 (349)

Remark: Review of carcingenicity, mutagenicity, irritation, reproductive effects/teratology, behavioral effects, immunotoxicity/sensitization, neurotoxicity, biochemistry/metabolism, and histopathology.
Reliability: (4) not assignable
4.2; review
27-MAR-1998 (154)

Remark: Review
Reliability: (4) not assignable
4.2; review
06-FEB-1998 (115)

Remark: Review of respiratory cancer
Reliability: (4) not assignable
4.2; review
10-MAR-1998 (508)

Remark: Review; data evaluation for MAK value and classification
Reliability: (4) not assignable
4.2; review
27-MAR-1998 (187)

Remark: Review; overall evaluation of the carcinogenic risk, up-date.
Reliability: (4) not assignable
4.2; review
06-FEB-1998 (347)

Remark: Review of the potential cancer risk to anatomists and other related health professionals.
Reliability: (4) not assignable
4.2; review
27-MAR-1998 (17) (18)

Remark: Review; data evaluation for risk in pregancy.
Reliability: (4) not assignable
4.2; review
27-MAR-1998 (188)

Remark: Review; data evaluation for MAK value and classification.
Reliability: (4) not assignable
4.2; review
06-FEB-1998 (189)

Remark: Review of human exposure, kinetics and metabolism, effects on man, incl. sensory, toxic, respiratory, sensitization, skin irritation, genotoxic, reproductive, and carcinogenic effects.
Reliability: (4) not assignable
4.2; review
10-MAR-1998 (702)

Remark: Review; documentation of threshold limit value.
Reliability: (4) not assignable
4.2; review
06-FEB-1998 (4)

Remark: Review of oral toxicity of FA and its derivates.
Reliability: (4) not assignable
4.2; review
10-MAR-1998 (560)

Remark: Review of animal and human toxicology and occupational exposure.
Reliability: (4) not assignable
4.2; review
10-MAR-1998 (612)

Remark: Review of risk assessment.
Reliability: (4) not assignable
4.2; review
10-MAR-1998 (318)

Remark: Review of epidemiological data.
Reliability: (4) not assignable
4.2; review
10-MAR-1998 (475)

Remark: Review of human cancer risk.
Reliability: (4) not assignable
4.2; review
10-MAR-1998 (205)

Remark: Review of the evaluation of the carcinogenic risk.
Reliability: (4) not assignable
4.2; review
10-MAR-1998 (350)

Remark: FA conc. in human blood were determined by analyzing venous blood samples before and after exp. of six volunteers to 1.9 +/- 0.1 ppm for 40 mminutes. Av. conc. (µg/g blood) were 2.61 +/- 0.14 before exp. and 2.77 +/- 0.28 after exposure. The effect was statistically not significant. Kinetik

Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles

09-AUG-2000 (304)

Remark: 70 persons occupationally exposed to FA, 30 medical students with short but intensive inhalational exp. during anatomic dissection and 8 pathological-anatomical laboratory employees were investigated for formic acid excretion. A value of 23 mg formic acid(g creatinine is given as the upper normal level for adults. Short but intensive FA exp. (0.32-3.48 ppm) did not change significantly the av. formic acid conc.. Continous exp. (0.03-0.83 ppm) during the working week was related to a continous increase from 8.7 mg/g creat. to 22.3 mg/g creat.. The change proved to be not significant and no linear correlation was detected.

Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles

06-FEB-1998 (589)

Remark: Review of FA and biomonitoring. Urine formiate and FA are not recommended for biomonitoring in environmental exposures.

Reliability: (4) not assignable
4.2; review

04-MAY-2000 (671)

Remark: In recent years, several regulatory agencies and professional societies have recommended an occupational exposure limit (OEL) for formaldehyde. This article presents the findings of a panel of experts, the Industrial Health Foundation panel, who were charged to identify an OEL that would prevent irritation. To accomplish this task, they critiqued approximately 150 scientific articles. Unlike many other chemicals, a large amount of data is available upon which to base a concentration-response relationship for human irritation. A mathematical model developed by Kane et al. (1979) for predicting safe levels of exposure to irritants based on animal data was also evaluated. The panel concluded that for most persons, eye irritation clearly due to formaldehyde does not occur until at least 1.0 ppm.
Information from controlled studies involving volunteers indicated that moderate to severe eye, nose, and throat irritation does not occur for most persons until airborne concentrations exceed 2.0-3.0 ppm. The data indicated that below 1.0 ppm, if irritation occurs in some persons, the effects rapidly subside due to "accommodation." Based on the weight of evidence from published studies, the panel found that persons exposed to 0.3 ppm for 4-6 h in chamber studies generally reported eye irritation at a rate no different than that observed when persons were exposed to clean air.

It was noted that at a concentration of 0.5 ppm (8-h TWA) eye irritation was not observed in the majority of workers (about 80%). Consequently, the panel recommended an OEL of 0.3 ppm as an 8-h time-weighted average (TWA) with a ceiling value (CV) of 1.0 ppm (a concentration not to be exceeded) to avoid irritation. The panel believes that the ACGIH TLV of 0.3 ppm as a ceiling value was unnecessarily restrictive and that this value may have been based on the TLV Committee's interpretation of the significance of studies involving self-reported responses at concentrations less than 0.5 ppm. The panel concluded that any occupational or environmental guideline for formaldehyde should be based primarily on controlled studies in humans, since nearly all other studies are compromised by the presence of other contaminants. The panel also concluded that if concentrations of formaldehyde are kept below 0.1 ppm in the indoor environment (where exposures might occur 24 h/d this should prevent irritation in virtually all persons. The panel could not identify a group of persons who were hypersensitive, nor was there evidence that anyone could be sensitized (develop an allergy) following inhalation exposure to formaldehyde. The panel concluded that there was sufficient evidence to show that persons with asthma respond no differently than healthy individuals following exposure to concentrations up to 3.0 ppm. Although cancer risk was not a topic that received exhaustive evaluation, the panel agreed with other scientific groups who have concluded that the cancer risk of formaldehyde is negligible at airborne concentrations that do not produce chronic irritation.

Reliability: (4) not assignable
4.2; review

Flag: Critical study for SIDS endpoint

02-OCT-2002 (538)

Remark: Odor
Odor threshold 1.0 ppm in four selected test persons.

Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles

09-AUG-2000 (421)

Remark: Odor threshold was 0.3 ppm in 24 test persons exp. for 4 h on each of 4 consecutive days.

Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles

27-MAR-1998 (167)

Remark: Odor threshold was 0.25-0.83 ml/m3 in 11 test persons.

Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles

06-MAR-1998 (606)

Remark: Odor threshold was 0.06-0.09 ppm in 12 test persons.

Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles

27-MAR-1998 (476)

Remark: Odor threshold was 0.06-0.08 ppm in 15 test persons.

Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles

27-MAR-1998 (223)

Remark: Odor threshold was 0.05-0.89 ppm in 64 test persons.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
06-MAR-1998 (543)

Remark: The threshold for odour detection was determined among 22 nonsmokers and 22 aged-matched, heavy smokers (all female). Odour was detected at 0.025-0.144 ppm by nonsmokers and at 0.020-0.472 ppm by smokers.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
09-AUG-2000 (63)

Remark: Eye and nose irritation at 13.8 ppm in 12 test persons exp. for 30 minutes.
Irritation
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
09-AUG-2000 (678)

Remark: Eye irritation at 1-5.2 ppm in 13-20 test persons exp. repeadly for 5-12 min..
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
06-FEB-1998 (624)

Remark: Eye irritation at 0.33-0.58 ppm in 3/53 test persons exp. for 3 h.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
Flag: Critical study for SIDS endpoint
06-FEB-1998 (543)

Remark: Irritation of the eyes, nose, and throat at 1.2-2.1 ppm in 33 test persons exposed contineously for 35 min. and in 48 test persons exp. discontinously (5 x 1.5 min.).
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
27-MAR-1998 (696)

Remark: Eye irritation at 0.25 - 0.83 ppm in 16 test persons exp. for 5 h.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
Flag: Critical study for SIDS endpoint
30-JUL-2001 (21)

Remark: Threshold conc. of 0.2 ppm for eye irritation in 10 - 22 test persons exp. for 5 min..
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
16-FEB-1998 (524)

Remark: Threshold conc. of 1 ppm for eye irritation in 5/28 test persons exp. for 6 min.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
Flag: Critical study for SIDS endpoint
20-NOV-2000 (61)

Remark: Initial eye irritation with rapid decline at 1 ppm in 15/18 test persons exposed for 90 min., irritation of the nose in 18 test persons with rapid acclimatization.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
Flag: Critical study for SIDS endpoint
14-NOV-2000 (174)

Remark: Two groups of male workers exp. to FA in phenol-FA-plastic foam matrix embedding of fiberglass (batt making) (N=45) and tissue fixation for histology (N=18) were studied for work-related neuro-behavioral, respiratory, and dermatological symptoms. Av. combined frequencies of symptoms were 17.3 (batt making - hot areas, machine operators who managed extrusion, matrix embedding, and oven setting) and 14.7 (batt making - cold areas, other operations within the building) 7.3 for tissue fixation, and 4.8 for the unexp. control group.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles

20-NOV-2000 (388)

Remark: Irritation of the eyes in 8/15, of the nose in 6/15, and the
throat in 5/15 test persons at 2 ppm exp. for 40 min. at rest and with exercise.
Reliability: (2) valid with restrictions
2.1; accepatable study, meets basic scientific principles
Flag: Critical study for SIDS endpoint
26-JUL-2002 (709)

Remark: Eye, nose, and throat irritation in 9 test persons exp. at 3
ppm for 3 h.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
Flag: Critical study for SIDS endpoint
14-NOV-2000 (585)

Remark: Case report of a 27-year-old neurology resident who noted progressive dyspnea and chest tightness after preparing formaldehyde-fixated tissues.
Reliability: (2) valid with restrictions
2.2; basic data given, restrictions
09-AUG-2000 (548)

Remark: Eye irritation at 1.0 ppm and nose and throat irritation at 0.5 ppm in healthy nonsmokers.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
21-NOV-2000 (411) (412)

Remark: Eye irritation in 66 % of 38 acid-hardening lacquer workers and nose and throat irritation in 39 % ($p<0.01$ vs. 18 contr.) at 0.33-0.58 ppm in a 8 h workday.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
Flag: Critical study for SIDS endpoint
27-MAR-1998 (13)

Remark: Cross-sectional study in particle board workers. Nose irritation in 2 % of workers, sore throat in 8 % at 0.1 ppm; nose irritation in 4 %, sore throat in 8 % at 0.2 ppm; nose irritation in 21 %, sore throat in 20 % at 0.5 ppm; nose irritation in 32 %, sore throat in 20 % at 0.8 ppm.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
Flag: Critical study for SIDS endpoint
14-NOV-2000 (340)

Remark: Study in 84 funeral service workers reported more frequently nasal and eye irritation than 38 controls. Exp. level 0.36 +/- 0.19 ppm during 22 embalming procedures.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
Flag: Critical study for SIDS endpoint
16-FEB-1998 (333)

Remark: Prospective evaluation in 103 medical students over a 7 months period. Eye and upper rspiratory tract irritation were significantly associated with exposure. Exp. level was generally <1 ppm and peak level <5 ppm.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
27-MAR-1998 (665)

Remark: Increased ill health complaints in workers in fabric stores at >= 0.13 ppm for 30-50 h/wk..
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
16-FEB-1998 (472)

Remark: Case report on a 47-year-old diary foreman, who had been exp. for 9 years to FA emitted from a milk-packing machine situated underneath his office. Under normal process conditions FA level was 0.03 mg/m3. A specific laryngeal provocation-test with FA was positive. His laryngitis was so serious that he retired.
Reliability: (2) valid with restrictions
2.2; basic data given, restrictions
27-MAR-1998 (567)

Remark: Pilot study on ill health complaints, physiology, and histology of the upper airways in two groups of medium density fiberboard (MDF) workers. The frequency of ill health complaints was higher, the sense of smell was poorer, and the frequency of nasal obstruction was higher for the MDF board workers in comparison to traditional borad workers and the reference group. Mucociliary activity was lower in the traditional board workers. Forced vital capacity was low in both groups when compared to expected values. Histologic changes did not differ significantly between the groups.

Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
Flag: Critical study for SIDS endpoint

02-OCT-2002 (329)

Remark: 34 workers in a gross anatomy laboratory were evaluated for pulmonary response. FA conc. ranged from 0.07 - 2.94 ppm during dissecting operations. Reported symptoms included irritation of eyes (88 %), nose (74 %), throat (29 %), and airways (21 %).
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
27-MAR-1998 (7)

Remark: Report of one case of upper respiratory tract irritation after accidental inhalation of FA, which was sent to the clinic for further treatment.
Reliability: (2) valid with restrictions
2.1; basic data given, restrictions
06-MAR-1998 (37)

Remark: Review of health risks in homes insulated with urea formaldehyde foam and details of 48 patients contacting a poison center.
Reliability: (4) not assignable
4.2; review
10-MAR-1998 (296)

Remark: Review of health risks in homes insulated with urea formaldehyde foam and details of 48 patients contacting a poison center.
Reliability: (4) not assignable
4.2; review
27-MAR-1998 (295)

Remark: Sixty-five mobile home households volunteered for an assessment of indoor FA gas. Sixty-one teenage and adult occupants completed health questionnaires. FA conc. ranged from <0.1 - 0.8 ppm. Ocular discomfort showed a positive dose-response relationship.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
16-FEB-1998 (291)

Remark: Review of health risks in homes insulated with urea formaldehyde foam.
Reliability: (4) not assignable
4.2; review
27-MAR-1998 (325)

Remark: Review; health risks in homes insulated with urea formaldeyhde foam.
Reliability: (4) not assignable
4.2; review
27-MAR-1998 (325)

Remark: Prevalence of selected symptoms were determined in 54 residents from 22 UFFI homes, 26 residents in 16 non-UFFI homes and 10 laboratory technicians. FA conc. were in UFFI homes 0.054 ppm, 0.051 in non-UFFI homes, and 0.125 ppm in the labs. Residents of UFFI homes reported a significantly higher prevalence of non-specific symptoms compared to the two other groups.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
16-FEB-1998 (91)

Remark: Positive dose-response of ill health complaints (eye irritation, nose/throat irritation, headache and skin rash) at FA conc. of 0.1 ppm and above was demonstrated in 2000 residents living in mobile and conventional homes.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
27-MAR-1998 (564)

Remark: Improvement of ill health complaints in a survey of 762 control and urea formaldehyde foam insulated houses 1 year after removal remedial of the foam or remedial work was not associated with changes in indoor FA levels. Other indoor contaminants were not determined.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
20-NOV-2000 (103) (106) (107)

Remark: Case report of a 27-year old neurology resident who noted progressive dyspnea and chest tightness after preparing formaldeyhde-fixated tissues.
Lung function
Reliability: (2) valid with restrictions
2.2; basic data given, restrictions
09-AUG-2000 (548)

Remark: Questionnaire and lung function tests were performed in five groups of phenol-formaldehyde resin workers. A slight excess of chronic cough and sputum production and a small decrease in lung function was seen.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
09-AUG-2000 (592)

Remark: Cross-sectional study in 73 men and women exp. to phenolic resin dust and/or processed cotton dust. There was a statisitically significant acute drop in FEV1 and FVC over the shift in workers exp. to dust containing phenolic resin; workers exp. to processed cotton dust only, showed no significant changes.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
20-FEB-1998 (618)

Remark: 47 subjects and 20 controls employed in a carpenter shop were studied for symptoms and lung function. Exp. level was 0.45 mg(m3 (mean). Changes in lung function suggesting bronchoconstriction were seen after a day of work and exp. to FA.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
20-FEB-1998 (11)

Remark: Morbidity study in 199 employees in Fa manufacturing and its processing to resins for up to 42 years. Exp. level before 1971 <5 ppm, after 1971 <1 ppm. (average shift). No changes in lung function in comparison to a control group of 91 steel construction workers were seen.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
20-FEB-1998 (261)

Remark: A population-based, retrosepctive survey of 395 urea-formaldehyde foam unsulated households and 400 controls showed a significant excess in two specific symptoms, "burning skin" and "wheezing or difficult breezing".
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
27-MAR-1998 (650)

Remark: No significant changes in lung function in 18 subjects exp. to 1-2 ppm FA for 90 min..
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
20-FEB-1998 (175)

Remark: No chronic bronchitis or lung function disorders in embalmers occupationally exp. to FA (0.4-2.1 peak conc.).
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
20-FEB-1998 (424)

Remark: No increase in airway resistance, neither at rest or during exercise in test persons with symptoms of asthma during exp. up to 3 ppm for 10 min..
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
20-FEB-1998 (602)

Remark: No changes in breathing capacity during working weeks in laboratory technicians. Ex. level up to 5.86 ppm (av. 0.125 ppm).
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
20-FEB-1998 (90)

Remark: Symptoms of astham in 5 of 15 test persons exp. up to 25 ppm and 30 min..
Reliability: (2) valid with restrictions
2.2; basic data given, restrictions

20-FEB-1998 (116)

Remark: Positive bronchial provocation test (1-2 ppm for 30 min.) in 12 of 230 persons exp. to FA and suffering asthma-like symptoms.
Reliability: (2) valid with restrictions
2.2; basic data given, restrictions
Flag: Critical study for SIDS endpoint
20-FEB-1998 (513)

Remark: No airway onbstruction in steel foundry workers occupationally exp. to up to 4 ppm FA in comparison to controls.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
20-FEB-1998 (435)

Remark: Slight changes in lung function parameters in test persons after 30 min. exp. at 3 ppm for 3 h; reversible within 1-3 hrs; no changes in asthmatic subjects.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
Flag: Critical study for SIDS endpoint
20-FEB-1998 (278) (585) (586)

Remark: No changes in lung function parameters in 15 test persons with bronchial hypersensitivity at 0.12 and 0.85 mg/m3 for 90 min..
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
Flag: Critical study for SIDS endpoint
20-FEB-1998 (298)

Remark: No changes in lung function in 30 test persons including 15 having asthma exp. to 2 ppm for 40 mi. at rest and exercise.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
Flag: Critical study for SIDS endpoint
26-JUL-2002 (588) (708) (709)

Remark: No significant decrements in lung function or increase in bronchial reactivity with exp. to 3 ppm at rest or to 2 ppm at exercise in healthy nonsmokers.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
Flag: Critical study for SIDS endpoint
21-NOV-2000 (410) (412)

Remark: No changes in lung function in 15 hospital laboratory workers exp. to 2.0 ppm for 40 min. on four occasions (two at rest and two during exercise).
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scienticfic principles

Flag: Critical study for SIDS endpoint
20-FEB-1998 (587)

Remark: No chronic decrements in lung function in 38 acid-hardening paint workers in comparison to 18 controls. Mean exp. conc. wa 0.4 mg/m3 FA.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
Flag: Critical study for SIDS endpoint
14-NOV-2000 (13)

Remark: No changes in lung function in residents of mobile and conventional homes and mobile offices exp. to 0.006-1.6 ppm Fa.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
20-FEB-1998 (105) (105) (106) (450)

Remark: Cross-sectional study in 109 particle board workers and 254 controls. No evidence of a chronic decrement in lung function after a mean exp. of 0.17-2.93 ppm for ten years.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
20-FEB-1998 (339)

Remark: Cross-sectional study in three groups (70 chemical plant workers, 100 furniture production workers, 36 clerks). No signs that duration of exp. or level of exp. (0.05-0.5, 02-0.3, or 0.09 mg/m3) to FA had any influence on the severity or symptoms or impairment of lung function parameters.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
20-FEB-1998 (330)

Remark: Cross-sectional study in 176 strandboard production workers.
Ex. to FA was low (<0.01 - 0.06 ppm). measured dust was low to moderate (.01 - 0.57 mg/m3). No evidence of an acute effect on lung function.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
23-FEB-1998 (348)

Remark: Prospective study in 47 woodworkers and 20 controls first examined in 1980. A dose-response relationship was found between exp. to FA (0.3 - 0.7 mg/m3) and decrease in lung function. The impairment, however, can be reversed within 4 weeks of no exposure.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
Flag: Critical study for SIDS endpoint
14-NOV-2000 (12)

Remark: Small, but not clinically significant pulmonary response in 24 healthy volunteers exposed while exercising for 2 h to 3 ppm or a mixture of FA and 0.5 mg/m3 of respirable dust.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles

Flag: Critical study for SIDS endpoint

27-MAR-1998 (279) (563) (566)

Remark: Cross-sectional study in 84 funeral service workers revealed no significant change in lung function in comparison to controls. Exp. level was 0.36 +/- 0.19 ppm during 22 embalming procedures.
Reliability: (2) valid with restrictions
2.1; acceptables study, meets basic scientific principles
23-FEB-1998 (333)

Remark: Prospective study in 103 medical students (TWA < 1 ppm, peak < 5 ppm) showed no pattern of bronchoconstriction in response to exp. after either 2 weeks or 7 months. Twelve subjects had a history of asthma; they were no more likely to have smyptoms than those without such a history.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
23-FEB-1998 (664)

Remark: No changes in lung function or increase in bronchial reactivity in 15 asthmatic subjects exp. to 0.008 - 0.85 mg/m3 for 90 min..
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
23-FEB-1998 (299)

Remark: The respiratory health status of 186 male plywood workers was evaluated by spirometric tests, respiratory questionnaires, and chest x-ray. Area con. ranged from 0.28 - 3.48 ppm. The av. personal exp. was 1.13 ppm. Exp. was associated with decrements in the baseline spirometric values and with several respiratory symptoms and diseases, incl. cough, phlegm, asthma, chronic bronchitis, and chest colds.
Reliability: (2) valid with restrictions
2.1; acceptable Study, meets basic scientific principles
Flag: Critical study for SIDS endpoint
14-NOV-2000 (453)

Remark: The long term effects on the respiratory tract have been investigated in a group of 164 workers exp. daily during the production of urea formaldehyde resin together with 129 workers not exp. to free FA. Exp. was classified as high (TWA > 2 ppm), medium (TWA 0.6 - 2 ppm), or low (0.1 - 0.5 ppm). The proportion with self reported respiratory symptoms was similar in the two groups. The initial FEV1 was within 0.5 l of the predicted value for both groups
The mean decline in FEV1 was 42 ml a year for the exp. and 41 ml for the controls.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
Flag: Critical study for SIDS endpoint
14-NOV-2000 (515)

Remark: Nonmalignant respiratory disease (NMRD) mortality was examined among woodworkers. During the 6-year prospective follow-up, there were 97 NMRD deaths among 11,541 men

reporting employment in wood-related occupations an 1,334 NMRD deaths among 317,424 men reporting no exposure to wood dust or wood-related jobs. An excess of NRMD was observed among woodworkers reporting exposure to asbestos (RR=1.59, 95 % CI=0.85-2.96), as well as the small number of woodworkers reporting exposure to FA (RR=1.95, 95 % CI 0.63-6.06), but men not reporting exposure these substances als ohad an ecess risk.

Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles

04-MAY-2000 (183)

Remark: Case report on airways obstruction after exp. to FA.

Reliability: (2) valid with restrictions
2.2; basic data given, restrictions

02-OCT-2002 (512)

Remark: Hypersensitivity was shown by inhalation provocation tests in two nurses with attacks of wheezing accomponied by productive cough. Two ot three firther members of the staff of 28 who had developed similar recurrent but less frequent episodes did not produce these symptoms under inhalative provocation. Single episodes of these symptoms had been notes by three additional staff members. The exp. did not seem to be directly responsible in all cases, it might have increased susceptibility to other provoking agents or induced a hyperreactive responsiveness of the airways.

Reliability: (2) valid with restrictions
2.1; basic data given, restrictions

27-MAR-1998 (317)

Remark: Case report; bronchial challenge at 3 ppm was negative in a patient with severs asthma after use of urea-formaldehyde foam.

Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles

23-FEB-1998 (235)

Remark: Reinvestigation of two nurses who have shown positive inhalation provocation tests. In one nurse a 15 min. exp. to 6 ppm provoked no reaction; in the other a 5 min. exp. to 3 ppm provoked a late asthmatic reaction.

Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles

27-MAR-1998 (316)

Remark: 13 selected patients with symptoms suggestive of asthma who suspected exposure to formaldehye as a cause were studied. The level of exposure at their homes or at work ranged from 0.1 to 1.2 ppm of formaldehyde gas. The patients were tested with bronchial challenges of 0.1, 1, and 3 ppm formaldehyde gas and randomly interspersed room-air placebos. No patient had a significantly greater decrease in the forced expiratory volume in 1 second after exposure to formaldehyde than after exposure to air. In no case asthmatic symptoms were caused or aggrevated.

Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles

Flag: Critical study for SIDS endpoint

06-AUG-2001 (236)

Remark: Bronchial provocation (0.1, 1, 10, 20, and 25 %) was performed in 15 workers occupationally exp. to FA were performed. Three showed asthma with late asthmatic reactions and six immediate reactions, which were likely to be due to direct irritant effects. FA conc. required to elicit these irritant reactions was 4.8 mg/m3 (mean).
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
27-MAR-1998 (116)

Remark: Immunological test in 23 asthmatic subjects who lived in urea-formaldehyde foam-insulated homes and on 4 asthmatic subjects living in conventionally insulated homes showed after long-term exp. no , and at short-term exp. minor changes.
Reliability: (2) valid with restrictions
2.1; acceptables study, meets basic scientific principles
27-MAR-1998 (550)

Remark: No IgE-mediated sensitization could be attributed to FA in 86 subjects living or working in rooms or places were formaldheyde-containing construction materials were used.
Reliability: (2) valid with restrictions
2.2; basic data given, restrictions
27-MAR-1998 (404)

Remark: Clinical and immunological evaluation or 37 workers exp. to gaseous FA. None of the workers had IgE or IgG antibody to F-HAS or an immunologically mediated respiratory or ocular disease by FA; however some of the workers appeared to experience irritant symptoms.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
27-MAR-1998 (273)

Remark: Report on 61 serum samples analyzed for IgG antibodies against F-HSA. There is no evidence that gaseous FA meets the criteria for causation of inhalational IgG-mediated lung disease by clincial or serological studies.
Reliability: (2) valid with restrictions
2.1; acceptables study, meets basic scientific principles
27-MAR-1998 (536)

Remark: 55 subjects were studied to determine if the presence of IgE or IgG antidbodies to F-HSA was associated with exp. to gaseous FA or with respiratory or cunjunctival symptoms. IgE antibody specific for FA-HSA was deteced by ELISA in three subjects; immediate-type skin testing was negative in two of these subjects, and not interpretables in one. A respiratory challenge at 2 ppm in one of these subjects with history or respiratory symptoms showed no changes in lung function.
A relationship between presence of antibodies or respiratory or conjunctival symptoms and histroy of gaseous FA exp. could not be defined.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
23-FEB-1998 (203)

Remark: Study on prevalence of atopy and hypersensitivity to FA in

pathologists. None of 63 subjects had allergen-specific IgE, although 29 subejcts complained of sensitivity.

Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles

23-FEB-1998 (581)

Remark: Ten subjects purposed to have FA rhinits and asthma an 10 healthy subjects submitted to an inhalation provocation in an exposure chamber with FA at a dose of 0.5 mg/m3 over 2 hr. Provocation with FA caused only transient symptoms of rhinits in both groups. None of the subjects supposed to have occupational asthma developed clinical symptoms of bronchial irriatation. No specific IgE antibodies to FA were detected in persons with occupational exposure to FA. No difference in the nasal response to FA were found between subjects reporting to have occupational allergic respiratory disease and healthy subjects (P > 0.05). Inhaled FA at a level as low as 0.5 mg/m3 did not induce a specific allergic response either in the upper or in the lower part of the respiratory tract. Moreover, ther is no difference in nasal response to FA in asthmatic subjects occupationally exposed to FA and healthy sujects.

Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles

09-AUG-2000 (403)

Remark: The relation of chronic respiratory symptoms and pulmonary function to FA in homes was studied in a sample of 298 children (6-15 years of age) and 613 adults. Significantly greater prevalence rates of asthma and chronic bronchitis were found in children from houses wiht FA levels 60-120 ppb than in those less exposed, especially in children also exposed to environmental tobacco smoke. The effects in adults were less evident: decrements in peak expiratory flow rates due to FA over 40 ppb were seen only in the morning, and mainly in smokers.

Reliability: (2) valid with restrictions
2.2; basic data given, restrictions

Flag: Critical study for SIDS endpoint

20-NOV-2000 (409)

Remark: Exhaled nitric oxide (eNO) and FA levels was measured in 224 healthy children (6-13 years of age) and in their homes, respectively. There was no effect of FA levels on spirometric variables. However, eNO levels were significantly elevated in children living in homes with av. FA levels >= 50 ppb. Exhaled NO levels were 15.5 ppb for children from homes with FA conc. >= 50 ppb compared with 8.7 ppb for children with FA conc. < 50 ppb.

Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles

26-JUL-2002 (233)

Remark: Case report of a worker with clinical symptoms compatible with bronchospasm caused by formaldehyde exposure. An enzyme-linked immunosorbent assay showed positive IgE and IgG titers to formaldehyde-human serum albumin. A cutaneous test for formaldehyde-human serum albumin was positive. The worker had negative methacholine challenge at 25 mg/ml and

negative formaldehyde inhalation challenges at 0.3, 1, 3, and 5 ppm for 20 minutes. It is concluded, that the worker´s symptoms were not caused by immunologically mediated asthma.

Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles

Flag: Critical study for SIDS endpoint

15-AUG-2001 (274)

Remark: Case report of 4 patients and experiment in 14 volunteers of contact urticaria to FA. The contact urticaria appeared on healthy skin only following repeated open applications or after single application on slightly diseased skin.

Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles

Flag: Critical study for SIDS endpoint

02-OCT-2002 (20)

Remark: Prevalence rate of FA skin sensitivity in 4,553 male and 6,479 female patients tested from 1984-1989 was 2.2 % for the men and 3,7 % for the women. Source of exp. in men was occupational (31 %), domestic (10 %), and unknown (48 %). 95 of the female cases were sensitized by FA donating cleaning products and 117 cases by FA itself.

Reliability: (2) valid with restrictions
2.2; basic data given, restrictions

Flag: Critical study for SIDS endpoint

20-NOV-2000 (164)

Remark: 23 patients with a history of a positive epicutaneous test to FA were studied for specific IgE antibodies. On RAST-test, only two nonatopic patients had specific IgE antibodies. The study does not support the hypothesis that specific IgE antidbodies are active in the pathogenesis of contact sensitivity either in atopic or in nonatopic patients.

Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles

Flag: Critical study for SIDS endpoint

14-NOV-2000 (429)

Remark: Case report on contact urticaria in a pathology laboratory worker (open patch test: 1 % and 2 % pruritic flares, 0.5 % neg.).

Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles

Flag: Critical study for SIDS endpoint

14-NOV-2000 (432)

Remark: Case report on contact urticaria from FA treated leather (pos. patch-test at 2 %).

Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles

27-MAR-1998 (309)

Remark: Outcome of simulataneous testing with FA 1 % and 2 % in consecutively patch-tested patients was compared. The study included 3,734 consecutively patch test patients. 121 gave

a positive reaction to 1 % an/or 2 % FA in water. There was no statistically significant difference between 1 and 2 % with respect to allergic reactions, but 2 % gave significantly more irritant reactions. A 1 % patch test concentration for FA is recommended.

Reliability: (1) valid without restriction
1.1; method and performance conform to standard

Flag: Critical study for SIDS endpoint

14-NOV-2000 (659)

Remark: Reports of primary skin irriatation and allergic dermatitis as a result of skin contact with water solutions of formaldehyde were reported. A threshold for induction of an allergic dermatitis has not been clearly defined, but it is estimated to be a water solution containing less than 5 % formaldehyde. The threshold for elicitation of allergic contact dermatitis in sensitized humans subjects ranges from 30 ppm (w/w) for patch testing to 60 ppm (w/w) for products containing formaldehyde.

Reliability: (4) not assignable
4; review

Flag: Critical study for SIDS endpoint

02-OCT-2002 (16)

Remark: Questionnaire study among 70 employees at day care centers and 34 controls. Median exp. level was 0.43 mg/m3, resp. 0.08 mg/m3. Exp. employees showed a significantly higher frequency of mucous membran irriatation, headache, abnormal tiredness, menstrual irregularities, and use of analgetics.

Reliability: (2) valid with restrictions
2.1; basic data given, restrictions

02-OCT-2002 (527)

Remark: Two groups of male worker exp. to phenol-FA-plastic foam and tissue fixation for histology were studied for work-related neuro-behavioral, respiratory, and dermatological symptoms.
Av. combined frequencies were 17.3 and 14.3 for the plastic foam workers, 7.3 for the histology technicians, and 4.8 for unexp. hospital workers.

Reliability: (2) valid with restrictions
2.2; basic data given, restrictions

30-AUG-2001 (387)

Remark: Case report of a 26-year-old female who had accidentally ingested 45 ml of a 37 % (v/v) FA solution. Examination of the oropharynx after reference to the clinic four days after ingestion revealed ulceration and sloughing of soft palate and posterior pharyngeal wall. Gastrointestinal endoscopy showed oedematous and ulceration of the oesophagal mucosa with patches of black slough along its whole length. Corrosiveness

Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles

Flag: Critical study for SIDS endpoint

02-OCT-2002 (398)

Remark: Case report of four cases of nephrotic syndrome after exposure to FA in newly built homes. Membranous nephropathy was confirmed by biopsy. The four patients shared a

particular histocompatibility leukocyte antigen (HLA). FA conc. ranged from 0.10-0.49 ppm.
Repeated dose toxicity
Reliability: (2) valid with restrictions
2.2; basic data given, restrictions
02-OCT-2002 (92)

Remark: Impaired nervous system function was seen in three patients using FA and phenol in fixation of animals for 14-30 years and a fourth patient covered several times in FA and phenol spills. They had elevated mood state and symptom frequency scores compared to controls. There was excessive fatigue, somnolence, headache, difficulty remembering, irritability, and instability of mood.
Reliability: (2) valid with restrictions
2.2; basic data given, restrictions
Flag: Critical study for SIDS endpoint
14-NOV-2000 (385)

Remark: Nasal lavage fluid was investigated in 11 healthy subjects and 9 patients with specific skin sensitization after provocation with FA (0.5 mg/m3 for 2 h). Increases in eosinophiles and elevated albumin and total protein levels were observed. No difference was found between healthy subjects and patients.
Sensitisation
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
02-OCT-2002 (539)

Remark: Eight symptomatic subjects exp. to indoor FA at 0.07-0.55 ppm were compared to 8 nonexposed with respect to immunological parameters. Anti-FA-HAS IgG, but no IgE antibodies were detected in the 8 exposed; none were found in 7 of the unexposed. Proportion of peripheral T cells were decreased in the exposed in comparison to the controls.
Reliability: (2) valid with restrictions
2.2; basic data given, restrictions
25-FEB-1998 (57) (280) (657)

Remark: 6 patients with multiple subjective ill health complaints and exp. to FA during education and occupation showed changes in immunological parameters; two showed IgE, 3/4 tested IgM and 5 IgG. All 6 had elevated t cells (antigen memory cells).
Reliability: (2) valid with restrictions
2.2; basic data given, restrictions
27-MAR-1998 (57) (281) (656)

Remark: Four groups of patients with long-term inhalation exp. showed significantly higher antibody titers to FA-HAS and significant increases in Ta1+, IL2+, and B cell lymphocytes compared to controls with short term periodic exp..
Reliability: (2) valid with restrictions
2.2; basic data given, restrictions
27-MAR-1998 (658)

Remark: Three years following exp. to emissions from a overheated tanker containing urea-FA resin immunological parameters were investigated in 42 exp. subjects and 29 controls.

There was a significant difference for CD26 cells, autoantibodies, and titers of IgG and IgM to FA-HSA.
Reliability: (2) valid with restrictions
2.2; basic data given, restrictions
27-MAR-1998 (444)

Remark: Case report of anaphylaxis in patients during dental treatment using paraformaldehyde and cresol. Specific IgE against formaldehyde-human serum-albumin was found in ther sera of the patients.
Reliability: (2) valid with restrictions
2.1; acceptable study meets basic scientific principles
Flag: Critical study for SIDS endpoint
19-OCT-2000 (204)

Remark: Reaction time was measured in 385 female formaldehyde and solvent-exposed histology technicians, and 79 unexposed female laboratory workers. Increasing age was the only significant factor in lengthening reaction time.
Repeated dose toxicity
Reliability: (2) valid with restrictions
2.2; basic data given, restrictions
Flag: Critical study for SIDS endpoint
06-AUG-2001 (386)

Remark: Neurobehavioral functions were studied by periodic testing of 318 histology technicians and by a single session testing 494 of such technicians from 1982 through 1986. Tests included immediate recall of stories, of drawings, and of number series from the Wechsler Memory SCale, block designs from the Wechsler Adult Intelligence Scale (WAIS), slotted pegboard, trail making A and B, embedded figures, number writing on the fingers, visual simple and two-choice reaction time, balance (speed of body sway), and the profile of mood state (POMS) score. Variations in results of tests given across 4 years were small.

No cumulative effects of occupational exposures or of aging were found. Formaldehyde levels in workplace air varied from 0.2 to 5 ppm.
Reliability: (2) valid with restrictions
2.1; basic data given, restrictions
Flag: Critical study for SIDS endpoint
06-AUG-2001 (389)

Remark: Corrosiveness
Report of a case of voluntary poisoning with formalin (a gulp of a 40 % v/v soluntion) in a 47-year-old man. The corrosive damage to the gastrointestinal tract required an oesogastrectomy and three months later a colic transplant.
Reliability: (2) valid with restrictions
2.2; basic data given, restrictions
Flag: Critical study for SIDS endpoint
09-AUG-2001 (227)

Remark: Cytogenetic evaluation of 15 employees exp. in FA manufacturing and processing for 23 to 35 years (28 years average) revealed no statistically significant increase in chromosome aberration rates in lymphocytes as compared with a matched control group. Exp. level <1971: 5 ppm and >1971: 1 ppm. Genetic toxicity

Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic sceintific principles
Flag: Critical study for SIDS endpoint
02-OCT-2002 (229)

Remark: No significant difference in chromosome aberrations or SCE frequencies in lymphocytes between 6 exp. pathology workers and 5 controls. Ex. level 1.8-3.9 ppm.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
Flag: Critical study for SIDS endpoint
25-FEB-1998 (648)

Remark: Eleven hospital autopsy service workers and 11 mated controls were evaluated for sperm count, abnormal sperm morphology and frequency of one or two fluorescent bodies. No sigficant difference was observed. Exp. was intermittent, with a TWA of 0.61-1.32 ppm.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
14-NOV-2000 (693)

Remark: Significant difference in some cytogenetic measures (dicentrics or ring chromosomes), but not in SCE, in lymphocytes in 20 exp. paper factory workers and 20 controls. Exp. level 1-3 ppm.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
Flag: Critical study for SIDS endpoint
25-FEB-1998 (52)

Remark: Small but significant increase in SCE in lymphocytes in 8 exp. anatomy students when compared to samples obtained before exp.. Exp. level 1.2 ppm. Phenol was also present in the embalming fluid.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
Flag: Critical study for SIDS endpoint
31-JUL-2001 (715)

Remark: Cytologic examination of exfoliated nasal mucosa cells in 42 phenol-FA and Fa process workers showed no statistical realtionship to FA exp. in compariosn to 38 controls. Ex. level was 0.02-2 ppm.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets bsic scientific principles
Flag: Critical study for SIDS endpoint
25-FEB-1998 (64)

Remark: A significant difference of histology index in the nasal musosa but no relation to dose or duration of FA exp. was found in 75 particle board workers and 25 controls. Exp. level was 0.08-1.0 ppm.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
Flag: Critical study for SIDS endpoint
27-MAR-1998 (210) (211)

Remark: A significant difference of histology index in nasal mucosa but no relation to dose and duration of FA exp. was found in 62 resin manufacturing workers and 32 controls. Exp.

level was 0.04-0.4 and 0.17-0.25 ppm.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
Flag: Critical study for SIDS endpoint
27-MAR-1998 (328)

Remark: No significant difference of histology index in nasal mucosa in 37 workers and 37 controls. Fa exp. level 0.5->2 ppm.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
Flag: Critical study for SIDS endpoint
21-NOV-2000 (89)

Remark: Cross-sectional study in 16 MDF- and 29 traditional board workers and 36 controls. Nasal epithelial dysplasia were seen in a few cases of the traditional board group, but histological changes in terms of scoring did not differ significantly between the groups.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
25-FEB-1998 (329)

Remark: The frequency of mirconucleated buccal cells (MN) and cytology of respiratory nasal mucosa cells were evaluated in 15 workers in a plywood factory compared to a control group.
Exp. level ranged from 0.1 to 0.39 mg/m3 for FA and contemporary wood dust (0.23-0.73 mg/m3). A higher frequency of MN and a chronic phlogosis in the nasal mucosa with metaplasia cells was observed in the exposed versus controls, but no dose-response effect.

Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
Flag: Critical study for SIDS endpoint
20-NOV-2000 (36)

Remark: Workers of a plywood production plant (n=9), a chipboard impregnation facility (n=10), and a fiber glass factory (n=9) exp. appr. to 0.1, 0.2, and 0.3 resp. were studied for MN in buccal mucosa cells. For comparison MN were also scored in blood lymphocytes. The exp. workers showed more than twice as much MN-buccal mucosa cells than a control group (n=34). A dose-response relationship could not be demonstrated. MN in lymphocytes were only related to age.
Reliability: (4) not assignable
4.1; abstract
27-MAR-1998 (514)

Remark: Metaplasia of nasal mucosa with corresponding retardation of mucociliar clearance were detected in 9 of 18 workers and in 6 a deterioration of olfactory function. FA exp. duration was 11.3 years (mean); conc. was 2.54 ppm (mean out of several single measurements during one year).
Reliability: (2) valid with restrictions
2.2; basic data given, restrictions
26-FEB-1998 (558)

Remark: 20 workers in manufacture of wood splinter materials were investigated for chromosomal aberrations. Significant

differences were observed in mitogen-induced proliferation of lymphocytes between the exposed and controls. FA conc. ranged from 0.55-10.36 mg/m3.

Reliability: (2) valid with restrictions
2.2; basic data given, restrictions

27-MAR-1998 (679)

Remark: Exfoliated buccal and nasal cells from 35 mortuary science students exposed to embalming fluid containing FA were examined before and after a 90-day course. In buccal cells, total MN frequency was significantly increased, whereas in nasal cells it was nt. Mean formaldehyde exposure was 14.8 ppm-hours for subjects with data on buccal cells and 16.5 ppm for subjects with data on nasal cells. A notable correlation between frequency on MN and any measure of formaldehyde exposure was not fouot.

Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles

Flag: Critical study for SIDS endpoint

31-JUL-2001 (653)

Remark: Significantly increased micornucleated cells from buccal area and blood lymphocytes, but not from nasal cells in a 85 day study period in 29 mortuary students. Results differ for men and women.

Reliability: (2) valid with restrictions
2.2; basic data given, restrictions

Flag: Critical study for SIDS endpoint

20-NOV-2000 (628)

Remark: Modified cytokinesis blocked micronucleus assay was applied to detect abnormalities in human peripheral lymphocytes of thirteen students exposed to formaldehyde during a 12-week (10 h per week) anatomy class. Breathing zone air samples showed a mean concentration of 2.37 ppm. Ten students without exposure served as controls. The micronuclei rate (6.38 +- 2.50 %) and the chromosome aberration rate (5.92 +-2.40 %) in the exposed group showed a significant increase when compared with those of the controls (3.15 +- 1.46 % and 3.4 +- 1.57 %). Sister chromtid exchange was only slightly increased (5.91 +- 0.71 %) compared to controls (5.26 +- 0.51 %).

Reliability: (2) valid with restrictions
2.2; basic data given, restrictions

Flag: Critical study for SIDS endpoint

30-AUG-2001 (303)

Remark: Twenty-three non-smoking students in the study had inhalation exposure to 0.423 +- 0.249 ppm of formaldehyde for a period of 8 weeks during anatomy classes. Different lymphocyte subsets showed an increase (CD19, B cells), whereas others showed a decrease (CD3, total T cells; CD4, T helper -inducer cells; CD8, T cytotoxic-suppressor cells).
No significant difference was reported for lymphocyte proliferation rate and sister-chromatod exchanges at the exposure leveland duration. However, each cell type of the lymphocytes subsets fell within the expected reference ranges and the biological significance of the changes observed is therefore unclear.

Reliability: (2) valid with restrictions
2.1; accpetable study, meets basic scientific principles
Flag: Critical study for SIDS endpoint
30-AUG-2001 (722)

Remark: Cancerogenicity - Cohort studies-Industrial workers
Morbidity study in 199 employees in FA manufacturing and its processing to resins for up to 42 years. Exp. level before 1971: <5 ppm, after 1971 <1 ppm (average shift). No nasal or lung tumors were observed.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
09-AUG-2000 (260)

Remark: Retrospective cohort mortality study with 26,561 subjects first employed before 1966 and followed until 1980 for vital status, which included plants reported on previously by other researchers. Job exp. matrix was developed for 6,700 job titles. There was no overall cancer excess (SMR 101, 95 % CI: 93-109). Nasal cancer showed no excess risk (2 obs. vs. 2.2 expect.) as for buccal cavity and pharynx (SMR=96, 95 % CI: 57-152), brain (SMR=81, 95 % CI:47-130), and leukemia (SMR=80, 95 % CI: 47-130). Lung cancer was slightly but not significantly above expectation (SMR=112, 95 % CI: 97-128), and was not correlated with intensity or duration of exp., cumulative exp., or peak exp..

Although mortality for buccal cavitiy and pharynx cancer was not elveated (SMR=96), when the numerous subsites were examined, an excess risk for nasopharyngeal cancer (NPC) was seen (7 obs. vs. 2.2 expect.). Of the 7 NPSCs, 6 were associated with exp. to FA (SMR=300). There was a suggestive non-significant trend with cumulative exp.. However, for the other sites of the buccal cavity and the pharynx there was an inverse association with the level of exp.. Only 1 unspecified oral/pharyngeal cancer death was found in the FA cohort vs. 4.4 expected. Correction for the differences in diagnostic criteria used and misclasification reduced the significance of the excess risk of NPC. Further analysis found that although short term workers had higher total cancer risk, their exp. was not greater than long-term workers. Follow-up studies within this industrial group have provided little additional evidence of exposure-response (i.e. cumulative, average, peak, duration, intensity) except in the presence of other substances.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
Flag: Critical study for SIDS endpoint
14-NOV-2000 (80) (81) (82) (83) (117) (146) (220) (430) (436) (459) (551) (625) (710)

Remark: Retrospective cohort mortality study from 1959 to 1980 and follow-up to 1986 in 1,332 subjects of a resin manufacturing plant. Mean level exp. was 0.2-3.8 ppm. No nasal cancers or NPC were reported. SMR on oral/phyrngeal cancer, brain cancer or leukemia were not presented. A SMR for hematologic cancer (SMR=154, 95 % CI: 50-359, 5 deaths) was presented.

A statistically significant SMR of 186 for lung cancer (SMR 136, 95 % CI: 44-318) was at lower risk than those with "other" or "unknown" exp.. For the FA group there was no relation between risk of lung cancer and duration of employment or latency. In an update of this cohort, overall lung cancer mortality was no longer in excess.

Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles

Flag: Critical study for SIDS endpoint

14-NOV-2000 (68) (69)

Remark: Cohort study in 521 workers in the abrasive manufacturing industry. Exp. was 5 mg/m3 total dust, silica 0.1 mg/m3, FA 0.1-1 mg/m3 with intermittent peaks uo to 20-30 mg/m3 in 59 workers. No excess of cancer incidence or mortality; no nasal or nasopharyngeal cancer reported.

Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles

26-FEB-1998 (209)

Remark: Cohort study in 11,030 female textile workers in three plants starting use fo FA in 1955 and 1959. No deaths of nasal cancer or NPC were observed. The SMR for brain cancer was 71 (90 % CI: 28-149) and for leukemia was 114 (90 % CI: 60-200). There was a non-significant elevation in lung cancer mortality (SMR=114, 90 % CI: 86-149) according to an elevated risk among short-term workers, where exp. to FA was recent and much lower than in the past. A statistically significant elevation of buccal cavity cancer, 4 obs. vs. 1.2 expect. (SMR=343, 90 % CI: 118-786) was reported. The SMR is no longer significant calculating conventional 95 % CI. Snuff dipping has to be considered. There was no excess of pharyngeal cancer deaths.

Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles

Flag: Critical study for SIDS endpoint

14-NOV-2000 (621) (622)

Remark: Reanalysis of lung cancer mortality study among industrial workers exp. to FA. No statistically significant positive trend for lung cancer with cumulative FA exp. was found.

Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles

Flag: Critical study for SIDS endpoint

26-FEB-1998 (461)

Remark: Extended cohort study of mortality and incidence in 14,017 Fa industry workers followed up to 1989 in 6 plants, 7,660 employed before 1965 and 6,357 first employed after 1964. There was one death from nasal cancer vs. 1.74 expect. in the low exp. category (0.1 -0.5 ppm). There were no deaths from NPC (vs. 1.3 expect.). There was a slight non-significant excess risk of oral/pharyngeal cancer (SMR=110, 95 % CI: 59-189), 21 brain cancer deaths vs. 23 expect., and 19 leukemia deaths vs. 21.2 expect.. For lung cancer a slight siginficant SMR of 112 (95 % CI: 100-124) were seen for workers employed before 1965, while the slight excess in SMR (113, 95 % CI: 85-147) in workers employed after 1964 was not statistically significant.

Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
Flag: Critical study for SIDS endpoint
14-NOV-2000 (5) (242)

Remark: Meta-analysis of epidemiologic studies on FA exp. and respiratory cancer did not indicate an excess risk or an exposure-response gradient forlung cancer. An exposure-response gradient was seen for both sinonasal and nasopharyngeal cancers.

Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
26-FEB-1998 (535)

Remark: A mortality study in a subcohort of 3,929 workers in an automotive iron foundry with exp. to FA found no relation to cancer risk. There were no deaths reported from nasal cancer, and one death from NPC in a non-exp. worker.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
Flag: Critical study for SIDS endpoint
26-FEB-1998 (25) (26)

Remark: An updated historical cohort mortality study in 7,359 chemical plant workers exp. to FA, particulates froms resins and moulding compounds and pigements (not speciefied) was performed. Long-term workers showed a generally similar to more favourable mortality than that of the general public.

For several causes including lung cancer, death rates among short-term workers were significantly increased. Overall and in the separate time periods of hire, consistently higher percentages of long-term workers were ever exposed to pigment, FA and pigment, FA>=0.2 ppm, and FA>=0.7 ppm.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
Flag: Critical study for SIDS endpoint
20-NOV-2000 (460) (462)

Remark: A meta-analysis for formaldehyde exposure and upper respiratory tract cancers (lung, nose/nasal sinuses, and naspharynx. The analysis indicate that workers with formaldehyde exposure have essentially null findings for lung cancer and a slight deficit of sinonasal cancer. Naspharyngeal cancer rates were elevated moderately in a minority of studies. Most studies, however, did not find any nasopharyngeal cancers, and many failed to report their findings. After correcting for underreporting, a meta relative risk of 1.0 (95 % CI, 0.5 to 1.8) for cohort studies was found. Case-control studies had a meta relative risk of 1.3 (95 % CI, 0.9 to 2.1). The nasopharyngeal cancer case-control studies represented much lower and less certain exposures than the cohort studies.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
Flag: Critical study for SIDS endpoint
15-MAY-2003 (148)

Remark: Association of cancer mortality and wood dust exposure was investigated in 45,399 men enrolled in the American Cancer Society´s Cancer Prevention Study-II reported either employment in a wood-related occupation od exposure to wood dust. RR of lung cancer for FA exposure only was 0.93 (95 % CI 0.73-1.18) and for FA exposure and occupation 2.63 (95 % CI 1.25-5.51). Excess sino-nasal cancer was not observed, but the number of cases was small.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
04-MAY-2000 (623)

Remark: A nested case-control study was performed, in which cases of lung cancer and controls from a cohort of pulp and paper industry workers were selected. The study covered 79 cases of deaths from lung cancer and 237 controls. Smoking proved to be a significant causal factor responsible for the development of lung cancer in thecohort studied. Chemical factors specific to pulp and paper industry did not exert a significant effect on the risk of death from lung cancer.
Reliability: (4) not assignable
4.1; only abstract available
07-AUG-2001 (636)

Remark: Carcinogenicity - Cohort Studies-Professionals
Mortality study in 2,079 pathologists and 12,944 medical laboratory assistants studied from 1955 to 1973 (path.) and 1963 to 1973 (ass.). No deaths from nasal cancer, oral/pharyngeal cancer, NPC or brain cancer were reported. Lung cancer risk was low (path.: SMR=39, 95 %CI: 20-70; ass.: 59, 95 % CI: 30-100). Only cancer with increases risk was that of lymphoma and hematoma (SMR=200, 95 % CI: 86-394). Follow-up of the pathologists from 1974 through 1980 showed no deaths from nasal cancer, oral/pharyngeal cancer or NPC. Lung cancer deaths were still significantly low. There was an excess of brain cancer deaths (SMR=331, 95 %CI: 90-847). In contrast to the earlier report, there was no excess of deaths from lymphtic or hematopoetic cancers (9 vs. 11.7). A further follow-up reported no cases of nasal or nasopharyngeal cancer; and no cancer sites were observed to be significantly in excess of expected.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
09-AUG-2000 (289) (293) (294)

Remark: Association in 84 cases of lung cancer in Danish physicians were xamined compared to 252 controls. No lung cancer cases were found in pathologists, and the risk in other medical specialities did not differ significantly from the risk in general practitioners. The lung cancer risk associated with employment at some time during professional carrer was not increased either.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
27-MAR-1998 (360)

Remark: Proportional mortality study in 1,132 embalmers died between 1925 and 1980. No nasal cancers or NPC were reported. There were 8 deaths from oral and pharyngeal cancer compared with 7.1 expected (PMR=113, 95 % CI: 49-222).

For lung cancer, there were 72 deaths vs. 66.8 expected (PMR=108, 95 %CI: 85-136). There were 9 deaths from brain cancer compared with 5.8 expected (PMR=156, 95 % CI: 72-296); and 12 leukemia deaths compared with 8.5 expected (PMR=140, 95 % CI: 72-244). For colon cancer PMR was 143 (95 % CI: 96-205) and 221 for skin cancer (95 % CI: 95-435).

Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles

26-JUL-2002 (689)

Remark: Proportional mortality study in 1,007 embalmers started in 1925 and lasted through 1980. No nasal cancer deaths occured and no NPC deaths were reported. Eight oral and pharyngeal cancer deaths occured vs. 6.1 expected (PMR=131, 95 % CI: 56-258). There were 41 lung cancer deaths compared with 42.9 expected (PMR=96, 95 % CI: 69-130). Nine deaths from brain cancer were seen vs. 4.7 expected (PMR=194, 95 % CI: 89-368). Leukemia deaths were also greater than expected (12 observed vs. 6.9 expected, PMR=175, 95 % CI: 90-305).
PMR for colon cancer was significantly raised at PMR=187 (30 vs. 16.0 expected) and for prostate cancer at PMR=175 (23 vs. 13.1 expected).

Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles

27-FEB-1998 (688)

Remark: Retrospective cohort mortality study of 1,477 morticians examined for the period 1950 through 1977. There were no nasal or NPC deaths. One death from oral and pharyngeal cancer was observed vs. 2.1 expected. Nineteen lung cancer deaths were seen vs. 20.2 expected (SMR=94, 95 % CI: 57-147). Three brain cancer deaths were reported compared with 2.6 expected (SMR=115, 95 % CI: 23-336). For leukemia 8 deaths were reported vs. 6.5 expected (SMR=160, 95 % CI: 44-409). The most striking cause of deaths was cirrhosis of the liver (SMR=238, significantly increased, 18 deaths vs. 7.6 expected).

Reliability: (2) valid with restrictions
2.1; acceptables study, meets basic scientific principles

02-MAR-1998 (423)

Remark: Retrospective cohort mortality study of 2,317 anatomists. The mortality follow-up was for the period 1925 through 1979. Overall cancer mortality was remarkably low (SMR=64, 95 % CI: 53-76). There were no deaths from nasal cancer or NPC. There was only one death from all oral and pharyngeal cancers combined compared with 6.8 expected (SMR=20, 95 % CI: 0-80). For lung cancer 13 deaths were observed with 43.1 expected (SMR=30, 95 % CI: 10-50). Leukemia showed some increases with an SMR=150 (95 % CI: 70-270). One cancer site was significantly elevated indicating brain cancer with a SMR=270 (95 % CI: 130-500).

Reliability: (2) valid with restrictions
2.; acceptable study, meets basic scientific principles

Flag: Critical study for SIDS endpoint

02-MAR-1998 (626)

Remark: Proportional mortality study in 4,046 embalmers and funeral directors for the period 1975 to 1985. No nasal cancer

deaths were observed compared with 1.7 expected. Four NPC were seen vs. 1.85 expected (PMR=216, 95 % CI: 59-554). For oral and pharyngeal cancer deaths, 30 were seen vs. 25 expected (PMR=120, 95 % CI: 81-171). There was no excess of lung cancer deaths (308 vs. 324.5, PMR =95, 95 % CI: 85-106). For brain cancer deaths, 24 were observed vs. 19.4 expected (PMR=123, 95 % CI: 80-184). A significantly high proportion of lympathic and hematologic malignancies was reported (PMR=157, 95 % CI: 115-167), mostly as a result of an excess of deaths from myeloid leukemia (PMR=157, 95 % CI: 101-234) and "other and unspecified leukemias" (PMR=228, 95 % CI: 139-352).

Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles

Flag: Critical study for SIDS endpoint

02-MAR-1998 (301)

Remark: Retrospective cohort study of 6,411 pathologists followed for vital status from 1925 to 1978. The overlap between this study population and that of Logue et al. (1986) is unknown.

There were no nasal or NPC deaths reported. There were significantly fewer oral/pharyngeal cancer deaths than expected (13 vs. 25, SMR=52, 95 % CI: 28-89). Lung cancer occurrred at almost half the expected rate (77 vs. 137.5, SMR=56, 95 % CI: 44-70). A non-significant increase in brain cancer was seen (SMR=134, 95 % CI: 71-229). There were elevated but non-significant SMRs for some lymphatic-hematopoetic malignancies. SMR for hypopharyngeal cancer was elevated (not NPC) (3 vs. 0.64, SMR=470, 95 % CI: 97-1370). particularly since total oral/pharyngeal cancer deaths were significantly reduced (SMR=52, 95 % CI: 28-89).

Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles

Flag: Critical study for SIDS endpoint

14-NOV-2000 (468)

Remark: The risk for cancer morbidity in Denmark during 1970-84 was estimated from standardized proportionate incidence ratios (SPIR) among men whose longest employment had been held since 1964, at least 10 years before diagnosis, in 265 companies in which exposure to formaldehyde was identified. The results do not support the hypothesis that formaldehyde is associated with lung cancer (SPIR = 1.0, 410 cases). Significantly elevated risks were found for cancers of the colon (SPIR = 1.2, 166 cases), kidney (SPIR = 1.3, 60 cases), and sino-nasal cavities (SPIR = 2.3, 13 cases). For sino-nasal cancer, a relative risk of 3.0 (95 percent confidence interval = 1.4-5.7) was found among blue-collar workers with no probable exposure to wood dust, the major confounder.

Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles

Flag: Critical study for SIDS endpoint

02-OCT-2002 (292)

Remark: A meta-analysis 14 epidemilogy studies of workers exposed to formaldehyde where pancreatic cancer rates were reported was performed. A small increase of pancreatic cancer risk (mRR 1.1, 95% CI 1.0-1.3) was found. The increased risk was limited to embalmers, pathologists and anatomists. There was no increased risk among industrial workers (mRR 0.9, 95% CI 0.8-1.1), who on average had the highest formaldehyde exposures.
13-MAR-2001 (149)

Remark: Carcinogenicity - Case-control studies
Case-control study of cancer mortality among FA workers. Deaths from 1957 through 1979 were studied. 142 of 481 cancer deaths were among workers with potential exp. to FA. OR of cancer was not significantly greater than 1.0 (p>0.05). There were no nasal cancer deaths and no lung cancer excesses. Slightly but nonsignificant elevations were observed for prostatic and bladder cancer.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
02-OCT-2002 (221)

Remark: Hospital-based case-control study of cancers of the nasal cavity and paranasal sinuses (160 vs. 290 controls). OR=0.35 (95 % CI: 0.1-1.8) for ever exposed to FA.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
02-OCT-2002 (102)

Remark: Death certificate-based case-control study of lung and bladder cancer (598 and 287 cases, 1,758 controls). OR=1.5 (95 CI: 1.2-1.8) for lung and OR=1.0 (95 % CI: 0.7-1.3) for bladder cancer and ever exp., and OR= 0.9 (95 % CI: 0.6-1.4)
and lung and OR=1.5 (95 % CI: 0.9-2.5) and bladder cancer and heavy exposure.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
02-OCT-2002 (144)

Remark: Linked-registery study with controls on nasal and nasopharyngeal cancer (488 and 266 cases, 2,465 controls). OR=2.8 (95 % CI:1.8-4.3) for nasal and ever exp. in men, OR=2.8 (95 % CI: 0.5-14.3) for nasal and ever exp. in women,
OR=0.7 (95 % CI: 0.3-1.7) for nasopharyngeal and ever exp. in men,
OR=2.6 (95 % CI: 0.3-21.9) for nasopharyngeal and ever exp. in women,
OR=1.6 (95 % CI: 0.7-3.6) for nasal and exp. > 10 years previously (adjusted for wood dust).
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
02-OCT-2002 (528)

Remark: Linked-registry study with controls on nasal and nasopharyngeal cancer (488 and 266 cases, 2,465 controls). After adjustment for wood dust exposure a OR=2.3 (95 % CI: 0.9-5.8) for nasal squamous cell carcinoma and ever exp., OR=2.2 (95 % CI: 0.7-7.2) for nasal adenocarcinoma and ever

exposed to formaldehyde was observed. There was no association with histologically verified nasopharyngeal cancers. Exposure assessment was based on job description filed in a central population registry.

Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles

Flag: Critical study for SIDS endpoint

02-OCT-2002 (526)

Remark: Population-based study of nasal, nasopharyngeal and other pharynx cancers (53, 27, and 205 cases, 552 controls). OR=0.3 (95 % CI: 0-1.3) for nasal and medium or high occup. exp., OR=1.4 (95 % CI: 0.4-4.7) for nasopharynx and medium or high exp., OR=0.6 (95 % CI: 0.1-2.7) for other pharynx and medium or high exp., OR=0.6 (95 % CI: 0.2-1.7) for nasal and mobil home residence >10 years, OR=5.5 (95 % CI: 1.6-19.4) for nasopharynx and mobile home residence >10 years, and OR=0.8 (95 % CI: 0.2-2.7) for other pharynx and mobile home residence >1 years. No association were found between any of the cancers and a history of exposure to new constructions containing particleboard and plywood, or to urea-formaldehyde foam insulation. The association found with living in a mobile home is based on a small number of cases. Living is a mobil home is a poor proxy for exposure.

Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles

Flag: Critical study for SIDS endpoint

02-OCT-2002 (681)

Remark: Case-control study of nasal cancer (91 cases, 195 controls).
OR=2.5 (90 % CI: 1.2-5.0) for ever exp. low wood dust, and assessment A, and OR=1.6 (90 % CI: 0.9-2.8) for ever exp., low wood dust, and assessment B.

Reliability: (2) valid with restrictions
2.2; basic data given, restrictions

02-OCT-2002 (302)

Remark: Nested case-control study of lung cancer among among FA workers (308 cases, 2 x 308 controls). OR=0.62 (95 % CI: 0.29-1.34) for ever exp. workers.

Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles

Flag: Critical study for SIDS endpoint

14-NOV-2000 (84)

Remark: Case-control study of nasal and nasopharyngeal cancer (198 and 173 cases, 605 controls). OR=0.8 (95 % CI: 0.5-1.3) for nasal and probably exp., OR=1.0 (95 % CI: 0.6-1.7) for nasopharynx and probably exp., OR=1.5 (95 % CI: 0.6-3.9) for nasal and probably exp. to high levels >20 years before death, and OR=2.3 (95 % CI: 0.9-6.0) for nasopharynx and probablay exp. to high level >20 years before death. Exposure assessment, resp. classification of probalitiy and degree of exposure by an industrial hygienist, was based only on city directories and death certificates.

Reliability: (2) valid with restrictions
2.2; basic data given, restrictions

Flag: Critical study for SIDS endpoint

02-OCT-2002 (568)

Remark: Multiple site case-control study (3,726 cases, 533 controls) showed quite low exp. levels of FA. There was no persuasive evidence of an increased risk of any type of cancer.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
Flag: Critical study for SIDS endpoint
14-NOV-2000 (249)

Remark: Nested case-control study of nasal, oral/pharyngeal, larynx, and lung cancer among FA workers (1, 5, 12, and 118 cases, 408 controls). OR=0.69 (95 % CI: 0.21-2.24) of ever exp. and OR=0.89 (95 % CI: 0.26-3.00) of exp. with 10 years latency.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
02-OCT-2002 (534)

Remark: Population-based case-control study of laryngeal cancer (235 cases, 547 controls).
OR=1.0 (95 % CI: 0.6-1.7) for low,
OR=1.0 (95 % CI: 0.4-2.1) for medium, and OR=2.0 (95 % CI: 0.2-1.95) for high exposure.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
02-OCT-2002 (712)

Remark: Hospital-based case-control study of sinonasal cancer (207 cases, 409 controls).
OR=0.96 (95 % CI: 0.38-2.42) for
possible and
OR=0.68 (95 % CI: 0.27-1.75) for >20 years exposure.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles

Flag: Critical study for SIDS endpoint

02-OCT-2002 (437)

Remark: Nested case-control study of Hodgkin`s, Non-Hodgkin`s disease, and leukemias (4, 8, and 12 cases, 152 controls).
OR=2.27 (95 % CI: 0.64-7.98) for ever exposed.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
02-OCT-2002 (533)

Remark: Nested case-control study of lung cancer (220 cases, 2220 controls).
OR=1.31 (95 % CI: 0.83-2.07) for zero,
OR=0.95 (95 % CI: 0.57-1.57) for ten,
OR=0.85 (95 % CI: 0.50-1.45)
for 15, and OR=0.84 (95 % CI: 0.44-1.60) for 20 year lag period.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
Flag: Critical study for SIDS endpoint
02-OCT-2002 (27)

Remark: Population-based case-control study of nasopharyngeal cancer (NPC) (104 cases, 104 and 101 controls) in the

Philippines.
OR=2.7 (95 % CI: 1.1-6.6) for duration of exposure < 15 years and
OR=1.2 (95 % CI: 0.48-32) for duration >=15 years.
Risk factor information was obtained through personal interview and from job titles alone. Dust and exhaust exposure were also found to be significantly associated with NPC. The effect of dust exposure did not appear to be limited to exposure to wood dust. The observe positive association between fresh fish consumption and NPC, and the negative association between processed meat consumption and NPC is unclear. The reuslts of the study also suggest a potential influence on NPC of herbal medicine use and burning of anti-mosquito coils (compounds in the smoke not defined).

Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles

Flag: Critical study for SIDS endpoint

02-OCT-2002 (701)

Remark: Population-based case-control study of oral/pharyngeal cancer 86 cases, 373 controls).
OR=1.6 (95 % CI: 0.92-2.8) for ever exp. and
OR=1.8 (95 % CI: 0.6-5.5) for probable or definite exposure.

Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles

02-OCT-2002 (477)

Remark: Report of three cases of nasal melanoma. All three were ocupationally exp. to FA (FA spraying in a chicken farm, histological preparations with FA, handling or urea formaldehyde foam in construction building).

Reliability: (2) valid with restrictions
2.2; basic data given, restrictions

06-MAR-1998 (332)

Remark: As part of a case-control study of subjects with nasal and nasopharyngeal cancer, nine of fourteen cases of nasal and nasopharyngeal melanoma were interviewed. None reported knowledge of specific occupational exposure to FA.

Reliability: (2) valid with restrictions
2.2; basic data given, restrictions

03-MAR-1998 (262)

Remark: A population-based case-control study based on death certificates from 24 U.S. states was conducted to determine associtation of occupations/industries with pancreatic cancer. The case were 63,097 persons who died from pancreatic cancer occuring in the period 1984-1993. The controls were 252,386 persons who died from other causes. Occupational exposure to FA was associate with a moderately increased risk of pancreatic cancer, with ORs of 1.2 (95 % CI 1.1-1.3), 1.2 (95 % CI 1.1-1.3), 1.4 (95 % CI 1.2-1.6) for subjects with low, medium, and high probabilities of exposure and 1.2 (95 % CI 1.1-1.3), 1.2 (95 % CI 1.1-1.3), and 1.1 (95 % CI 1.0-1.3) for subjects with low, medium, and high intensity of exposure respectively.

Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles

04-MAY-2000 (383)

Remark: In a community-based case-referent study aetiological factors for squamous cell carcinoma of the oral cavity, pharynx, larynx, and oesophagus were investigated. 545 cases and 641 referents were interviewed about several lifestyle factors and a life history of occupations and work tasks.
The exposure to 17 specific agents were coded by an occupational hygienst. Exposure to wood dust was associated with a decreased risk of cancer at the studied sites. For formaldehyde no significantly increased risk was observed. The findings of an increased risk (OR=1.9, 95 % CI 0.99-3.63) of oesophageal cancer after exposure to formaldehyde give no strong evidence in the absence of a dose-response.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
Flag: Critical study for SIDS endpoint

02-OCT-2002 (288)

Remark: A population-based case-control study was undertaken to evaluate the risk of lung cancer associated with several occupational factors. Incident cases were 429 and controls 1,021. Exposure to formaldehyde was not associated with an increase risk for lung cancer. Occupational exposure was ascertained by questionnaire.
Reliability: (2) valid with restrictions
2.2; basic data given, restrictions
Flag: Critical study for SIDS endpoint
09-AUG-2001 (108)

Remark: A meta-analysis for formaldehyde exposure and upper respiratory tract cancers (lung, nose/nasal sinuses, and naspharynx. The analysis indicate that workers with formaldehyde exposure have essentially null findings for lung cancer and a slight deficit of sinonasal cancer. Naspharyngeal cancer rates were elevated moderately in a minority of studies. Most studies, however, did not find any nasopharyngeal cancers, and many failed to report theri findings. After correcting for underreporting, a meta relative risk of 1.0 (95 % CI, 0.5 to 1.8) for cohort studies was found. Case-control studies had a meta relative risk of 1.3 (95 % CI, 0.9 to 2.1). The nasopharyngeal cancer case-control studies represented much lower and less certain exposures than the cohort studies.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
Flag: Critical study for SIDS endpoint
26-JUL-2002 (147)

Remark: Reproductive Effects
The incidence of spontaneous abortion was studied among hospital staff in sterilizing units. The rate associated with FA, with or without other agents, was 8.4 %, which was comparable to the reference level of 10.5 %.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
09-AUG-2000 (313)

Remark: Record linkage study in nurses. 217 women treated for spontaneous abortion and 46 notified to the register of Congenital Malformations were matched on age and hospital with three controls. For exposure assessment head nurses were asked to ascetain the occupation of the nurses and whether they had been exposed to listed exposures (incl. anaestetic gases, sterilising agents, disinfectant soaps, cytostatic drugs, and x-ray radiation). No quantitative exposure assessment was done. Exp. to FA during pregnancy was reported for 3.7 % of the nurses who were later treated for abortion and for 5.2 % of their controls, yielding a crude odds ratio of 0.7 (95 % CI: 0.28-1.7) and for 8.8 % of the nurses who gave birth to a malformed child and for 5.3 % of the controls (OR=1.7, 95 % CI: 0.39-7.
Reliability: (2) valid with restrictions
2.1; acceptable study, meets basic scientific principles
Flag: Critical study for SIDS endpoint
31-JUL-2001 (314)

Remark: Retrospective case-control study of spontaneous malformations (206 cases, 329 controls) and congenital malformations among women working in laboratories (36 cases, 105 controls). Exposure to individual chemicals was assessed on the basis of self-reports and the description of the work task and the use of solvents. No quantitative measurements were done. Associations with spontaneous abortion were found for exposure to toluene (OR=4.7, 95 % CI: 1.4-15.9), xylene (OR= 3.1, 95 % CI: 1.3 to 7.5) and formaldehyde (OR=3.5, 95 % CI: 1.1-11) for spontaneous abortion. Most women exposed to formaldehyde and xylene were working in pathology or histology laboratories. No association was observed for congenital malformations. The results concerning individual chemicals are influenced the simultaneouse exposure to several solvents and chemicals in laboratory assistants.
Reliability: (2) valid with restrictions
2.2; basic data given, restrictions
Flag: Critical study for SIDS endpoint
31-JUL-2001 (642)

Remark: FA-based disinfection products use, number of hours worked per day in cosmetology, number of sevices performed per week, and work in salons where nail sculpering was performed by other employees was associated with an elevated risk for spontaneous abortion in 96 cosmetologists ranging from 1.4 to 2.0. Exposure assessment was done by categorizing the woman´s work status and self-reported work characteristics.
No quantitative measuements were peformed. Since cosmetology
involves exposure to chemical mixtures from multiple sources, it is difficult to identify effects associated with
specific agents.
Reliability: (2) valid with restrictions
2.2; basic data given, restrictions
Flag: Critical study for SIDS endpoint
31-JUL-2001 (364)

Remark: A nationwide data base of medically diagnosed spontaneous abortions and other pregnancies and national census data was used to evaluate the effect of men´s occupational exposure on risk of spontaneous abortion in 99,186 pregnancies in Finland. Census data from the years 1975 and 1980 provided information about ocupation, industry, and socioeconomic status. A job-exposure classification was developed to classify women and their husbands according to possible occupational exposures. Moderate or high exposure included jobs in which the level of exposure to mutagens was continously at least half of the htreshold limit value or higher or in which the exposure exceeded threshold limit values and the prevalence of exposure was high. Potential low exposure denoted either (a) jobs with low level but high prevalence of exposure to mutagens, (b) jobs which lacked industrial hygiene measurements but which were reported to the register or (c) jobs with a high level and unknown prevelence of exposure.
Adjusted odds ratio of spontaneous abortion for paternal exposure to low FA exposure was 1.1 (95 % CI 0.9-1.4) and 1.0 (95 % CI 0.8-1.4) for moderate or high FA exposure.
Reliability: (2) valid with restrictions
2.2; basic data given, restrictions
Flag: Critical study for SIDS endpoint
31-JUL-2001 (431)

Remark: Retrospective cohort study on time-to-pregnancy in female wood workers who had given birth during 1985-1995. 699 (64 %) of 1,094 workers participated in the study. Data on pregnancy history, time-to-pregnancy, occupational exposures, and potential confounders were collected by a questionnaire. An estimation of mean daily exposure during the time-to-pregancy was calculated on the bases of industrial hygiene measurements from the factory or other work places of the same industrial activity. Information on the exposure of the fathers was based on the reports of the women. Adjusted fecundability density ratio (FDR) for high exposure (mean=0.33 ppm) was 0.64, for medium exposure (mean=0.14 ppm) was 0.96, and for low exposure (mean=0.07 ppm) was 1.09, compared to an FDR for unexposed of 1.00. Other occupational exposures were not significantly associated with FDR. Additionally, an association was observed between exposure to formaldehyde and an increased risk of spontaneous abortion (concerning previous spontaneous abortion, reported by the women). OR for spontaneous abortion in 52 women having the same work place during the year of spontaneous abortion was 3.2 (95 % CI 1.2-8.3) in the high exposure, 1.8 (95 % CI 0.8-4.0) in the medium exposure, and 2.4 (95 % CI 1.2-4.8) in the low exposure category. Exposure to formaldehyde at the high level was also associated with an increased risk (OR 4.5, 95 % CI 1.0-20.0) of endometriosis.
Reliability: (2) valid with restrictions
2.2; basic data given, restrictions
Flag: Critical study for SIDS endpoint
30-AUG-2001 (643)

Remark: A population based epidemiological study was undertaken to assess the prenatal formaldehyde exposure effect on the incidence of low birth weight newborns in Kaunas area 1994.

244 cases of low birth weigth newborns were compared with 4,089 controls. The comparison involved questionnaire information on 26 potential risk factors. Adjustment for age, occupation, education, marital status, hypertonic disease, last pregnancy outcome, parents smoking, hazardous work, formaldehyde, ozone and total suspended particulate (TSP) decreased the formaldehyde effect, OR 1.44 (95 % CI=0.9-2.09), and ozone effect, OR 1.44 (95 % CI=0.47-4.41), and increased the TSP effect, OR 2.58 (95 % CI=1.34-4.99).
The TSP exposure had a statistically significant effect on low birth weight risk.

Reliability: (2) valid with restrictions
2.2, basic data given, restrictions

Flag: Critical study for SIDS endpoint

07-AUG-2001 (277)

5.11 Additional Remarks

Type: Biochemical or cellular interactions

Result: Endogenous formaldehyde
Formaldehyde (HCHO) is an essential intermediate in cellular metabolism, serving as a precursor for the biosynthesis of amino acids, purines, and thymine. Major sources of endogenous formaldehyde are glycine and serine, both of which are metabolized in the presence of tetrahydrofolic acid to N5,N10-methylene-tetrahydrofolate. This adduct is commonly denoted by the term, active formaldehyde, but this term is misleading, because it implies that formaldehyde not bound to tetrahydrofolate is inactive. In fact, formaldehyde not bound to tetrahydrofolate, which includes free (hydrated) formaldehyde, the hemithioacetal adduct of HCHO with glutathione (GSH), and adducts formed with other nucleophilic substituents, is highly reactive and rapidly metabolized. Therefore, it is appropriate to use the term, reactive formaldehyde, to denote formaldehyde existing in these other forms. Thus, although active formaldehyde is of vital importance to the biochemistry of formaldehyde, several of the adducts of reactive formaldehyde, such as DNA-protein cross-links (DPX), are of critical importance to the toxicology of HCHO.
Active formaldehyde is directly utilized for the biosyn-thesis of serine and thymine. By oxidation of active formaldehyde to active formate (N10-formyl-tetrahydrofolate), the carbon atom of HCHO can be incorporated into purines. Reduction of active formaldehyde to 5-methyl-tetrahydrofolate allows the carbon atom to be incorporated into methionine. Dehydration of serine yields pyruvate, which can be transaminated to alanine and eventually be incorporated into numerous other products. Serine is also a precursor of cysteine, tryptophan, and sphingolipids. Thus, the introduction of labeled formaldehyde molecules into the one-carbon pool results in the labeling of most major classes of macromolecules.

Reliability: (2) valid with restrictions

Flag: Critical study for SIDS endpoint

16-OCT-2000 (126) (509)

Type: Cytotoxicity

Remark: Cytotoxicity test in B6C3F1 mouse embryos:
treatment up to 120 h post fertilization, blastocyst development and hatching
significant effects in culture media with BSA at 1 mM, in culture media without BSA starting with 0.05 mM.

Reliability: (2) valid with restrictions

21-AUG-2001 (447)

Type: Metabolism

Result: Reactive formaldehyde can be introduced directly into cells and tissues by inhalation or oral routes. It can also be generated by the metabolism of certain xenobiotics or endogenous compounds, including the oxidative cleavage of N-, O- or S- methyl compounds catalyzed by cytochrome P450-dependent monooxygenases (Sipes and Gandolfi, 1986), the metabolism of dihalogenated methanes catalyzed by glutathione-S-transferase (Anders, 1982), the oxidative dehalogenation of monohalogenated methanes (Anders and Pohl, 1985), the oxidation of methanol catalyzed by alcohol dehydrogenase or the catalase-H2O2 system (Bosron and Li, 1980), and the oxidation and hydrolysis of certain secondary amines catalyzed by flavin-containing amine monooxygenase (Ziegler, 1980). Metabolism of reactive formaldehyde occurs by a variety of pathways, which are described later in this chapter.
The interactions among the various components of endogenous formaldehyde in vivo are not understood in detail, but it would be incorrect to regard active and reactive formaldehyde as separate entities. Reactive formaldehyde can also enter into the one-carbon pool via a direct reaction with tetrahydrofolate (Kallen and Jencks, 1966) or by oxidation to formate followed by incorporation of this molecule into the one-carbon pool. Conversely, active formaldehyde may dissociate to yield various forms of reactive formaldehyde. Thus, active and reactive formaldehyde do not in reality represent separate pools. The major difference between these two forms is the source of formaldehyde and the manner with which it is metabolized. Although active formaldehyde is the form that is utilized for one-carbon biosynthetic reactions, this form accounts for only a very small fraction of the total HCHO that is normally present in cells. The total concentration of a pool of folates in the livers of Sprague-Dawley rats including active formaldehyde and unsubstituted tetra- and dihydrofolates was 2.65 µM (Eto and Krumdieck, 1982). In contrast, the total concentration of formaldehyde, both free and reversibly bound, in freshly-collected and frozen livers of F344 rats was about 188 ± 30 µM (Heck et al., 1982). Thus, neglecting possible strain differences in folate or formaldehyde levels, it would appear that less than 2% of the formaldehyde in rat liver is in the form of active formaldehyde. The remaining > 98% of the formaldehyde

exists, therefore, in the various forms of reactive formaldehyde noted above.
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint

25-APR-2003 (19) (86) (219) (308) (374) (609) (726)

Type: Metabolism

Result: A substantial portion of the formaldehyde denoted as reactive is probably bound to GSH. The nonprotein sulfhydryl (mainly GSH) concentration in normal rat liver is approximately 5.5 6.5 mM (Chasseaud, 1976; Casanova and Heck, 1987), and the equilibrium dissociation constant of the formaldehyde adduct, S-hydroxymethylglutathione, is about 1.5 1.6 mM at 25°C (Uotila and Koivusalo, 1974a; Pourmotabbed et al., 1989). Therefore, the equilibrium concentration of S-hydroxymethylglutathione could be as high as 150 µM, or about 80% of the total formaldehyde in rat liver. The remaining HCHO (ca. 40 µM) may be either hydrated or bound to other nucleophiles.
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint

04-DEC-2002 (123) (139) (549) (673)

Type: Metabolism

Result: The total concentration of formaldehyde in freshly isolated nasal mucosal tissue of F344 rats, which is the primary target tissue for inhaled HCHO, is approximately 420 ± 90 µM (Heck et al., 1982), i.e., about twofold higher than in the liver. (The apparently higher concentration of HCHO in nasal tissue may be due in part to the glycogen content of liver, which imparts to hepatocytes a larger cellular weight and volume than are characteristic of nasal epithelial cells.) However, the GSH concentration in the nasal mucosa is about 3.0 mM, i.e., about half the liver value (Casanova and Heck, 1987). Therefore, the equilibrium concentration of S-hydroxymethylglutathione could be as high as 270 µM, or about 64% of the total formaldehyde. If the GSH concentration were depleted, one would expect an increase to occur in the amount of reactive HCHO bound to other molecules. When nasal GSH was depleted with phorone (Casanova and Heck, 1987) or acrolein (Lam et al., 1985), an increase was observed in the amount of inhaled HCHO covalently bound to nasal mucosal DNA.
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint

04-DEC-2002 (123) (308) (415)

Type: Metabolism

Result: Detoxication of inhaled formaldehyde occurs via folate-dependent incorporation into amino acids, purines, and thymidine, and by folate-independent pathways of oxidation to formate. The oxidation of formaldehyde is catalyzed by enzymes located in the cytosol and in mitochondria. In the cytosol, HCHO reacts with GSH forming the hemithioacetal adduct, S-hydroxymethylglutathione, which

is a substrate for the enzyme, formaldehyde dehydrogenase [formaldehyde:NAD+ oxidoreductase (glutathione-formylating), EC 1.2.1.1]. This enzyme catalyzes the oxidation of the adduct to a thiol ester of formic acid, S-formylglutathione (Uotila and Koivusalo, 1974a). The thiol ester is rapidly hydrolyzed to free formate by another cytosolic enzyme, S-formylglutathione hydrolase, which regenerates GSH (Uotila and Koivusalo, 1974b).

All animal tissues tested for formaldehyde dehydrogenase have contained the enzyme (Uotila and Koivusalo, 1983). In particular, formaldehyde dehydrogenase was detected in the respiratory and olfactory nasal mucosa of rats (Casanova-Schmitz et al., 1984a; Keller et al., 1990), the former being the primary target tissue for inhaled formaldehyde in this species. Formaldehyde dehydrogenase has recently been shown to be structurally identical to another enzyme, class III alcohol dehydrogenase, which catalyzes the oxidation of long-chain primary alcohols to aldehydes (Holmquist and Vallee, 1991; Kaiser et al., 1991; Danielsson and Jörnvall, 1992). The enzyme known as formaldehyde dehydrogenase appears, therefore, to have multiple functions.

Class III alcohol dehydrogenase differs from the more familiar class I alcohol dehydrogenase [alcohol:NAD+ oxidoreductase, EC 1.1.1.1] in having a low affinity for ethanol and in not being inhibited by 4-methylpyrazole. Class III alcohol dehydrogenase does not require GSH for the oxidation of primary alcohols, but a thiol group is essential for the oxidation of formaldehyde, presumably because the adduct, S-hydroxymethylglutathione, is structurally similar to a primary alcohol. Several thiols other than GSH can participate in the oxidation of formaldehyde at nearly the same rate as glutathione (Holmquist and Vallee, 1991), but aldehydes other than formaldehyde are not oxidized by the enzyme, presumably because the structures of their GSH adducts would resemble a secondary alcohol.

Owing to the identity of formaldehyde dehydrogenase and class III alcohol dehydrogenase, it cannot be concluded that the primary function of formaldehyde dehydrogenase in vivo is to catalyze the oxidation of formaldehyde to formate. It is likely, however, that formaldehyde dehydrogenase is involved in the detoxication of inhaled formaldehyde. Depletion of glutathione in the rat nasal mucosa, either by i.p. injection of phorone (Casanova and Heck, 1987) or by inhalation of acrolein (Lam et al., 1985), increased the quantity of DPX formed in this tissue relative to that in rats that had not been depleted of GSH. These results demonstrate that the amount of reactive HCHO had increased, despite the presence of other enzymes that are capable of metabolizing HCHO. However, in preparations from rat liver, phorone also inhibited a mitochondrial low-Km aldehyde dehydrogenase [aldehyde:NAD+ oxidoreductase, EC 1.2.1.3], which is also capable of oxidizing formaldehyde (Dicker and Cederbaum, 1985, 1986). Therefore, the effects of phorone on DPX formation in the nose may have been caused both by inhibition of the mitochondrial low-Km aldehyde dehydrogenase and by depletion of GSH.

An aldehyde dehydrogenase having a Km with respect to formaldehyde variously estimated as 0.19 mM (Heck and Casanova, 1987) or 0.4 0.6 mM (Casanova-Schmitz et al.,

1984a) was detected in crude homogenates of the rat nasal respiratory and olfactory mucosa. This enzyme might be the mitochondrial low-Km aldehyde dehydrogenase, because the Km of the mitochondrial enzyme with respect to HCHO in rat liver preparations was found in different assays to be 0.19 mM (Dicker and Cederbaum, 1984) or 0.38 mM (Cinti et al., 1976), values which are similar to the nasal mucosal estimates. Other investigators, using perhaps more highly purified preparations, reported a Km with respect to formaldehyde equal to 0.031 mM (Siew et al., 1976).

The Km of the mitochondrial aldehyde dehydrogenase with respect to formaldehyde measured in rat liver preparations (Siew et al., 1976; Cinti et al., 1976; Dicker and Cederbaum, 1984) is of the same order of magnitude as the concentration of formaldehyde measured in these tissues (see above; Heck et al., 1982).

A corollary of the Segel (1975) hypothesis is that the Km values of other enzymes that act on formaldehyde should be similar to that of the mitochondrial enzyme. This hypothesis appears to be inconsistent with the fact that the Km of formaldehyde dehydrogenase with respect to its substrate, S-hydroxymethylglutathione, (1 µM) (Uotila and Koivusalo, 1974a; Casanova-Schmitz et al., 1984a; Pourmotabbed et al., 1989) is about two orders of magnitude smaller than the estimated tissue concentration of the GSH adduct of formaldehyde (150 µM in rat liver (see above)). Therefore, formaldehyde dehydrogenase should be almost fully saturated with S-hydroxymethylglutathione, which appears to contradict the Segel (1975) hypothesis. However, the substrates for formaldehyde dehydrogenase include compounds other than S-hydroxymethylglutathione (Holmquist and Vallee, 1991; Kaiser et al., 1991; Danielsson and Jörnvall, 1992), and competition with other substrates in vivo may increase the effective Km of formaldehyde dehydrogenase with respect to S-hydroxymethylglutathione. In addition, the local concentration of S-hydroxymethylglutathione in the vicinity of the enzyme at a particular site, e.g., the nucleus (Keller et al., 1990), may be lower than the average concentration measured in a tissue homogenate.

In addition to the two (or possibly three (Tank et al., 1981)) isozymes of aldehyde dehydrogenase that are present in mitochondria, as many as five isozymes are thought to exist in rat liver cytosol and at least one isozyme is present in microsomes (Tank et al., 1981). The mitochondrial aldehyde dehydrogenases include both low- and high-Km forms, but only the low-Km form(s) can efficiently oxidize formaldehyde (Koivula and Koivusalo, 1975a; Siew et al., 1976; Lebsack et al., 1977). Formaldehyde is not considered to be a substrate for either cytosolic (Koivula and Koivusalo, 1975a) or microsomal (Koivula and Koivusalo, 1975b) aldehyde dehydrogenases, but at the relatively high concentrations of HCHO that may be present in the nasal mucosa during an inhalation exposure, these isozymes could also contribute to the oxidation of formaldehyde.

Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint

04-DEC-2002 (123) (126) (141) (171) (190) (191) (192) (305) (308) (327) (372) (381) (400) (401) (415) (417) (549) (605) (641) (673) (674) (675)

Type: Metabolism

Result: Formaldehyde can also be oxidized to formic acid by the peroxisomal enzyme, catalase. In this reaction, HCHO serves as a hydrogen donor for the decomposition of the catalase-hydrogen peroxide complex. Oxidation by catalase probably represents only a minor pathway for formaldehyde metabolism, due to the rate limiting generation of hydrogen peroxide (Waydhas et al., 1978). Hydrogen peroxide is also decomposed by the glutathione peroxidase system, which results in the depletion of GSH and the production of oxidized glutathione. When glutathione is depleted, hydrogen peroxide production is increased, which may increase the oxidation of formaldehyde by catalase (Jones et al., 1978).
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint

04-DEC-2002 (368) (695)

Type: Toxicokinetics

Result: The biological fate of inhaled formaldehyde was studied in Fischer 344 rats exposed to either 0.63 or 13.1 ppm of H14CHO for 6 hr (Heck et al., 1983). About 40% of the inhaled 14C was exhaled in the expired air as 14CO2 during the 70-hr postexposure period, 17% was excreted in the urine, 5% was eliminated in the feces, and 35-39% remained in the tissues and carcass, presumably as products of metabolic incorporation. Analysis of the residual radioactivity in the blood following inhalation of H14CHO showed that the profiles of total 14C in plasma and erythrocytes were virtually identical to those following i.v. injection of [14C]formate, suggesting that formaldehyde is rapidly oxidized to formate and incorporated into biological macromolecules. The characteristic pharmacokinetic profiles showed that the 14C atom had been incorporated into serum proteins and erythrocytes, which were subsequently released into the circulation (Heck et al., 1983). The tissue distribution of 14C in the rat is widespread throughout the organism and has been investigated using whole-body autoradiography (Chang et al., 1983).
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint

23-JUL-2002 (135) (307)

Type: Toxicokinetics

Result: The HCHO concentrations in the blood of F344 rats, rhesus monkeys, and adult humans were analyzed before, during, or immediately after an exposure to airborne HCHO to determine whether inhaled HCHO can be detected in the blood.

Exposure concentrations and times were 14.4 ppm, 2 hr (rats); 6 ppm, 6 hr/day, 5 days/week, 4 weeks (monkeys); and 1.9 ppm, 40 min (humans). Preexposure blood concentrations of endogenous formaldehyde were similar in the three species: 74.7 ± 0.2, 80.7 ± 0.3, and 87 ± 5 µM, respectively, and the blood concentrations were not increased significantly by exposure (Heck et al., 1985; Casanova et al., 1988).

Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint

04-DEC-2002 (125) (306)

Type: Toxicokinetics

Result: Despite the substantial quantities of endogenous HCHO normally present in tissues and fluids, it has been suggested that exposure of humans to low concentrations of HCHO may cause various forms of distant site toxicity, including hepatotoxicity, leukemia, or DNA-protein cross-link formation in peripheral lymphocytes (Beall and Ulsamer, 1984; Soffritti et al., 1989; Shaham et al., 1996).

These hypotheses have been disputed (Gibson, 1984; Feron et al., 1990; Casanova et al., 1996), and they are inconsistent with a number of studies including: (1) distant site toxicity associated with HCHO exposure has not been observed in at least four inhalation bioassays of formaldehyde (Kerns et al., 1983; Sellakumar et al., 1985; Woutersen et al., 1987; Appelman et al., 1988; Monticello, 1990); (2) formaldehyde concentrations in the blood of rats, monkeys, and humans were not increased by inhalation exposure (Heck et al., 1985; Casanova et al., 1988); (3) chromosomal aberrations in peripheral lymphocytes of rats were not induced by exposure to a high airborne concentration of HCHO (15 ppm; 6 hr/day, 5 days) (Kligerman et al., 1984), although chromosomal aberrations can be induced by HCHO in vitro (IARC, 1995, and chapter 4.7 of this report); (4) chronic administration to rats of very high doses of formaldehyde in the drinking water did not induce hepatotoxicity or cancer (Til et al., 1989); and (5) inhalation of formaldehyde did not cause DNA-protein cross-link formation in the rat bone marrow even under conditions of GSH depletion (Casanova-Schmitz et al., 1984b; Casanova and Heck, 1987). The localization of HCHO toxicity in the upper respiratory tract of rats and the absence of distant site toxicity are consistent with the high reactivity and rapid metabolism of inhaled formaldehyde.
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint

04-DEC-2002 (28) (56) (123) (124) (125) (126) (226) (252) (306) (346) (384) (397) (487) (599) (601) (616) (651) (713)

Type: other: Carcinogenicity (HMT)

Result: Rats were given 1% hexamethylenetetramine in the drinking water for 3 consecutive generation, up to the ages of 40 weeks in both the F1 and F2 generation and up to the age of 20 weeks of the F3 generation. The P, F1, F2, and F3 group consisted of 6 males and 12 females, 13 males and 7 females,15 males and 11 females, and 12 males and 12 females, respectively. Aditionally, a group of offsprings of parents treated with 2% of hexamethylenetetramine (16 males and 16 females) were treated with 2% of the test substance for 50 weeks. The control group consisted of 48 rats of each sex and remained untreated. All groups were observed for more than 2 years of age. According to the authors, no evidence of carcinogenicity due to the test substance was

observed.
Test substance: hexamethylenetetramine (HMT; in vivo release of formaldehyde); no data on purity of the compound
Reliability: (2) valid with restrictions

04-DEC-2002 (181) (182)

Type: other: Combination toxicity

Remark: Simultaneous inhalation exposure of Wistar rats to formaldehyde, acetaldehyde and acrolein for up to 3 days (Cassee et al, 1994, Cassee, 1995; Cassee et al, 1996) at concentrations representing individual NOAECs was not associated with a greater hazard than treatment with individual compounds. When rats were treated with 9 chemicals by inhalation and oral route (2 compounds inhaled: formaldehyde and dichloromethane; 7 compounds oral: cadmium and stannous chloride, loperamide, spermine, aspirin, DEHP and BHA) for 4 weeks, there was some increased incidence of transitional epithelial hyperplasia at the individual NOAEC of formaldehyde (1 ppm). Overall the authors conclude that simultaneous treatment with several different compounds at or below individual NOAELs does not constitute an evidently increased hazard (Groten et al, 1994; 1996; 1997).

04-DEC-2002 (127) (128) (129) (282) (283) (284)

Type: other: Developmental Toxicity/Teratogenicity (GF)

Result: The malformations experimentally induced by intramuscular injection of glycerol formal were studied. Ninety-three rats were divided into 12 groups. One group was administered saline ("negative control") and one group was administered 0.5 ml/kg/d (ca. 600 mg/kg/d; see Aliverti et al) on days 6 to 15 of gestation ("positive control"). The remaining 10 groups were injected 0.5 or 1.5 ml/kg/d (ca. 1800 mg/kg/d) on days 7 and 8, 9 and 10, 11 and 12, 13 and 14, or 15 and 16 of gestation, respectively. On day 21 of pregnancy, all rats were sacrificed; the fetuses were excised and examined for malformations. According to the authors, glycerol formal induced skeletal malformations in all groups treated with the test substance; visceral malformations and malformations of the great vessels were observed in the groups treated on days 10-11 and 12-13 of gestation.
Strain: Sprague-Dawley; Abstract only in Italian.
Test substance: glycerol formal(GF); no data on purity of the compound
Reliability: (2) valid with restrictions

30-JUN-1998 (251)

Type: other: Developmental Toxicity/Teratogenicity (GF)

Result: Doses: 300, 600, 1200 mg/kg/d (0.25, 0.5, 1)
Strain: Sprague-Dawley
The effects of glycerol formal on embryonal development was studied in groups of 10 rats. The test substance was administered from day 6 to 15 of pregnancy by i.m. injection; the rats were sacrificed on day 21 of pregnancy, the fetuses were examined for malformations. In treated rats, the number of absorptions and the number of dead fetuses was significantly increased; fetal weight was

significantly reduced. The number of gross visceral, and skeletal malformations was increased in treated rats showing a trend to dose-response. According to the authors, glycerol formal did not induce systemic toxicity in dams, but showed an embryotoxic and teratogenic activity.
Publication in Italian language, short abstract in English.
Test substance: glycerol formal (GF); no data on purity of the compound
Reliability: (2) valid with restrictions

19-JUN-1998 (15)

Type: other: Developmental Toxicity/Teratogenicity (GF)

Result: Doses: 600 mg/kg/d (0.5 ml/kg/d)
Strain: Rat Sprague-Dawley
The cardiovascular malformations experimentally induced by subcutaneous injection of glycerol formal were studied. The test substance was administered s.c.to 40 rats from day 6 to 15 of pregnancy; 20 control rats were treated with saline in the same manner. On day 21 of pregnancy, all rats were sacrificed; the fetuses (193 from treated rats, 119 from control rats) were removed and examined for visceral malformations.
About 40% of the fetuses of the treated group showed anomalies of the interventricular septum; this malformation was associated in nearly 50% of the cases with serious anatomic alterations of the main blood vessels departing from the heart. The anomalies of the interventricular septum were of different types and gravity. In most cases, these anomalies were located at the interventricular foramen (between the muscular septum and the endocardial cushions). Totally, 76/193 of the fetuses of treated dams had cardiovascular malformations.
Test substance: glycerol formal (GF); no data on purity of the compound
Reliability: (2) valid with restrictions

19-JUN-1998 (250)

Type: other: Developmental Toxicity/Teratogenicity (HMT)

Remark: Doses: 15, 31 mg/kg/d (600, 1250 ppm)
Result: The effects of hexamethylenetetramine (HMT), which releases formaldehyde in vivo, on reproduction was studied in 30 female dogs. The dogs were fed normal diet (control, 11 mated, 9 pregnant) or diet containing HMT (9 mated and 8 pregnant in the low dose group; 10 mated and 9 pregnant in the high dose group) on days 4 to 56 of pregnancy. On day 56, the dogs were transferred into a whelping room and were allowed to litter. The treatment did not affect the pregnancy rate, the weight gain of the pregnant dogs, the length of gestation or the size of the 28 litters (9, 8, and 8 litters in the control,low dose, and high dose group, respectively). Mean length of gestation was 65.8, 63.3, and 63.5 days in the untreated,low dose, and high dose group, respectively. The high dose led to a slight decrease of survival and growth of the pups. No malformations (either external of skeletal) were observed in the 150 live-born and 8 still-born pups (56, 48, and 46 live-born in the control, low dose, and high dose group, respectively; 4, 2, and 2 still-born pups in control, low, and high dose group, respectively).

Test substance: hexamethylenetetramine (HMT; in vivo release of formaldehyde); no data on purity of the compound
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint

19-JUN-1998 (109) (345)

Type: other: Multi Generation Carcinogenity (HMT)

Result: Rats were given 1% hexamethylenetetramine in the drinking water for 3 consecutive generation, up to the ages of 40 weeks in F1 and F2 generation and up to the age of 20 weeks of the F3 generation. The P, F1, F2, and F3 group consisted of 1 male and 2 females, 13 males and 7 females, 15 males and 11 females, and 12 males and 12 females, respectively.
Findings:
P: 10 pups per dam, 7f/13m
F1: 1 dam died during delivery, 36 pups out of 6 dams, 10 pups died during lactation period, surviving pups constituted F2
F2: 99 pups out of 11 dams, 12f and 12m constituted F3. No malformations or pathological findings.
Aditionally, a group of offsprings of 5 females treated with 2% of hexamethylenetetramine (16 males and 16 females) were treated with 2% of the test substance for 50 weeks and was observed up to week 130.
Findings:
49 pups out of 5 dams from which F1 was chosen. No abnormalities detected
Test substance: hexamethylenetetramine (HMT; in vivo formation of formaldehyde); no data on purity of the compound
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint

19-JUN-1998 (182)

Type: other: Repeated dose toxicity (HMT)

Remark: Species/Strain : Rat wistar
Sex: male/female
Route of admin.: oral feed
Exposure period: until natural death
Doses: 0.16 % hexamethylenetetramine in the diet
Control group: yes, concurrent no treatment
Result: Sixteen 2-month-old animals/sex were treated with hexamethylenetetramine in the diet which is converted to formaldehyde in vivo. Another 16 animals/sex were given normal diet (control). Voluntary muscular activity was determined after 11 days, 3, 7, and 14 months of treatment. According to the authors, the mean values for the voluntary activity were slightly decreased in the treated rats. However, considering the great individual variations, these differences were very small and they were not statistically significant.
These experiments were part of a fertility study.
Test substance: hexamethylenetetramine (HMT; in vivo formation of formaldehyde); no data on purity of the compound
Reliability: (2) valid with restrictions

10-AUG-1999 (506)

Type: other: Repeated dose toxicity (HMT)

Remark: Species/Strain : Rat wistar
Sex: male/female
Route of admin.: oral feed
Exposure period: until natural death
Doses: 0.16 % hexamethylenetetramine in the diet
Control group: yes, concurrent no treatment

Result: Twenty-four rats (12 males, 12 females) were offered both control diet (diet without any contaminant) and test diet (diet containing the test substance). The animals were allowed to choose their diet. The aim of the test was to evaluate whether the rats would avoid the food containing the test substance or not. Food consumption was recorded; the amounts of the test and control diet consumed over a 28-day period were calculated.
In the first part of the first 28-day trial, the rats ate more food containing the test substance, but in the latter part, the females, but not the males ate a little more of the control food. According to the authors, over the entire period, both sexes consumed little more test diet than control diet; however, the differences were negligible and not significant. The total amount of food eaten was fairly constant throughout the study; ca. 26 g/day for the males and ca. 18 g/day for the females.
These experiments were part of a fertility study.

Test substance: hexamethylenetetramine (HMT; in vivo formation of formaldehyde); no data on purity of the compound

Reliability: (2) valid with restrictions

19-JUN-1998 (506)

Type: other: Reproduction (HMT)

Result: Wistar rats 1% HMT in drinking water from 8 weeks of age to 20 weeks post partum (including pregnancy and lactation period of F1), 12 females and 6 males were used per group, treated group and control group). After 2 weeks of treatment, the rats were mated; the females were kept under treatment during pregnancy and lactation. Twelve treated and eleven controls became pregnant and gave birth to 124 and 118 pups, respectively. Out of these, 24 males and 24 females were treated with the test substance up to an age of 20 weeks, another 24/sex were used as untreated controls. At the end of treatment, the groups were sacrificed and examined macroscopically and histopathologically.
According to the authors, no adverse effects were observed when the rats were treated with hexamethylenetetramine which is formaldehyde releaser in vivo. No malformations were observed in the offsprings. The body weights of treated animals was significantly reduced compared to controls. In offsprings, this finding was recorded up to the 9th and 13th week of age in males and females, respectively.
Original in Italian with English abstract.

Test substance: hexamethylenetetramine (HMT; in vivo formation of formaldehyde); no data on purity of the compound

Reliability: (2) valid with restrictions

Flag: Critical study for SIDS endpoint

30-JUN-1998 (182) (351)

Type: other: Reproduction (HMT)

Result: Sixteen 2-month-old animals/sex were treated with 0.16% hexamethylenetetramine in the diet which is a formaldehyde releaser in vivo. Another 16 animals/sex were given normal diet (control). After 3 months of treatment (at the age of 5 months), females were mated with males of the same group and the numbers of offspring were recorded. In both, the test group and the control group, 16 males and 16 females of this F1 generation were fed the same diet as the parents from weaning onwards. They were weighed at the age of 7 and 15 weeks. At the age of 123 days, half of these rats were sacrificed and autopsied; livers, kidneys, adrenals, and gonads were weighed.
No significant differences in body weights and relative organ weights was observed between treated and untreated animals of both parents and offsprings. The post-mortem examinations revealed no signs of any disease attributable to the test substance. No significant differences in fertiliy were found in both parents and offsprings.

Test substance: hexamethylenetetramine (HMT; in vivo release of formaldehyde); no data on purity of the compound

Reliability: (2) valid with restrictions

Flag: Critical study for SIDS endpoint

24-JUL-2002 (109) (351) (506)

Type: other: Reviews

Reliability: (2) valid with restrictions

Flag: Critical study for SIDS endpoint

10-SEP-2001 (109) (346) (351)

6.1 Analytical Methods

6.2 Detection and Identification

7.1 Function

7.2 Effects on Organisms to be Controlled

7.3 Organisms to be Protected

7.4 User

7.5 Resistance

8.1 Methods Handling and Storing

Safe Handling: Ensure thorough ventilation of stores and work areas. Handle in accordance with good industrial hygiene and safety practice.

Fire/Exp. Prot.: Take precautionary measures against static discharges. Vapours may form explosive mixture with air. Keep away from sources of ignition - No smoking.

Storage Req.: Storage temperature: 55°C

Remark: PERSONAL PROTECTIVE EQUIPMENT

Respiratory protection:
Suitable respiratory protection for lower concentrations or short-term effect: Suitable respiratory protection for higher concentrations or Iong-term effect: Gas filter EN 141 Type B for gases/vapours of inorganic compounds.
Self-contained breathing apparatus.

Hand protection:
Chemical resistant protective gloves (EN 374)
Suitable materials also with prolonged, direct contact (Recommended: Protective index 6, corresponding > 480 minutes of permeation time according to EN 374):
butyl rubber (butyl) - 0.7 mm coating thickness
nitrile rubber (NBR) - 0.4 mm coating thickness

Eye protection:
Tightly fitting safety goggles (splash goggles) (EN 166)

Body protection:
chemical-protection suit (according to DIN-EN 465)

General safety and hygiene measures:
Take off immediately all contaminated clothes.

TRANSPORT INFORMATION

Land transport

ADR	Class	8
	Packaging group	III
	Substance no.	2209
	Designition of goods	FORMALDEHYDE SOLUTION
RID	Class	8
	Packaging group	III
	Substance no.	2209
	Designition of goods	FORMALDEHYDE SOLUTION

Inland waterway transport

ADNR	Class	8
	Item/Letter	63c)
	Packaging group	III
	Substance no.	2209

	Designition of goods	FORMALDEHYDE SOLUTION
Sea transport		
IMDG/	Class	8
GGVSee	Packaging group	III
	UN-number	2209
	Marine pollutant	NO
	Exact technical name	FORMALDEHYDE SOLUTION
Air transport		
ICAO/	Class	8
IATA	Packaging group	III
	UN-number	2209
	Exact technical name	FORMALDEHYDE SOLUTI

Refers to 49 - 49.3 % aqueous solution of formaldehyde
Flag: non confidential, Critical study for SIDS endpoint
15-MAY-2003 (42)

8.2 Fire Guidance

Ext. Medium: water, foam

Remark: Refers to 49 - 49.3 % aqueous solution of formaldehyde.
Flag: non confidential, Critical study for SIDS endpoint
23-DEC-2002 (42)

8.3 Emergency Measures

Type: other: general advice

Remark: Immediately remove contaminated clothing. If danger of loss of consciousness, place patient in recovery position and transport accordingly. Apply arificial respiration if necessary. First aid personel should pay attention to their own safety.

Refers to 49 - 49.3 % aqueous solution of formaldehyde
Flag: non confidential, Critical study for SIDS endpoint
23-DEC-2002 (42)

Type: injury to persons (skin)

Remark: Immediately wash thoroughly with plenty of water, apply sterile dressings, consult a skin specialist.

Refers to 49 - 49.3 % aqueous solution of formaldehyde
Flag: non confidential, Critical study for SIDS endpoint
23-DEC-2002 (42)

Type: injury to persons (eye)

Remark: Immediately wash affected eyes for at least 15 minutes under running water with eyelids held open, consult an eye specialist.

Refers to 49 - 49.3 % aqueous solution of formaldehyde
Flag: non confidential, Critical study for SIDS endpoint
23-DEC-2002 (42)

Type: injury to persons (oral)

Remark: Rinse mouth immediately and then drink plenty of water, seek medical attention.

Refers to 49 - 49.3 % aqueous solution of formaldehyde
Flag: non confidential, Critical study for SIDS endpoint
23-DEC-2002 (42)

Type: injury to persons (inhalation)

Remark: Keep patient calm, remove to fresh air, seek medical attention. Inhale corticosteroid dose aerosol (e.g. dexamethazone).

Refers to 49 - 49.3 % aqueous solution of formaldehyde
Flag: non confidential, Critical study for SIDS endpoint
23-DEC-2002 (42)

Type: accidental spillage

Remark: Methods for cleaning up or taking up:
For small amounts: Sweep/shovel up. Pick up with suitable absorbent material (e.g. sand, sawdust, general-purpose binder, kieselguhr).
For large amounts: Sweep/shovel up. Pick up with suitable absorbent material (e.g. sand, sawdust, general-purpose binder, kieselguhr).

Refers to 49 - 49.3 % aqueous solution of formaldehyde
Flag: non confidential, Critical study for SIDS endpoint
23-DEC-2002 (42)

8.4 Possib. of Rendering Subst. Harmless

8.5 Waste Management

Memo: Possibility of destruction: water purification

Remark: H2O2 and lime water (Ca(OH)2 in water) or sodium hydroxide solution.
Flag: non confidential, Critical study for SIDS endpoint

23-DEC-2002 (132)

Memo: other: incinerate in suitable incineration plant, observing local authority regulations

Remark: Refers to 49 - 49.3 % aqueous solution of formaldehyde.
Flag: non confidential, Critical study for SIDS endpoint
23-DEC-2002 (42)

8.6 Side-effects Detection

8.7 Substance Registered as Dangerous for Ground Water

8.8 Reactivity Towards Container Material

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10.1 End Point Summary

10.2 Hazard Summary

10.3 Risk Assessment

09-AUG-2000

OSHA comments from the January 19, 1989 Final Rule on Air Contaminants Project extracted from 54FR2332 et. seq. This rule was remanded by the U.S. Circuit Court of Appeals and the limits are not currently in force.

201-16190B

2007 MAR 29 RECEIVED OPPT CBIC

ETHANOLAMINE

CAS: 141-43-5; Chemical Formula: $NH_2CH_2CH_2OH$

OSHA formerly had an 8-hour TWA limit of 3 ppm for ethanolamine. The ACGIH has the same TWA limit, along with a 15-minute STEL of 6 ppm. OSHA proposed to retain the 8-hour TWA PEL of 3 ppm and to supplement this limit with a 6-ppm STEL; NIOSH (Ex. 8-47, Table N1) concurred with the proposed limits, and the final rule establishes them. Ethanolamine is a colorless liquid with a mild smell like that of ammonia.

The health hazards associated with exposures to ethanolamine include irritation and necrosis of the skin and central nervous system depression. The oral LD(50) in rats is reported as 3.32 g/kg, and the intraperitoneal LD(50) in rats is 981 mg/kg (Hartung and Cornish 1968/Ex. 1-328). The dermal toxicity of ethanolamine is considerably higher, with an LD(50) of 1 mg/kg reported in the rabbit. Dermal application of the undiluted liquid also caused redness, swelling, and burns comparable to mild first-degree burns (Union Carbide Corporation, as cited in ACGIH 1986/Ex. 1-3, p. 235). The eye injury potential of ethanolamine is just slightly less than that of undiluted ammonia (Carpenter and Smyth 1946/Ex. 1-859). Rats fed 0.5 percent (320 mg/kg/day) ethanolamine in their food for 90 days (Smyth, Carpenter, and Weil 1951/Ex. 1-439) showed no adverse effects, but at 1.28 g/kg/day, fatalities occurred. Treon, Cleveland, Stemmer, and associates (1957/Ex. 1-1172) reported lung, liver, and kidney damage in various species exposed to high concentrations of the vapor and mist. In tests of various species, Weeks and co-workers (1960/Ex. 1-941) reported marked dermal effects from continuous exposures (24 hours/day, seven days/week, for from 24 to 90 days) at various concentrations of the vapor; at 12 to 26 ppm, dermal effects were less severe, but at 5 ppm, skin irritation was still evident. After 90 days of exposure to 5 ppm, dogs also experienced a slight and temporary weight loss as well as decreased activity and alertness (Weeks, Downing, Musselman et al. 1960/Ex. 1-941). Luck and Wilcox (1953/Ex. 1-917) demonstrated that a portion of low doses of ethanolamine is not excreted and is presumably retained in the body of cats, rats, and rabbits.

In studies of anesthetized dogs, Priddle (1954, as cited in ACGIH 1986/Ex. 1-3, p. 235) reported that sublethal doses of ethanolamine cause central nervous system stimulation, while lethal doses cause CNS depression. Ethanolamine's irritant and necrotic effects on the skin are not related to its alkalinity (Hinglais 1947/Ex. 1-909). OSHA received no comments, other than the one by NIOSH (Ex. 8-47), on this substance.

In the final rule, OSHA is establishing a PEL of 3 ppm as an 8-hour TWA and a 15-minute STEL of 6 ppm for ethanolamine. The Agency concludes that both of these limits are required to protect workers against the significant risk of irritation and neuropathic effects, which constitute material health impairments that are potentially associated with exposure to ethanolamine at levels permitted above the 8-hour TWA limit. The Agency has determined that these limits will substantially reduce this significant risk.

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ETHANOLAMINE **ICSC: 0152**

Date of Peer Review: October 2002

2-Hydroxyethylamine
2-Aminoethanol

201-16190C

CAS #	141-43-5	C_2H_7NO / $H_2NCH_2CH_2OH$
RTECS #	KJ5775000	Molecular mass: 61.1
UN #	2491	
EC #	603-030-00-8	

TYPES OF HAZARD / EXPOSURE	ACUTE HAZARDS / SYMPTOMS	PREVENTION	FIRST AID / FIRE FIGHTING
FIRE	Combustible. Gives off irritating or toxic fumes (or gases) in a fire.	NO open flames.	Powder, alcohol-resistant foam, water spray, carbon dioxide.
EXPLOSION	Above 85°C explosive vapour/air mixtures may be formed.	Above 85°C use a closed system, ventilation.	
EXPOSURE		**STRICT HYGIENE! PREVENT GENERATION OF MISTS!**	
Inhalation	Cough. Headache. Shortness of breath. Sore throat.	Ventilation, local exhaust, or breathing protection.	Fresh air, rest. Refer for medical attention.
Skin	Redness. Pain. Skin burns.	Protective gloves. Protective clothing.	Remove contaminated clothes. Rinse skin with plenty of water or shower. Refer for medical attention.
Eyes	Redness. Pain. Severe deep burns.	Face shield, or eye protection in combination with breathing protection.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion	Abdominal pain. Burning sensation. Shock or collapse.	Do not eat, drink, or smoke during work.	Rinse mouth. Give plenty of water to drink. Do NOT induce vomiting. Refer for medical attention.

SPILLAGE DISPOSAL	PACKAGING & LABELLING
Collect leaking liquid in sealable containers. Cautiously neutralize spilled liquid. Then wash away with plenty of water. (Extra personal protection: filter respirator for organic gases and vapours.)	Do not transport with food and feedstuffs. **EU Classification** Symbol: Xn R: 20-36/37/38 S: (2) **UN Classification** UN Hazard Class: 8 UN Pack Group: III
EMERGENCY RESPONSE	**STORAGE**

Transport Emergency Card: TEC (R)-80GC7-II+III NFPA Code: H3; F2; R0	Separated from strong oxidants, strong acids, aluminium, food and feedstuffs. Dry. Ventilation along the floor.

IPCS
International Programme on Chemical Safety

UNEP

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SEE IMPORTANT INFORMATION ON BACK

ETHANOLAMINE — ICSC: 0152

IMPORTANT DATA

PHYSICAL STATE; APPEARANCE:
COLOURLESS, VISCOUS, HYGROSCOPIC LIQUID, WITH CHARACTERISTIC ODOUR.

CHEMICAL DANGERS:
The substance decomposes on heating and on burning producing toxic and corrosive gases including nitrogen oxides. The substance is a medium strong base. Reacts with cellulose nitrate causing fire and explosion hazard. Reacts violently with strong acids and strong oxidants. Attacks copper, aluminium and their alloys, and rubber.

OCCUPATIONAL EXPOSURE LIMITS:
TLV: as TWA 3 ppm; as STEL 6 ppm (ACGIH 2002).
MAK: 2 ppm 5.1 mg/m³ Sh; Peak limitation category: I (2); MAK: class Pregnancy risk group: C (2002)

ROUTES OF EXPOSURE:
The substance can be absorbed into the body by inhalation, by ingestion and through the skin.

INHALATION RISK:
A harmful contamination of the air will be reached rather slowly on evaporation of this substance at 20° C; on spraying or dispersing, however, much faster.

EFFECTS OF SHORT-TERM EXPOSURE:
The substance is corrosive to the respiratory tract, the skin and the eyes. Corrosive on ingestion. The vapour is irritating to the eyes, the skin and the respiratory tract. The substance may cause effects on the central nervous system. Exposure could cause lowering of consciousness.

EFFECTS OF LONG-TERM OR REPEATED EXPOSURE:
Repeated or prolonged contact may cause skin sensitization.

PHYSICAL PROPERTIES

Boiling point: 171°C
Melting point: 10°C
Relative density (water = 1): 1.02
Solubility in water: very good
Vapour pressure, Pa at 20°C: 53
Relative vapour density (air = 1): 2.1

Relative density of the vapour/air-mixture at 20°C (air = 1): 1.00
Flash point: 85°C c.c.
Auto-ignition temperature: 410°C
Explosive limits, vol% in air: 5.5-17
Octanol/water partition coefficient as log Pow: -1.31 (estimated)

ENVIRONMENTAL DATA

NOTES

Depending on the degree of exposure, periodic medical examination is indicated. The odour warning when the exposure limit value is exceeded is insufficient. Do NOT take working clothes home.

ADDITIONAL INFORMATION

LEGAL NOTICE Neither the CEC nor the IPCS nor any person acting on behalf of the CEC or the IPCS is responsible for the use which might be made of this information

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See Also:

Ethanolamine (CHEMINFO)

Chemical Sampling Information Ethanolamine

Chemical Sampling Information - Table of Contents

Field Definitions

Analytical Methods

General Description

NAME: Ethanolamine

SYNONYM(s): Ethylolamine; Monoethanolamine; beta-Aminoethyl alcohol; 2-Aminoethanol; 2-Hydroxyethylamine

IMIS: 1030

CAS: 141-43-5

NIOSH: RTECS KJ5775000; 34181

DOT: UN2491 Corrosive Material

DESCRIPTION:

Colorless liquid with a mild ammonia-like odor
MW: 61.08
BP: 338 F
VP: <1 mm
MP: 51 F
MOLFM: C2H7NO

INCOM: Strong oxidizers and acids

Exposure Limits

OSHA GENERAL INDUSTRY PEL: 3 ppm, 6 mg/m3

OSHA CONSTRUCTION INDUSTRY PEL: 3 ppm, 6 mg/m3 TWA

ACGIH TLV: 3 ppm, 7.5 mg/m3 TWA; 6 ppm, 15 mg/m3 STEL

NIOSH REL: 3 ppm TWA, 6 ppm STEL

Health Factors

SYMPTOM(s): Respiratory system, skin, and eye irritation; lethargy

HEALTH EFFECTS: Irritation-Eye, Nose, Throat, Skin---Marked (HE14) Cumulative liver, lung and kidney damage (HE3) Narcosis (HE8)

ORGAN: Skin, eyes, respiratory system

NIOSH/OSHA/DOE Health Guideline

Monitoring

PRIMARY SAMPLING/ANALYTICAL METHOD (SLC1):

MEDIA: Coated XAD-2 Tube (80/40 sections, 20/60 mesh); coating is 10% (w/w) 1-Naphthylisothiocyanate (NITC)
ANL SOLVENT: Dimethylformamide
MAX V: 10 Liters **MAX F:** 0.1 L/min (TWA)
MAX V: 1.5 Liters **MAX F:** 0.1 L/min (STEL) ANL: High Performance Liquid Chromatography; HPLC/UV
REF: 2 (OSHA In-house File)
CLASS: Partially Validated

ART: 1) Bouyoucos, Spiros A.; Melcher, Richard G. "Am. Ind. Hyg. Assoc. J." 1986, 47(3), 185-186. Collection of Ethanolamines in Air and Determination by Mobile Phase Ion Chromatography 2) Languardt, Patrick W.; Melcher, Richard G. "Analytical Chemistry" 1980, 52, 664-6 Determination of Ethanol- and Isopropanolamines in Air at Parts per Billion Level. ...Collection: Alumina Tubes (400/200 mg Sections) ...Air Volume: 30 Liters Flow rate: 0.1 L/min ...Analysis: Desorbed with water in article #1 and an aqueous 1-octanesulfonic acid solution in #2. Analysis by IC in article #1 and GC/FID after derivatization with HFBI in article #2 ...Keywords: Isopropanol amines

COND: Column: CN Mobile Phase: 80:20 Isooctane:Isopropanol Detector Wavelength: 254 or 280nm Detection Limit: 8.1 ng/inj

SECONDARY SAMPLING/ANALYTICAL METHOD (SAM2):

MIRAN 1A & 1B: MIN. Det. Con. 2.9 ppm at 13.0 um

Chemical Sampling Information - Table of Contents

Revision Date: 08/24/1992

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3.3 HUMAN HEALTH AND ECOLOGICAL HAZARDS SUMMARY

This section presents a summary of the human health and ecological hazards data that were used in the risk characterization.[8] This information is summarized from toxicity profiles prepared for non-proprietary chemicals identified as constituents in the baths for the MHC technologies evaluated. Table 3.23 lists these chemicals and identifies the MHC process or processes in which these chemicals are used. The electroless copper process is the predominant method now used in MHC. Section 2.1.4 includes more detailed information on bath constituents and concentrations. Throughout this section, toxicity data for proprietary chemicals are not presented in order to protect proprietary chemical identities.

Table 3.23 Known Use Cluster Chemicals and Associated MHC Processes

Chemical List	Electroless Copper	Carbon	Conductive Ink	Conductive Polymer	Graphite	Non-Formaldehyde Electroless Copper	Organic-Palladium	Tin-Palladium
2-Ethoxyethanol	✔							
1,3-Benzenediol								✔
1H-Pyrrole				✔				
2-Butoxyethanol Acetate; Butylcellusolve Acetate			✔					
Ammonia					✔			
Ammonium Chloride	✔							
Benzotriazole	✔							
Boric Acid	✔							
Carbon Black		✔	✔					
Copper (I) Chloride; Copper	✔		✔					✔
Copper Sulfate; or Cupric Sulfate	✔	✔			✔	✔		✔
Diethylene Glycol n-Butyl Ether			✔					
Diethylene Glycol Ethyl Ether			✔					
Diethylene Glycol Methyl Ether			✔					
Dimethylaminoborane	✔							
Dimethylformamide	✔							
Ethanolamine; Monoethanolamine; 2-Aminoethanol	✔	✔			✔			✔
Ethylene Glycol	✔	✔						
Ethylenediaminetetraacetic Acid (EDTA)	✔							
Fluoroboric Acid; Sodium Bifluoride	✔							✔
Formaldehyde	✔							
Formic Acid	✔							

[8] Risk was not characterized for the conductive ink technology but human health and ecological hazards data are presented here.

Chemical List	Electroless Copper	Carbon	Conductive Ink	Conductive Polymer	Graphite	Non-Formaldehyde Electroless Copper	Organic-Palladium	Tin-Palladium
Graphite			✔		✔			
Hydrochloric Acid	✔					✔	✔	✔
Hydrogen Peroxide	✔					✔		✔
Hydroxyacetic Acid	✔							
Isophorone			✔					
Isopropyl Alcohol; 2-Propanol	✔					✔		✔
Lithium Hydroxide								✔
m-Nitrobenzene Sulfonic Acid; Sodium m-Nitrobenzenesulfonate	✔							
Magnesium Carbonate	✔							
Methanol	✔		✔					
p-Toluene Sulfonic Acid; Tosic Acid	✔							
Palladium	✔							✔
Palladium Chloride								✔
Peroxymonosulfuric Acid; Potassium Peroxymonosulfate	✔			✔	✔			
Phenol-Formaldehyde Copolymer			✔					
Phosphoric Acid				✔				✔
Potassium Bisulfate	✔							
Potassium Carbonate		✔			✔			✔
Potassium Cyanide	✔							
Potassium Hydroxide	✔	✔				✔		
Potassium Persulfate	✔					✔		
Potassium Sulfate	✔							
Potassium-Sodium Tartrate	✔							
Silver			✔					
Sodium Bisulfate	✔						✔	✔
Sodium Carbonate	✔			✔			✔	
Sodium Chloride								✔
Sodium Chlorite	✔					✔		
Sodium Cyanide	✔							
Sodium Hydroxide	✔			✔		✔		✔
Sodium Hypophosphite	✔						✔	
Sodium Persulfate		✔			✔		✔	✔
Sodium Sulfate	✔							
Stannous Chloride; Tin (II) Chloride	✔					✔		✔
Sulfuric Acid	✔	✔		✔	✔	✔		✔
Tartaric Acid	✔							
Triethanolamine; or 2,2',2" - Nitrilotris Ethanol	✔							✔

Chemical List	Electroless Copper	Carbon	Conductive Ink	Conductive Polymer	Graphite	Non-Formaldehyde Electroless Copper	Organic-Palladium	Tin-Palladium
Trisodium Citrate 5.5-Hydrate; Sodium Citrate							✔	
Vanillin								✔
Proprietary Chemicals (no. known for alternative)	12				5		1	5

3.3.1 Carcinogenicity

Table 3.24 summarizes the available information pertaining to carcinogenicity for the MHC chemicals, including classifications describing evidence of chemical carcinogenicity. Due to the large number of chemicals in commerce, including approximately 15,000 non-polymeric chemicals produced in significant amounts (i.e., > 10,000 lbs/year), many chemicals have not yet been tested or assigned carcinogenicity classifications. The classifications referenced in this risk assessment are defined below:

EPA Weight-of-Evidence Classification: In assessing the carcinogenic potential of a chemical, EPA classifies the chemical into one of the following groups, according to the weight-of-evidence from epidemiologic, animal and other supporting data, such as genotoxicity test results:

- Group A: Human Carcinogen (sufficient evidence of carcinogenicity in humans).
- Group B: Probable Human Carcinogen (B1 - limited evidence of carcinogenicity in humans; B2 - sufficient evidence of carcinogenicity in animals with inadequate or lack of evidence in humans).
- Group C: Possible Human Carcinogen (limited evidence of carcinogenicity in animals and inadequate or lack of human data).
- Group D: Not Classifiable as to Human Carcinogenicity (inadequate or no evidence).
- Group E: Evidence of Non-Carcinogenicity for Humans (no evidence of carcinogenicity in adequate studies).

EPA has proposed a revision of its guidelines that would eliminate the above discrete categories while providing a more descriptive classification.[9]

International Agency for Research on Cancer (IARC) Classification: This is a similar weight-of-evidence method for evaluating potential human carcinogenicity based on human data, animal data, and other supporting data. A summary of the IARC carcinogenicity classification system includes:

[9] The "Proposed Guidelines for Carcinogen Risk Assessment" (EPA, 1996a) propose use of weight-of-evidence descriptors, such as "Likely" or "Known," "Cannot be determined," and "Not likely," in combination with a hazard narrative, to characterize a chemical's human carcinogenic potential; rather than the classification system described above.

- Group 1: Carcinogenic to humans.
- Group 2A: Probably carcinogenic to humans.
- Group 2B: Possibly carcinogenic to humans.
- Group 3: Not classifiable as to human carcinogenicity.
- Group 4: Probably not carcinogenic to humans.

Both of these classification schemes represent judgements regarding the likelihood of human carcinogenicity. Table 3.24 lists all MHC chemicals which have been classified by EPA or IARC. The National Toxicology Program (NTP) is an additional source used to classify chemicals, but its classifications are based only on animal data from NTP studies.

Table 3.24 Available Carcinogenicity Information

Chemical Name[a]	Cancer Slope Factor $(mg/kg\text{-}day)^{-1}$	Comments/Classifications
Formaldehyde	0.046[b]	EPA Group B1 (EPA, 1995b)[c]; IARC Group 2A (IARC, 1995)[c]
Carbon Black	ND	IARC Group 2B (IARC, 1996)[d]
Dimethylformamide	ND	IARC Group 2B (IARC, 1989)[d]
1,3-Benzenediol	ND	IARC Group 3 (IARC, 1987)[e]
Hydrochloric Acid	ND	IARC Group 3 (HSDB, 1995)[e]
Hydrogen Peroxide	ND	IARC Group 3 (IARC, 1987)[e]
Copper (I) Chloride	ND	EPA Group D (EPA, 1995c)[f]
Copper (II) Chloride	ND	EPA Group D (EPA, 1995c)[f]
Palladium; Palladium Chloride	ND	No classification; rats developed respiratory tumors and leukemia at 5 ppm in water (Schroeder & Mitchener, 1971)
Sodium Sulfate	ND	No classification; "equivocal evidence" of tumorigenicity in mice (RTECS, 1995)
Triethanolamine; or 2,2',2"-Nitrilotris Ethanol	ND	No classification; equivocal carcinogenic evidence in animals (NTP, 1994)
Cyclic Ether[g]	not reported[h]	Possible/probable human carcinogen[i]
Alkyl Oxide[g]	not reported[h]	Probable human carcinogen[i]
Trisodium Acetate Amine B[j]	ND	Possible human carcinogen[i]

[a] Only those chemicals with available data or classifications are listed.
[b] Unit risk units were converted from $1.3 \times 10^{-5}\ \mu g/m^{3\ -1}$ to slope factor units of $(mg/kg\text{-}day)^{-1}$ using 20 m^3/day inhalation (breathing) rate and 70 kg body weight.
[c] EPA Group B: Probable Human Carcinogen (B1 - limited evidence of carcinogenicity in humans); IARC Group 2A: Possibly carcinogenic to humans.
[d] IARC Group 2B: Possibly carcinogenic to humans.
[e] IARC Group 3: Not classifiable as to human carcinogenicity.
[f] EPA Group D: Not classifiable as to human carcinogenicity (inadequate or no evidence).
[g] In graphite and electroless copper technologies.
[h] Cancer slope factors are available but not reported in order to protect proprietary chemical identities.
[I] Specific EPA and/or IARC groups not reported in order to protect proprietary chemical identities.
[j] In electroless copper technology.
ND: No Data. A cancer slope factor has not been determined for this chemical.

For carcinogenic effects, there is presumably no level of exposure that does not pose a small, but finite, probability of causing a response. This type of mechanism is referred to as "non-threshold." When the available data are sufficient for quantification, EPA develops an estimate of the chemical's carcinogenic potency expressed as a "slope factor." The slope factor (q_1*) is a measure of an individual's excess risk or increased likelihood of developing cancer if exposed to a chemical (expressed in units of [mg/kg-day]$^{-1}$). More specifically, q_1* is an approximation of the upper bound of the slope of the dose-response curve using the linearized multistage procedure at low doses. "Unit risk" is an equivalent measure of potency for air or drinking water concentrations and is expressed as the upper bound excess lifetime cancer risk per μg/m^3 in air, or as risk per μg/L in water, for continuous lifetime exposures. (Unit risk is simply a transformation of slope factor into the appropriate scale.) Slope factors and unit risks can be viewed as quantitatively derived judgements of the magnitude of carcinogenic effect. These estimates will continue to be used whether the current EPA weight-of-evidence guidelines are retained or the new proposals are adopted. Their derivation, however, may change for future evaluations.

EPA risk characterization methods require a slope factor or unit risk to quantify the upper bound excess cancer risk from exposure to a known or suspected carcinogen. Therefore, formaldehyde is the only non-proprietary chemical for which cancer risk was characterized (see Section 3.4, Risk Characterization).

3.3.2 Chronic Effects (Other than Carcinogenicity)

Adverse effects other than cancer and gene mutations are generally assumed to have a dose or exposure threshold. Therefore, a different approach is needed to evaluate toxic potency and risk for these "systemic effects." Systemic toxicity means an adverse effect on any organ system following absorption and distribution of a toxicant to a site in the body distant from the toxicant's entry point. A reference dose (RfD) is an estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure through ingestion to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious non-cancer effects during a lifetime (in mg/kg-day). Similarly, a reference concentration (RfC) is an estimate (with uncertainty spanning perhaps an order of magnitude) of the daily inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious non-cancer effects during a lifetime (in mg/m^3) (Barnes and Dourson, 1988). RfDs and RfCs can also be derived from developmental toxicity studies. However, this was not the case for any of the MHC chemicals evaluated. RfDs and RfCs are derived from EPA peer-reviewed study results (for values appearing in EPA's Integrated Risk Information System [IRIS]), together with uncertainty factors regarding their applicability to human populations. Table 3.25 presents a summary of the available RfC and RfD information obtained from IRIS and EPA's Health Effects Assessment Summary Tables (HEAST). One proprietary chemical, in the tin-palladium alternative, has an RfD available; this is not reported to protect the identity of the proprietary chemical.

Table 3.25 Summary of RfC and RfD Information

Chemical Name[a]	Inhalation RfC (mg/m^3)	Comments[c] (Inhalation)	Oral/Dermal RfD (mg/kg-day)	Comments[b] (Oral/Dermal)
2-Butoxyethanol Acetate	0.02	Rat, 13 weeks, hematological and liver effects (EPA, 1995d)[c, d]	ND	
2-Ethoxyethanol	0.2	Rabbit, 13 weeks, reduced spleen, testicular weights, and white blood cell counts (EPA, 1996b)	0.4	Gavage, rat and mouse, 103 weeks, reduced body weight, testicular degeneration, and enlargement of adrenal gland (EPA, 1995d)
Ammonia	0.1	Occupational study, lack of irritation to workers exposed to 9.2 ppm concentration (EPA, 1997)	ND	
Diethylene Glycol Ethyl Ether and Acetate	ND		2	Oral, rat, 3-generation study (chronic reproductive), kidney and bladder damage (EPA, 1995d)
Diethylene Glycol n-Butyl Ether	0.02	Inhalation, rat, 7 hours (EPA, 1995c,d)[d]	ND	
Dimethylformamide	0.03	Inhalation, human, 5+ years, 54 workers for hepatoxicity effects (EPA, 1996b)	ND	
Ethylene Glycol	ND		2	Oral, rat, 2 years, decreased growth, renal calculi (EPA, 1995c)
Formaldehyde	ND		0.2	Oral, rat, 2 years, GI tract and histopathological changes (EPA, 1995b)
Hydrochloric Acid	0.007	Rat, respiratory tract hyperplasia, lifetime exposure (EPA, 1995c)	ND	
Isophorone	ND		0.2	Oral, dog, 90 days, no signs of cellular changes (EPA, 1995d)
Methanol	ND		0.5	Gavage, rat, 90 days, decreased brain weights (EPA, 1995c)
Potassium Cyanide	ND		0.05	Oral, rat, 2 years, no treatment effects on weight gain (EPA, 1995c)
Silver	ND		0.005	Oral, human, 2 - 9.75 years, argyria of skin, eyes, mouth, and throat (EPA, 1996b)
Sodium Cyanide	ND		0.04	Oral, rat, 2 years (EPA, 1995c)

Chemical Name[a]	Inhalation RfC (mg/m^3)	Comments[c] (Inhalation)	Oral/Dermal RfD (mg/kg-day)	Comments[b] (Oral/Dermal)
Stannous Chloride	ND		0.62	Rat, 105 weeks (EPA, 1994a)[e]

[a] Only those chemicals with available data are listed. Proprietary chemical data are not presented in order to protect proprietary chemical identities.
[b] Comments may include exposure route, test animal, duration of test, effects, and source of data.
[c] Based on data for 2-butoxyethanol.
[d] Provisional RfC or RfD.
[e] Based on data for tin.
ND: No data. An RfD or RfC has not been determined for this chemical.

When an RfD or RfC was not available for a chemical, other toxicity values were used, preferably in the form of a no-observed-adverse-effect level (NOAEL) or lowest-observed-adverse-effect level (LOAEL). These toxicity values were obtained from the published scientific literature as well as unpublished data submitted to EPA on chemical toxicity in chronic or subchronic studies. Typically, the lowest NOAEL or LOAEL value from a well-conducted study was used. (If study details were not presented or the study did not appear to be valid, the reported NOAEL/LOAELs were not used.) But unlike the majority of RfD/RfCs, NOAEL/LOAELs have not received EPA peer-review of the studies on which the values are based, and uncertainty factors have not been considered.

The LOAEL is the lowest dose level in a toxicity test at which there are statistically or biologically significant increases in frequency or severity of adverse effects in the exposed population over its appropriate control group (in mg/kg-day, or mg/m^3 for inhalation). The NOAEL is the highest dose level in a toxicity test at which there is no statistically or biologically significant increase in the frequency or severity of adverse effects in the exposed population over its appropriate control (in mg/kg-day, or mg/m^3 for inhalation). LOAEL values are presented only where NOAELs were not available. Table 3.26 presents a summary of the available NOAEL and LOAEL values.

Table 3.26 NOAEL/LOAEL Values

Chemical Name[a]	Inhalation NOAEL/ LOAEL[b] (mg/m^3)	Comments (Inhalation)	Oral/Dermal NOAEL/ LOAEL[b] (mg/kg-day)	Comments (Oral/Dermal)
1,3-Benzenediol	ND		100 (N)[c]	Gavage, rat/mouse, 2 years (NTP, 1992)
Ammonium Chloride	ND		1,691 (N)	Oral, mouse, developmental study in drinking water (Shepard, 1986)
Benzotriazole	ND		109 (L)	Oral, rat, 26 weeks, induced anemia, endocrine effects (RTECS, 1995)
Boric Acid	ND		62.5 (L)	Gavage, rabbit, developmental study showed cardiovascular defects (U.S. Borax Co., 1992)

Chemical Name[a]	Inhalation NOAEL/ LOAEL[b] (mg/m^3)	Comments (Inhalation)	Oral/Dermal NOAEL/ LOAEL[b] (mg/kg-day)	Comments (Oral/Dermal)
Carbon Black	7.2 (L)	Human, 14 years, decrease in lung function: vital capacity (IARC, 1984)	ND	
Copper (I) Chloride	0.6 (L)	Human, dust caused leukocytosis/anemia, respiratory irritant (U.S. Air Force, 1990)	0.07 (L)	Oral, human, 1.5 years, GI tract effects (ATSDR, 1990a)
Diethylene Glycol Methyl Ether	ND		1,000 (N)	Oral, rat, 13 weeks, kidney damage, (HSDB, 1995)
Diethylene Glycol n-Butyl Ether	NA		191	Dermal, rat, 90 days, hemolytic effects (RM1, 1992)
Dimethylformamide	NA		125 (L)	Oral, rat, 100 days, liver weight increases and body weight gains (Trochimowicz et al., 1994)
Ethanolamine	12.7 (L)	Rat, dog, guinea pig, 90 days, skin irritation/ weight loss (ACGIH, 1991)	320 (N)	Oral, rat, 90 days, altered liver/kidney weights at higher concentrations (ACGIH, 1991)
Ethylene Glycol	31	Human, headache, respiratory tract irritation, lymphocytosis (ATSDR, 1993)	NA	
Fluoroboric Acid	ND		0.77	Human, 2 years, bone disease, GI problems & osteoarticular pain in women (HSDB, 1995; based on 50-100 mg/d, for fluorides, adjusted for 65 kg body weight)
Formaldehyde	0.1 ppm (L)	Human, eye and upper respiratory tract irritation (EPA, 1991c)[d]	NA	
Formic Acid	59.2 (N)	Rat/mouse, 2 weeks, respiratory epithelial lesions (Katz and Guest, 1994)	ND	
Graphite	56 (L)	Human effect level for pneumoconiosis, nuisance from dust (Pendergrass, 1983)	ND	

Chemical Name[a]	Inhalation NOAEL/ LOAEL[b] (mg/m^3)	Comments (Inhalation)	Oral/Dermal NOAEL/ LOAEL[b] (mg/kg-day)	Comments (Oral/Dermal)
Hydrogen Peroxide	79	Mouse, 7/9 died from 79 mg/m^3 in 6 weeks (EPA, 1988)	630 (N)	Oral, developmental and reproductive studies for 5 weeks (rat) and 3 months (mouse), respectively (IARC, 1985)
Hydroxyacetic Acid	ND		250 (N)	Gavage, developmental rat study showed lung noise, reduced weight gain (DuPont, 1995)
Isopropyl Alcohol, 2-Propanol	980 (N)	Rat, 13 weeks (SIDS, 1995)	100 (N)	Oral, rat, 2-generation study (CMA, 1995; RM2, 1996)
Magnesium Carbonate	Generally regarded as safe (U.S. FDA as cited in HSDB, 1995).			
Methanol	1,596 - 10,640 (1,200 - 8,000 ppm)	Human, 4 year occupational study, vapor caused vision loss (ACGIH, 1991)	NA	
Palladium, Palladium Chloride	ND		0.95 (L)	Oral, rat, 180 days, decreased weight (Schroeder & Mitchener, 1971)
Potassium Hydroxide	7.1	Human, caused cough/bronchial effects, severe eye/skin irritant (Graham et al., 1984)	ND	
Potassium Sodium Tartrate	Generally regarded as safe (U.S. FDA as cited in HSDB, 1996).			
Potassium Sulfate	15 (TC_{LO})[e]	Rat, 4 hr/d for 17 weeks, metabolic effects (RTECS, 1995)	ND	
Sodium Carbonate	10 (N)	Rat, 4 hr/d, 5 d/w for 3.5 months, decreased weight gain, lung effects (Pierce, 1994)	ND	
Sodium Chlorite	ND		10 (N)	Gavage, rat, 13 weeks, hematological effects (Harrington et al., 1995)
Sodium Hydroxide	2 (L)	Human, dyspnea, irritant (ACGIH, 1991)	ND	
Sodium Sulfate	ND		420 (N)	Oral, rat, 16 weeks (Young, 1992)
Sulfuric Acid	0.066 (N)	Human (EPA, 1994a)	ND	

Chemical Name[a]	Inhalation NOAEL/ LOAEL[b] (mg/m^3)	Comments (Inhalation)	Oral/Dermal NOAEL/ LOAEL[b] (mg/kg-day)	Comments (Oral/Dermal)
Tartaric Acid	ND		8.7	Oral, dog study, 3/4 developed casts (color or tint) in urine, weight changes and advanced renal tubular degeneration, at 990 g/kg for 90-114 days (Informatics, Inc., 1974)
Triethanolamine; or 2,2',2"-Nitrilotris Ethanol	ND		32 (L)	Dermal, mouse, 105 weeks, irritation effects (NTP, 1994)
Vanillin	ND		64 (L)	Oral, rat, 10 weeks, growth depression and damage to kidney, myocardium, liver and spleen (Kirwin and Galvin, 1993)

[a] Only those chemicals with available data are listed. Proprietary chemical data are not presented in order to protect proprietary chemical identities.
[b] When more than one NOAEL and/or LOAEL was available, only the lowest available NOAEL or LOAEL was used and is listed here. If both NOAEL and LOAEL data are available, the NOAEL is used and is listed here.
[c] (N) = NOAEL; (L) = LOAEL. If neither is indicated, the toxicity measure was not identified as a NOAEL or LOAEL in the available information.
[d] This value is highly uncertain; precise thresholds for these irritant effects of formaldehyde have not been established. Estimates based on a large number of clinical and non-clinical observations indicate that most people have irritant reaction thresholds over the range of 0.1 to 3.0 ppm formaldehyde (EPA, 1991c).
[e] TC_{LO} = total concentration resulting in a sublethal effect.
ND: No Data. A NOAEL or LOAEL was not available for this chemical.
NA: Not Applicable. A NOAEL or LOAEL is not required because an RfD or RfD was available for this chemical.

Neither RfDs/RfCs nor LOAELs/NOAELs were available for several chemicals in each MHC process alternative. For these chemicals, no quantitative estimate of risk could be calculated. EPA's Structure-Activity Team (SAT)[10] has reviewed the chemicals without relevant toxicity data to determine if these chemicals are expected to present a toxicity hazard. This review was based on available toxicity data on structural analogues of the chemicals, expert judgement, and known toxicity of certain chemical classes and/or moieties. Chemicals received a concern level rank of high, medium, or low. Results of the SAT evaluation are presented in Table 3.27. A summary of the SAT results for proprietary chemicals is presented in Table 3.28. An overview of chemicals and available toxicity data is presented in Table 3.29.

[10] The SAT is a group of expert scientists at EPA who evaluate the potential health and environmental hazards of new and existing chemicals.

Table 3.27 Summary of Health Effects Information (from Structure-Activity Team Reports)

Chemical	SAT Health Effects (pertaining to dermal or inhalation exposure)	Overall Concern Level
Dimethylaminoborane	Absorption is expected to be good via all routes of exposure. This compound is corrosive when handled in concentrated form. There is concern for developmental toxicity and reproductive effects for the boron.	High concern
EDTA, Sodium Salt	Expect no absorption by skin, but expect absorption by lungs and GI tract. Compound is a chelator and is expected to chelate Ca and Mg. Concerns for developmental toxicity and cardiac arrhythmia due to ability to chelate Ca. Arrhythmia expected to occur only at high doses.	Low moderate concern
Fluoroboric Acid	Expect absorption via the skin following irritation. Expect good absorption via the lungs and GI tract. This compound is a severe skin irritant and may be corrosive. There is uncertain concern for developmental toxicity based on information for fluoride.	High concern
Graphite	Expect absorption to be nil by all routes. There is concern for lung effects through lung overall (fibrosis) with repeated inhalation exposure of respirable particles.	Low moderate concern
Magnesium Carbonate	Absorption is expected to be nil through the skin and good through the lungs and GI tract. This compound is used as an antacid.	Low moderate concern
m-Nitrobenzene Sulfonic Acid, Sodium Salt	Absorption is expected to be nil through the skin and good through the lungs and GI tract. The nitro group can be reduced to anamine. There is concern for methemoglobinemia as an aromatic amine compound. As a nitrobenzene derivative, there is concern for neutrotoxicity and developmental toxicity. Serious brain damage was noted at 125 ppm in a 2-week inhalation study with nitrobenzene. It is expected to be irritating to mucous membranes and the upper respiratory tract.	Moderate concern
Monopotassium Peroxymonosulfate	Absorption is expected to be nil through the skin and good through the lungs and GI tract. The peroxymonosulfate moiety is reactive with moisture (oxidizing agent). This material will be an irritant as a concentrated solution.	Moderate concern
Palladium Chloride	Absorption is expected to be nil through the skin and good through the lungs and GI tract. It is an irritant and is reported to be a dermal sensitizer in humans (HSDB).	Moderate high concern
Phosphoric Acid	Expect absorption by all routes. Compound is corrosive.	Moderate concern for corrosive effects to all tissues

Chemical	SAT Health Effects (pertaining to dermal or inhalation exposure)	Overall Concern Level
Potassium Bisulfate	Absorption is expected to be nil through the skin as the neat material and good through the lungs and GI tract. Expect absorption via the skin in solution because of damage to the skin. This compound is expected to be a severe irritant and/or corrosive to the skin, eyes, and mucous membranes because of its acidity.	Moderate concern
Potassium Carbonate	Absorption is expected to be nil through the skin and good through the lungs and GI tract. This material is an alkaline solution and is irritating to the skin, mucous membranes, and upper respiratory tract.	Low moderate concern
Potassium Persulfate	Absorption may occur through the skin following irritation of the skin. Absorption is expected to be good via the lungs and GI tract with reaction of the persulfate (oxidizing agent). This compound is irritating and/or corrosive to the skin, eyes, and mucous membranes. It may also be a dermal and respiratory sensitizer.	Moderate concern
Potassium Sulfate	Absorption is expected to be nil through the skin and good through the lungs and GI tract. No significant adverse effects expected.	Low concern
p-Toluene Sulfonic Acid	Expect no absorption by skin, moderate absorption by GI tract, and good absorption by lungs. TSCA Section 8e-10286 report that this chemical is a severe skin irritation. No other health concern identified.	Low moderate concern
Sodium Bisulfate	Absorption is expected to be nil through the skin as the neat material and good through the lungs and GI tract. Expect absorption via the skin in solution because of damage to the skin. This compound is expected to be a severe irritant and/or corrosive to the skin, eyes, and mucous membranes because of its acidity.	Moderate concern
Sodium Hypophosphite	Absorption is expected to be nil through the skin and good through the lungs and GI tract. It is irritating to mucous membranes and may cause dermal sensitization (HSDB).	Low moderate concern
Sodium Persulfate	Absorption may occur through the skin following irritation of the skin. Absorption is expected to be good via the lungs and GI tract with reaction of the persulfate (oxidizing agent). This compound is irritating and/or corrosive to the skin, eyes, and mucous membranes. It may also be a dermal and respiratory sensitizer. In an inhalation sensory irritation study in mice, mortality occurred at 0.77 mg/l and greater (TSCA Section 8e-12867 Report). Sodium peroxysulfate is positive for dermal sensitization in a human patch test (TSCA Section 8e-2767 Report). Ocular opacity was also reported.	Moderate concern

Table 3.28 Summary of EPA Structure-Activity Team Results for Proprietary Chemicals

Technology	No. of Additional Trade Secret Chemicals[a]	No. of Additional Trade Secret Chemicals With No Human Health Toxicity Data[b]	SAT Human Health Concern Rank (no. of proprietary chemicals)		
			Low	Low-Moderate	Moderate
Electroless Copper	9	4	1	2	1
Graphite	5	3	0	2	1
Tin-Palladium	5	4	2	1	1
Organic-Palladium	1	0	0	0	0

[a] New chemical for this process alternative.
[b] The toxicity data required to calculate cancer risk, hazard quotient, and MOE were not available.

Table 3.29 Available Toxicity Data for Non-Proprietary Chemicals

Chemical	Cancer: Slope Factor (SF), Weight-of-Evidence (WOE) Classification	Inhalation: RfC, NOAEL, or LOAEL	Oral/Dermal: RfD, NOAEL, or LOAEL	SAT
2-Ethoxyethanol		**RfC**	**RfD**	
1,3-Benzenediol	WOE		NOAEL	
2-Butoxyethanol Acetate; Butylcellusolve Acetate		**RfC**		
Ammonia		**RfC**		
Ammonium Chloride			NOAEL	
Benzotriazole			LOAEL	
Boric Acid			LOAEL	
Carbon Black	WOE	LOAEL		
Copper (I) Chloride; Copper	WOE	LOAEL	LOAEL	
Copper Sulfate; or Cupric Sulfate[a]				
Diethylene Glycol n-Butyl Ether		**RfC**	Other[b]	
Diethylene Glycol Ethyl Ether			**RfD**	
Diethylene Glycol Methyl Ether			NOAEL	
Dimethylaminoborane				✔
Dimethylformamide	WOE	**RfC**	LOAEL	
Ethanolamine; Monoethanolamine; 2-Aminoethanol		LOAEL	NOAEL	
Ethylene Glycol		Other[b]	**RfD**	
Ethylenediaminetetraacetic Acid (EDTA)				✔
Fluoroboric Acid; Sodium Bifluoride			Other[b]	✔
Formaldehyde	**SF**, WOE	LOAEL	**RfD**	
Formic Acid		NOAEL		
Graphite		LOAEL		✔
Hydrochloric Acid	WOE	**RfC**		

Chemical	Cancer: Slope Factor (SF), Weight-of-Evidence (WOE) Classification	Inhalation: RfC, NOAEL, or LOAEL	Oral/Dermal: RfD, NOAEL, or LOAEL	SAT
Hydrogen Peroxide	WOE	Other[b]	NOAEL	
Hydroxyacetic Acid			NOAEL	
Isophorone			**RfD**	
Isopropyl Alcohol; 2-Propanol		NOAEL	NOAEL	
Lithium Hydroxide				✔
m-Nitrobenzene Sulfonic Acid; Sodium m-Nitrobenzenesulfonate				✔
Magnesium Carbonate				✔
Methanol		Other[b]	**RfD**	
p-Toluene Sulfonic Acid; Tosic Acid				✔
Palladium			LOAEL	
Palladium Chloride			LOAEL	✔
Peroxymonosulfuric Acid; Potassium Peroxymonosulfate				✔
Phenol-Formaldehyde Copolymer				
Phosphoric Acid				✔
Potassium Bisulfate				✔
Potassium Carbonate				✔
Potassium Cyanide			**RfD**	
Potassium Hydroxide		Other[b]		
Potassium Persulfate				✔
Potassium Sulfate		Other[b]		✔
Potassium-Sodium Tartrate[c]				
Silver			**RfD**	
Sodium Bisulfate				✔
Sodium Carbonate		NOAEL		
Sodium Chloride[d]				
Sodium Chlorite			NOAEL	
Sodium Cyanide			**RfD**	
Sodium Hydroxide		LOAEL		
Sodium Hypophosphite				✔
Sodium Persulfate				✔
Sodium Sulfate			NOAEL	
Stannous Chloride; Tin (II) Chloride			**RfD**	
Sulfuric Acid		NOAEL		
Tartaric Acid			Other[b]	

Chemical	Cancer: Slope Factor (SF), Weight-of-Evidence (WOE) Classification	Inhalation: RfC, NOAEL, or LOAEL	Oral/Dermal: RfD, NOAEL, or LOAEL	SAT
Triethanolamine; or 2,2',2"-Nitrilotris Ethanol			LOAEL	
Trisodium Citrate 5.5-Hydrate; Sodium Citrate				✔
Vanillin			LOAEL	

[a] The toxicity data for copper (I) chloride was used to evaluate copper sulfate and cupric sulfate.
[b] Toxicity data other than an RfC, RfD, NOAEL, or LOAEL was used. See Table 3.26 for description of the toxicity data.
[c] Potassium-sodium tartrate added directly to human food is affirmed as generally regarded as safe when meeting specified food manufacturing requirements (U.S. FDA as cited in HSDB, 1996).
[d] Sodium chloride (table salt) is a necessary mineral and electrolyte in humans and animals, and under normal conditions the body efficiently maintains a systemic concentration of 0.9 percent by retaining or excreting dietary sodium chloride. It is not generally considered poisonous to humans or animals, its main systemic effect being blood pressure elevation.

Chemicals having potential developmental toxicity were identified based on the data provided in the toxicity profiles. The data are summarized in Table 3.30. The values listed in the table included the no-observable-effect level (NOEL) or, in the absence of a NOEL, the lowest-observable-effect level (LOEL) concentrations. Chemicals which have inconclusive data concerning the developmental toxicity, as a result of multiple studies having conflicting conclusions, are identified as possible developmental toxicants. The chemical is listed as a possible toxicant given the uncertainty in the data.

Table 3.30 Developmental Hazards Summary

Chemical Name	Oral NOEL (mg/kg/day)[a]	Comments	Inhalation NOEL (mg/m^3)[a]	Comments
Ammonium Chloride	1,691	Drinking water, mice, after day 7 of gestation. No congenital effects (Shepard, 1986).	NA	
Boric Acid	125	Oral, rabbits, gestation days 6-19. Prenatal mortality, interventricular septal defect, unspecified malformations (U.S. Borax Co., 1992).	NA	
2-Butoxyethanol - **possible inhalation**	100	Oral, rats, gestation days 9-11 or 11-13. Reduced prenatal viability noted (Gingell et al., 1994).	50 ppm	Rats exposed 6 hours/day on gestation days 6-15 to 100 and 200 ppm. Maternal toxicity noted and increased resorbed litters, decreased pup viability, and delayed ossification (Rohm and Haas, 1992). In another study, rats exposed 7 hours/day to 150 and 200 ppm on gestation days 7-15 had maternal toxicity (transient hemoglobinuria), but no developmental toxicity (Gingell et al., 1994).
Copper	51.7	Food, mice, 30 days before mating through day 19 of gestation. Malformations (EPA, 1984a).	NA	
Diethylene Glycol Methyl Ether	150 (LOEL)	Oral, mice, gestation days 6-15. Malformation of neural tube, heart, renal and skeletal systems (Price et al., 1987).	NA	
2-Ethoxyethanol	93.1	Oral, rats, gestation days 1-21. Increase major skeletal malformations (EPA, 1984b).	369 (LOEL)	Mice, exposure of 6 hours/day, days 6-15 of gestation. Developmental neurotoxicity (EPA, 1996b; 1985a).
Ethanolamine	50 (LOEL)	Oral, rats, gestation days 6-15. Increases in intrauterine deaths, malformations, and increased fetal weight (Mankes, 1986 as reported in TOXLINE, 1995).	NA	

Chemical Name	Oral NOEL (mg/kg/day)[a]	Comments	Inhalation NOEL (mg/m^3)[a]	Comments
Ethylene Glycol	500	Oral, mice, gestation days 6-15. Lower body weights and craniofacial and skeletal malformations (Shell Oil, 1992a).	150	Rats and mice, exposure of 6 hours/day, days 6-15 of gestation. Fetal malformations in mice (exencephaly, cleft palate, and abnormal rib and facial bones) (Shell Oil, 1992b; Union Carbide, 1991).
Ethylenediaminetetraacetic Acid (EDTA)	954 - LOEL	Diet, rats, gestation days 7-14. Maternal-toxicity and reduced litters, reduced fetal weight and malformations (EPA, 1987).	NA	
Hydrazine	NA	Subcutaneous, rats, gestation days 11-21. Injection of 8 mg/kg/day resulted in reduced ratio of fetal survivors to implantation sites, reduced fetal weight, and 100% mortality of pups within 24 hrs of birth (Lee and Aleyassine, 1970).	NA	
Hydrochloric Acid	NA		450 (LOEL)	Rats, exposure of 1 hour/day for 12-16 days prior to mating or on gestation day 9. Adults exhibited mortality. Increased fetal mortality, decreased fetal weight and increased fetal lung weights (EPA, 1995c).
Hydroxylamine Sulfate	NA	Mice. No details given for type of exposure, duration, or dose. Resulted in early fetal deaths and pre-implantation losses (Gross, 1985).	NA	
Isopropanol	480	Oral, rabbits, gestation days 6-18. Reduced fetal body weights noted in oral exposure of rats, but at concentrations with maternal toxicity. No teratogenic effects noted (Tyl, et al., 1995, as cited in CMA, 1995).	3,000 ppm (LOEL)	Rats, exposure of 7 hours/day, gestation days 1-19. Reduced fetal weight (Nelson et al., 1943 as cited in ACGIH, 1991).

Chemical Name	Oral NOEL (mg/kg/day)[a]	Comments	Inhalation NOEL (mg/m^3)[a]	Comments
Isophorone	NA		50 ppm	Rats, exposure of 6 hours/day, gestation days 6-15. Reduction in mean crown-rump length, significant decrease in maternal body weight noted (Bio/Dynamics Inc., 1984).
Lithium Hydroxide	NA	Studies indicate that the risk of major congenital malformations in offspring from women receiving lithium during early pregnancy is slightly higher (4-12%) than that among control groups (2-4%) (Cohen et al., 1994 as cited in Opresko, 1995). Lithium chloride has been shown to cause cleft palate in rats and mice, but lithium carbonate was negative for developmental effects in monkeys, rabbits, and rats (Beliles, 1994). However other studies have shown an increase incidence of cleft palate in mice (Szabo, 1970 as cited in Opresko, 1995).	NA	
Methanol	NA	Drinking water, folate-deficient rats, gestation days 6-15. Maternal toxicity (decreased weight gain) and developmental toxicity (increased resorption) observed at drinking water concentrations of 1% and 2% (Lington and Bevan, 1994).	6,650 (LOEL)	Mice, exposure of 7 hours/day, gestation days 7-9. Increased exencephaly (Lington and Bevan, 1994).
N,N-Dimethylformamide	200	Dermal, rats, gestation days 8-16 (EPA, 1986). Hydrocephalus, growth retardation, post-implantation losses, and increase mortality in offspring (IARC, 1989).	0.05 (LOEL)	Rabbits, exposure of 4 hours/day, days 1-19 of gestation. Reduced fetal growth (IARC, 1989).
Phenol	60	Oral, rats, gestation days 6-15. Reduced fetal body weights (EPA, 1996c).	NA	

Chemical Name	Oral NOEL (mg/kg/day)[a]	Comments	Inhalation NOEL (mg/m^3)[a]	Comments
Potassium Carbonate	NA	Epidemiology study of 226 males employed at potash mine. After starting work underground, mean birth weights increased slightly and there was a decrease in male/female ratio (Wiese and Skipper, 1986).	NA	
Potassium and Sodium Cyanide	NA (276.6 mg CN/kg diet)	Oral, pigs, through gestation and lactation. Fetuses had reduced thyroid, spleen, and heart weights. Sows showed hyperplasia of kidney glomeruli and histological changes in thyroid (Tewe and Maner, 1981).	NA	
Silver - **Possible**	NA	Silver concentrations in 12 anencephalic human fetuses was higher than silver concentrations in livers of 12 therapeutically aborted fetuses and 14 fetuses aborted spontaneously. Could not be determined if high silver concentrations were associated with the anencephalic malformation or with fetal age (ATSDR, 1990b).	NA	
Sodium Chloride	56,400 (TD_{LO})[b]	Oral, rats, day 5 or 7 pre-conception and one or more days post-conception. Unspecified toxic effects noted (RTECS, 1996).	NA	
Sodium Chlorite	1.4 (LOEL)	Drinking water, rats, 2.5 months prior to mating through gestational day 20. Increase in variation of sternum and increase in crown-rump length. Same study, oral dose 200 mg/kg/day and 2,800 mg/kg/day via drinking water, gestational days 8-15, no developmental effects (Perry et al., 1994).	NA	

Chemical Name	Oral NOEL (mg/kg/day)[a]	Comments	Inhalation NOEL (mg/m^3)[a]	Comments
Sodium Sulfate	2,800	Oral, mice, gestation days 8-12. No effect on body weights or litter sizes (Young, 1992). Parentally administered dose of 60 mg/kg on day 8 of gestation produced developmental abnormalities of the musculosketal system (RTECS, 1995).	NA	
Stannous Chloride	50	Oral, mice, 10 consecutive days, no effect on gestation of fetal survival (Gitilitz and Moran, 1983). Method of exposure unknown, rats, gestation days 7-12. 500 mg/kg resulted in teratogenic effects (Wu, 1990, as reported in TOXLINE, 1995).	NA	

[a] Unless otherwise noted.
[b] TD_{Lo} = The lowest dose of a chemical that is expected to cause a defined toxic effect.
NA: Not applicable. Data for calculating a dose were not available.

3.3.3 Ecological Hazard Summary

Table 3.31 presents a summary of the available ecological hazard information. Concern concentrations (CCs) were determined only for aquatic species (e.g., *Daphnia*, algae, and/or fish) using standard EPA methodology. Methods for determining CCs are summarized below. (*Cleaner Technologies Substitutes Assessment: A Methodology and Resources Guide* [Kincaid et al., 1996] presents the methods in more detail.)

Table 3.31 Aquatic Toxicity Information

Chemical Name[a]	LC_{50} (mg/L)[b]	Test Information	Species	CC (mg/L)[c]	Source
1,3-Benzenediol	> 100 0.25 88.6 262 > 100	all 96 hr	rainbow trout water flea minnow zebra fish snail	AsF = 100(2) 0.0025	AQUIRE, 1995
2-Butoxyethanol Acetate	150 960 > 500	48 hr 17 hr 72 hr	water flea protozoa green algae	AsF = 100(2) 1.5	Verschueren, 1996
2-Ethoxyethanol	> 5,000 > 10,000 7,660	24 hr 96 hr 48 hr IC_{50}[d]	goldfish bluegill & silversides water flea	AsF = 1,000(3) 5.0	AQUIRE, 1996; EPA, 1985a
Ammonia	0.42-0.84 1.74 1.58	8 hr 24 hr 24 hr	rainbow trout water flea snail	AsF = 100(2) CC = 0.0042	AQUIRE, 1995
Ammonium Chloride	640 139 50	24 hr TLm[e] 24-96 hr TLm 96 hr TLm	carp bluegill water flea	AsF = 1,000(3) 0.05	Verscheuren, 1983
Boric Acid	46-75 22-155 79-100	7 day 9 day 28 day	goldfish catfish rainbow trout	AsF = 1,000(3) 0.022	AQUIRE, 1995
Carbon Black	No information found in literature				
Copper	0.8-1.9 0.0885-21 0.13-0.5 0.125 10-33	96 hr 96 hr 96 hr 96 hr 24 hr	carp minnow rainbow trout salmon shrimp	AsF = 100(2) 0.00088	AQUIRE, 1995
Copper Chloride (Cuprous)	0.40-2.3	96 hr	mummichog (fish)	AsF = 1,000(3) 0.0004	AQUIRE, 1995
Copper Sulfate	0.18-12 0.096-0.12 0.036-1.38 0.002-160 0.10-0.24 0.002-23.6 0.56-40	96 hr 96 hr 96 hr 96 hr 96 hr 96 hr 96 hr	bullhead zebrafish goldfish carp salmon minnow oyster	AsF = 100(2) 0.00002	AQUIRE, 1995
Diethylene Glycol Methyl Ether	> 5,000 7,500	24 hr 96 hr	goldfish minnow	AsF = 1,000(3) 5.0	AQUIRE, 1995

Chemical Name[a]	LC_{50} (mg/L)[b]	Test Information	Species	CC (mg/L)[c]	Source
Diethylene Glycol Ethyl Ether	9,650-26,500 12,900-13,400 15,200 6,010 1,982-4,670	96 hr 96 hr 96 hr 96 hr 48 hr	minnow rainbow trout mosquito fish catfish water flea	AsF = 100[(2)] CC = 20	AQUIRE, 1996
Diethylene Glycol n-Butyl Ether	1,300 3,200 1,000	96 hr EC_{50}[f] decreased cell multiplication	bluegill water flea blue-green algae	AsF = 100[(2)] 10	AQUIRE, 1995
Dimethylformamide	1.2-2.5 1,300 > 1,000 9,860 18,800	MATC[g], chronic 24 hr 48 hr 96 hr 48 hr EC_{50}	water flea guppy medaka rainbow trout water flea	AsF = 10[(4)] CC = 0.12	EPA, 1986
Ethanolamine	170 40 & 70 140 0.75	96 hr 24 hr LC_0[h] & LC_{100}[i] 24 hr 8 day, toxicity threshold	goldfish creek chub water flea green algae	AsF = 10[(1)] CC = 0.075	AQUIRE, 1995
Ethylene Glycol	41,000 49,000-57,000 41,000-57,600 > 5,000 330	96 hr 96 hr 48 hr 24 hr 48 hr	rainbow trout minnow water flea goldfish African frog	AsF = 100[(2)] CC = 3.3	AQUIRE, 1995
Ethylenediaminetetraacetic Acid (EDTA)	129 625 59.8 41-532 280	96 hr 24 hr 96 hr 96 hr, varying pH 24 hr	catfish water flea minnow bluegill shrimp	AsF = 100[(2)] CC = 0.41	AQUIRE, 1995
Fluoroboric Acid	125 (as fluoride)	48 hr	brown trout	AsF = 1,000[(3)] CC = 0.125	Woodiwiss & Fretwell, 1974
Formaldehyde	25.2-40 47.2 6.7 25.5-26.3	96 hr 96 hr 96 hr 96 hr	bluegill rainbow trout striped bass catfish	AsF = 1,000[(3)] CC = 0.0067	EPA, 1985b
Formic Acid	175 80-90 151	24 hr 48 hr 48 hr	bluegill green crab water flea	AsF = 1,000[(3)] CC = 0.08	AQUIRE, 1995
Hydrochloric Acid	282 100 180	24-96 hr 96 hr produced no stress effects 96 hr	mosquito fish green crab goldfish	AsF = 1,000[(3)] CC = 0.1	AQUIRE, 1995
Hydrogen Peroxide	89 12 155	24 hr 228 hr LT_{50}[j] 24 hr	mackerel zebra mussel gobi	AsF = 10[(1)] CC = 1.2	AQUIRE, 1995
Isophorone	12.9 79 228	96 hr NOEC[k] 96 hr	mysid shrimp green algae minnow	AsF = 100[(2)] CC = 0.13	AQUIRE, 1996

Chemical Name[a]	LC_{50} (mg/L)[b]	Test Information	Species	CC (mg/L)[c]	Source
Isopropanol	> 1,400 900-1,100 1,150 1,800	96 hr 24 hr 96 hr toxicity threshold	mosquito fish creek chub shrimp green algae	AsF = 100(2) CC = 9.0	AQUIRE, 1995
Lithium Hydroxide	No aquatic toxicity information available				
m-Nitrobenzene Sulfonic Acid	8,600 > 500	24 &48 hr 48 & 96 hr	water flea trout, guppy, bluegill, minnow	AsF = 100(2) CC = 5	AQUIRE, 1995; Greim et al., 1994
Methanol	28,200 20,100 1,700 2.6-3.1% > 10,000	96 hr 96 hr 48 hr 10-14 day EC_{50} 24 hr LC_{50}	minnow rainbow trout goldfish algae brine shrimp	AsF = 100(2) CC = 17	AQUIRE, 1995
Palladium, Palladium Chloride	0.237 0.142	24 hr EC_{50} 48 hr EC_{50}	tubificid worm	AsF = 1,000(3) CC = 0.00014	AQUIRE, 1995
Phenol-Formaldehyde Copolymer	No aquatic toxicity information available. Once cured, PF copolymer is highly insoluble and is not expected to be toxic to aquatic life.				
Phosphoric Acid	138	TLm	mosquito fish	AsF = 1,000(3) CC = 0.138	HSDB, 1995
Potassium Cyanide, Sodium Cyanide	0.052 0.057 0.0079	96 hr 96 hr chronic value	brook trout rainbow trout brook trout	AsF = 10(1) CC = 0.79	EPA, 1980
Potassium Hydroxide	85 80 80	24 hr 48 hr 96 hr	mosquito fish mosquito fish guppy	AsF = 1,000(3) CC = 0.08	AQUIRE, 1995
Potassium Persulfate	1,360 234 845 92-251	48 hr 48 hr 48 hr 48 hr	carp rainbow trout guppy water flea	AsF = 100(2) CC = 0.92	AQUIRE, 1995
Potassium-Sodium Tartrate	No aquatic toxicity information available.				
Potassium Sulfate	112 1,180 3,550 2,380	all 96 hr	mussel adult snail bluegill bleak	AsF = 1,000(3) CC = 0.11	AQUIRE, 1995
1H-Pyrrole	210 856	96 hr 72 hr EC_{50}	minnow protozoan	AsF = 1,000(3) CC = 0.21	AQUIRE, 1996
Silver	0.0514 0.064 0.036 58	96 hr 96 hr 96 hr 98 hr	rainbow trout bluegill minnow minnow	AsF = 1,000(3) CC = 0.000036	AQUIRE, 1996
Sodium Bisulfate	58-80 190	24 & 48 hr immobilized after 48 hrs	mosquito larvae water flea	AsF = 1,000(3) CC = 0.058	AQUIRE, 1995
Sodium Carbonate	300-320 297 242 524	96 hr 50 hr 5 day 96 hr	bluegill guppy diatom (algae) water flea	AsF = 100(2) CC = 2.4	AQUIRE, 1995

Chemical Name[a]	LC_{50} (mg/L)[b]	Test Information	Species	CC (mg/L)[c]	Source
Sodium Chloride	4,324-13,750 17,550-18,100 23,000-32,000 280-1,940 1,500-5,000	24 hr-10 day 25-96 hr 24-96 hr ≥ 24 hr 24-96 hr	goldfish mosquito fish damsel fly water flea striped bass	AsF = 100(2) CC = 2.8	AQUIRE, 1996
Sodium Chlorite	75 0.65 0.161	96 hr 96 hr 48 hr	minnow mysid shrimp water flea	AsF = 1,000(3) CC = 0.00016	TR-Metro, 1994; Albright & Wilson, 1992a,b
Sodium Citrate	3,330	24 hr	water flea	AsF = 1,000(3) CC = 3.3	AQUIRE, 1995
Sodium Hydroxide	125 30 33-100 ≥ 25	96 hr 24 hr LC_{40}[l] 48 hr chronic	mosquito fish pikeperch poacher guppy	AsF = 10(1) CC = 2.5	AQUIRE, 1995; HSDB, 1995
Sodium Persulfate	1,667 64.6 388 631	48 hr 48 hr 48 hr 48 hr	carp water flea rainbow trout guppy	AsF = 1,000(3) CC = 0.065	AQUIRE, 1995
Sodium Sulfate	200-290 81 204 4,380 3,360	96 hr 96 hr 96 hr 96 hr 32 day	amphipoda bass larvae water flea bluegill *Myriophyllum spicatum*	AsF = 100(2) CC = 0.81	AQUIRE, 1995
Stannous Chloride[m]	0.6 2.1 0.09 0.4	30 day lethal conc 7 day 7 day 28 day	green algae goldfish eggs toad eggs rainbow trout eggs	AsF = 100(2) CC = 0.0009	AQUIRE, 1995
Sulfuric Acid	80-90 42 42.5 20	48 hr 96 hr 48 hr 7 day, no mortality	poacher mosquito fish prawn water flea	AsF = 10(1) CC = 2.0	AQUIRE, 1995
Tartaric Acid	250-320	LD_0[n]	paramecium	AsF = 10(1) CC = 1.0	Verschueren, 1983
	200	LD_0 longtime hardwater exp.	goldfish		
	10	LD_0 longtime softwater exp.			
Tetrasodium EDTA	360 663 1,033 11 1,030-2,070	72 hr 48 hr EC_{50} 8 day, decreased cell multiplication 96 hr	protozoa cryptomonad water flea green algae bluegill	AsF = 10(1) CC = 1.1	AQUIRE, 1995

Chemical Name[a]	LC_{50} (mg/L)[b]	Test Information	Species	CC (mg/L)[c]	Source
Triethanolamine; or 2,2',2"-Nitrilotris Ethanol	> 5,000 11,800 176-213 mg/kg 1.8	24 hr 96 hr 48 hr, LD_0 8 day, decreased cell multiplication	goldfish minnow carp green algae	AsF = 10[(1)] CC = 0.18	AQUIRE, 1995
Vanillin	112-121 57-123	96 hr 96 hr	minnow minnow	AsF = 1,000[(3)] CC = 0.057	AQUIRE, 1996; Verschueren, 1996

[a] Only those chemicals with data are listed. Proprietary chemical data are not presented in order to protect proprietary chemical identities.
[b] Lethal concentration (LC_{50}) = the concentration of a chemical in water that causes death or complete immobilization in 50 percent of the test organisms at the end of the specified exposure period. LC_{50} values typically represent acute exposure periods, usually 48 or 96 hours but up to 14 days for fish. Units are mg/L unless otherwise noted.
[c] Concern concentration (CC) = most sensitive toxicity value (mg/L) ÷ AsF. AsF = Assessment (uncertainty) factor.
[d] Concentration that immobilizes 50 percent of the test population.
[e] TLm = Median threshold limit value, or tolerance limit median - equivalent to an LC_{50} value.
[f] EC_{50} = Effective concentration to 50 percent of a test population.
[g] MATC = Maximum acceptable toxicant concentration. It is generally defined as the geometric mean of the highest concentration tested at which no significant deleterious effect was observed and the lowest concentration tested at which some significant deleterious effect was observed.
[h] LC_0 = Estimated maximum concentration that would not result in death of the exposed organisms.
[i] LC_{100} = Lethal concentration to 100 percent of a test population.
[j] LT_{50} = Time for 50 percent of the test population to die at a preselected concentration.
[k] NOEC = No-observed effect concentration.
[l] LC_{40} = Lethal concentration to 40 percent of a test population.
[m] Stannous chloride is expected to rapidly dissociate in water under environmental conditions, followed by formation of tin complexes and precipitation out of the water column. This process would make stannous chloride much less available for toxic effects to aquatic organisms.
[n] LD_0 = Estimated maximum dose that would not result in death of the exposed organisms.
(1) Chronic data available and was most sensitive endpoint, AsF = 10.
(2) Acute data available for multiple species and trophic levels, AsF = 100.
(3) Limited acute data available, AsF = 1,000.
(4) AsF of 10 used for MATC data.

The CC for each chemical in water was calculated using the general equation:

CC = acute or chronic toxicity value ÷ AsF

where:

CC = aquatic toxicity concern concentration, the concentration of a chemical in the aquatic environment below which no significant risk to aquatic organisms is expected.

AsF = assessment factor (an uncertainty factor), the adjustment value used in the calculation of a CC that incorporates the uncertainties associated with: 1) toxicity data (e.g., laboratory test versus field test, measured versus estimated data); 2) acute exposures versus chronic exposures; and 3) species sensitivity. This factor is expressed as an order of magnitude or as a power of ten (EPA, 1984c).

If several acute or chronic toxicity values are available, the lowest one is used (most sensitive tested species), unless poor or uncertain data quality disqualifies one or more of the values. The AQUIRE database, an extensive source of aquatic toxicity data, includes a numerical rating of study quality.

AsFs are dependent on the amount and type of toxicity data contained in a toxicity profile and reflect the amount of uncertainty about the potential effects associated with a toxicity value. In general, the more complete the toxicity profile and the greater the quality of the toxicity data, the smaller the AsF used.

The following approach was used, depending on availability and type of data:

- If the toxicity profile only contained one or two acute toxicity values (no chronic values), AsF = 1,000 and the CC was calculated by using the lower acute value.
- If the toxicity profile contained three or more acute values (no chronic values), AsF = 100 and the CC was calculated by using the lowest acute value.
- If the toxicity profile contained at least one chronic value, and the value was for the most sensitive species, AsF = 10 and the CC was calculated by using the lowest chronic value. Otherwise, AsF = 100 and the CC was calculated with the acute value for the most sensitive species.
- If the toxicity profile contained field toxicity data, AsF = 1 and CC was calculated by using the lowest value.

Aquatic toxicity values were estimated using the ECOSAR program (EPA, 1994b) for chemicals without available measured acute or chronic aquatic toxicity data. These values are presented in Table 3.32. An AsF of 1,000 was used to calculate all CCs based on such estimates.

Table 3.33 presents chemicals with aquatic toxicity CCs. The chemicals are listed in ascending order (i.e., the chemical with the lowest CC to the chemical with the highest CC for each of the alternatives). The lowest CC is for copper sulfate, based on fish toxicity data. The table also presents aquatic hazard concern levels; chemicals were assigned to aquatic toxicity concern levels according to the following EPA criteria:

<u>For chronic values</u>:

≤ 0.1 mg/L.....High concern
> 0.1 to ≤ 10 mg/L.....Moderate concern
> 10 mg/L.....Low concern

<u>For acute values</u>:

≤ 1 mg/L.....High concern
> 1 to ≤ 100 mg/L.....Moderate concern
> 100 mg/L.....Low concern

Chronic toxicity ranking takes precedence over the acute ranking.

It should be noted that aquatic hazard concern levels are derived from the lowest toxicity value available. Therefore, these rankings are derived separately from the CCs which are derived based on the amount of toxicity data available for a given chemical. A summary of the aquatic toxicity results for the known proprietary chemicals is presented in Table 3.34.

These rankings are based only on chemical toxicity to aquatic organisms, and are not an expression of risk. The number of chemicals with a high aquatic hazard concern level include two in carbon, two in conductive ink, none in the conductive polymer process, nine in the electroless copper process, three in graphite, three in non-formaldehyde electroless copper, two in organic-palladium, and nine in tin-palladium.

Table 3.32 Estimated Ecological (Aquatic)Toxicity Information for Non-Proprietary Chemicals

Chemical	Acute Toxicity (mg/L)			Chronic Toxicity (mg/L)			AsF, CC (mg/L)
	Fish (FW) 96 hr LC_{50}	Daphnid 48 hr LC_{50}	Green Algae 96 hr EC_{50}	Fish 14 day LC_{50}	Daphnid 16 day EC_{50}	Green Algae >96 hr ChV	
Benzotriazole[1]	45.3	378.1	23.4	ND	ND	ND	1,000 0.023
Dimethylaminoborane[2]	10	0.7	3.0	1.0	0.070	0.3	10 0.007
Graphite[2]	*	*	*	*	*	*	
Hydroxyacetic Acid[1]	> 1,000 *	> 1,000 *	> 1,000 *	ND	ND	ND	1,000 1
Magnesium Carbonate[2]	> 100	140	> 100	> 10	82	> 10	10 > 1.0
Peroxymonosulfuric Acid[2]	≤ 3.0	≤ 3.0	≤ 3.0	≤ 0.30	≤ 0.30	≤ 1.0	10 0.030
Potassium Bisulfate[2]	> 1,000	> 100	> 100	> 100	> 10	> 10	10 > 1.0
Potassium Carbonate[2]	1,300	330	100	100	190	> 30	10 > 3.0
p-Toluene Sulfonic Acid[2]	Predicted toxicity values of environmental base set all > 100 mg/L, chronic values all > 10.0 mg/L based on SARs for anionic LAS surfactants.						10 1.0
Sodium Hypophosphite[2]	> 100	> 100	0.030	> 10	> 10	0.060	10 0.006

[1] ECOSAR Program.
[2] SAT Report.
* No adverse effects expected in a saturated solution.
ND: No Data. ECOSAR (EPA, 1994b) did not include an estimating component for this endpoint for the chemical class.

Table 3.33 Aquatic Hazard Concern Concentrations (CCs) and Hazard Concern Levels by MHC Technology for Non-Proprietary Chemicals

Chemicals in MHC Processes[a]	CCs (mg/L)	Aquatic Hazard Concern Level[b]
Electroless Copper		
Copper Sulfate	0.00002(2)	High(A)
Palladium; Palladium Chloride	0.00014(3)	High(A)
Sodium Chlorite	0.00016(3)	High(A)
Copper Chloride	0.0004(3)	High(A)
Stannous Chloride[c]	0.0009(2)	High(A)
Sodium Hypophosphite	0.006(5)	Low(A)
Formaldehyde	0.0067(3)	Moderate(A)
Dimethylaminoborane	0.007(5)	High(C)
Boric Acid	0.022(3)	Moderate(A)
Benzotriazole	0.023(5)	Moderate(A)
Peroxymonosulfuric Acid	0.030(5)	Moderate(C)
Ammonium Chloride	0.05(3)	Moderate(A)
Sodium Bisulfate	0.058(3)	Moderate(A)
Ethanolamine	0.075(1)	High(A)
Potassium Hydroxide	0.08(3)	Moderate(A)
Formic Acid	0.08(3)	Moderate(A)
Potassium Hydroxide	0.08(3)	Moderate(A)
Hydrochloric Acid	0.1(3)	Moderate(A)
Potassium Sulfate	0.11(3)	Low(A)
Dimethylformamide	0.12(4)	Moderate(C)
Fluoroboric Acid	0.125(3)	Low(A)
Triethanolamine; or 2,2',2"-Nitrilotris Ethanol	0.18(1)	Moderate(C)
Ethylenediaminetetraacetic Acid (EDTA)	0.41(2)	Moderate(A)
Sodium Cyanide	0.79(1)	High(C)
Potassium Cyanide	0.79(1)	High(C)
Sodium Sulfate	0.81(2)	Moderate(A)
Potassium Persulfate	0.92(2)	Moderate(A)
Hydroxyacetic Acid	1(5)	Low(A)
Magnesium Carbonate	1.0(5)	Low(C)
p-Toluene Sulfonic Acid	1.0(5)	Low(C)
Tartaric Acid	1.0(1)	Moderate(C)
Potassium Bisulfate	>1.0(5)	Low(C)
Hydrogen Peroxide	1.2(1)	Low(C)
Sulfuric Acid	2.0(1)	Low(C)

Chemicals in MHC Processes[a]	CCs (mg/L)	Aquatic Hazard Concern Level[b]
Sodium Carbonate	2.4[(2)]	Low[(A)]
Sodium Hydroxide	2.5[(1)]	Low[(C)]
Ethylene Glycol	3.3[(2)]	Low[(A)]
m-Nitrobenzene Sulfonic Acid	5[(2)]	Low[(A)]
2-Ethoxyethanol	5.0[(3)]	Low[(A)]
Isopropanol	9.0[(2)]	Low[(A)]
Methanol	17[(2)]	Low[(A)]
Potassium-Sodium Tartrate	no data available	
Carbon		
Copper Sulfate	0.00002[(2)]	High[(A)]
Sodium Persulfate	0.065[(3)]	Moderate[(A)]
Ethanolamine	0.075[(1)]	High[(A)]
Potassium Hydroxide	0.08[(3)]	Moderate[(A)]
Sulfuric Acid	2.0[(1)]	Low[(C)]
Potassium Carbonate	> 3.0[(5)]	Low[(C)]
Ethylene Glycol	3.3[(2)]	Low[(A)]
Carbon Black	no data available	
Conductive Ink		
Silver	0.000036[(3)]	High[(A)]
Copper	0.00088[(2)]	High[(A)]
Isophorone	0.13[(2)]	Moderate[(A)]
2-Butoxyethanol Acetate	1.5[(2)]	Low[(A)]
Diethylene Glycol Methyl Ether	5.0[(3)]	Low[(A)]
Diethylene Glycol n-Butyl Ether	10[(2)]	Low[(A)]
Methanol	17[(2)]	Low[(A)]
Diethylene Glycol Ethyl Ether	20[(2)]	Low[(A)]
Graphite	not expected to be toxic[(5)]	Low
Phenol-Formaldehyde Copolymer	not expected to be toxic[(5)]	Low
Carbon Black	no data available	
Conductive Polymer		
Peroxymonosulfuric Acid	0.030[(5)]	Moderate[(C)]
Phosphoric Acid	0.138[(3)]	Low[(A)]
1H-Pyrrole	0.21[(3)]	Low[(A)]
Sulfuric Acid	2.0[(1)]	Low[(C)]
Sodium Carbonate	2.4[(2)]	Low[(A)]
Sodium Hydroxide	2.5[(1)]	Low[(C)]

Chemicals in MHC Processes[a]	CCs (mg/L)	Aquatic Hazard Concern Level[b]
Graphite		
Copper Sulfate	0.00002[(2)]	High[(A)]
Ammonia	0.0042[(2)]	High[(A)]
Peroxymonosulfuric Acid	0.030[(5)]	Moderate[(C)]
Sodium Persulfate	0.065[(3)]	Moderate[(A)]
Ethanolamine	0.075[(1)]	High[(A)]
Sulfuric Acid	2.0[(1)]	Low[(C)]
Potassium Carbonate	> 3.0[(5)]	Low[(C)]
Graphite	not expected to be toxic[(5)]	Low
Non-Formaldehyde Electroless Copper		
Copper Sulfate	0.00002[(2)]	High[(A)]
Sodium Chlorite	0.00016[(3)]	High[(A)]
Stannous Chloride[c]	0.0009[(2)]	High[(A)]
Potassium Hydroxide	0.08[(3)]	Moderate[(A)]
Hydrochloric Acid	0.1[(3)]	Moderate[(A)]
Potassium Persulfate	0.92[(2)]	Moderate[(A)]
Hydrogen Peroxide	1.2[(1)]	Low[(C)]
Sulfuric Acid	2.0[(1)]	Low[(C)]
Sodium Hydroxide	2.5[(1)]	Low[(C)]
Isopropanol	9.0[(2)]	Low[(A)]
Organic-Palladium		
Sodium Hypophosphite	0.006[(5)]	High[(C)]
Sodium Bisulfate	0.058[(3)]	Moderate[(A)]
Sodium Persulfate	0.065[(3)]	Moderate[(A)]
Hydrochloric Acid	0.1[(3)]	Moderate[(A)]
Sodium Carbonate, Sodium Bicarbonate	2.4[(2)]	Low[(A)]
Sodium Citrate	3.3[(3)]	Low[(A)]
Tin-Palladium		
Copper Sulfate	0.00002[(2)]	High[(A)]
Palladium Chloride, Palladium	0.00014[(3)]	High[(A)]
Copper	0.00088[(2)]	High[(A)]
Stannous Chloride[c]	0.0009[(2)]	High[(A)]
1,3-Benzenediol	0.0025[(2)]	High[(A)]
Dimethylaminoborane	0.007[(5)]	High[(C)]
Vanillin	0.057[(3)]	Moderate[(A)]
Sodium Bisulfate	0.058[(3)]	Moderate[(A)]
Sodium Persulfate	0.065[(3)]	Moderate[(A)]

Chemicals in MHC Processes[a]	CCs (mg/L)	Aquatic Hazard Concern Level[b]
Ethanolamine	0.075[(1)]	High[(A)]
Hydrochloric Acid	0.1[(3)]	Moderate[(A)]
Fluoroboric Acid	0.125[(3)]	Low[(A)]
Phosphoric Acid	0.14[(3)]	Low[(A)]
Triethanolamine; or 2,2',2"-Nitrilotris Ethanol	0.18[(1)]	Moderate[(C)]
Hydrogen Peroxide	1.2[(1)]	Low[(C)]
Sulfuric Acid	2.0[(1)]	Low[(C)]
Sodium Hydroxide	2.5[(1)]	Low[(C)]
Sodium Chloride	2.8[(2)]	Low[(A)]
Potassium Carbonate	> 3.0[(5)]	Low[(C)]
Isopropanol	9.0[(2)]	Low[(A)]
Lithium Hydroxide	no data available	

[a] Different supplier's product lines do not necessarily include all of the chemicals listed for a process alternative.
[b] Based on lowest available toxicity data:
[(A)] indicates the lowest acute value was used for hazard ranking.
[(C)] indicates the hazard ranking is based on a chronic value, if available and lower than any acute value.
[c] Stannous chloride is expected to rapidly dissociate in water under environmental conditions, followed by tin forming complexes and precipitating out of the water column. This process would make stannous chloride much less available for toxic effects to aquatic organisms.
Basis of Concern Concentrations:
[(1)] Chronic data.
[(2)] Acute data for multiple species and taxonomic groups.
[(3)] Limited acute data.
[(4)] Chronic MATC.
[(5)] Structure-activity relationship estimate using the ECOSAR program or SAT report.

Table 3.34 Summary of Aquatic Toxicity for Proprietary Chemicals

Technology	No. of Additional Trade Secret Chemicals[a]	Aquatic Toxicity Concern Rank			CC (mg/l)			
		Low	Moderate	High	< 0.1	0.9 - 0.99	1 - 10	> 10
Electroless Copper	9	6	3	0	1	2	5	1
Graphite	5	4	1	0	0	2	2	1
Tin-Palladium	5	2	1	2	2	1	1	1
Organic-Palladium	1	0	0	1	1	0	0	0

[a] Includes chemicals not previously identified in the publicly-available bath chemistry data for a technology.

3.3.4 Summary

For human health hazards, toxicity data in the form of RfDs, RfCs, NOAELs, LOAELs, and cancer slope (cancer potency) factors were compiled for inhalation and dermal pathways. Formaldehyde was the only non-proprietary chemical with an established cancer slope (cancer potency) factor. Other non-proprietary chemicals in the MHC processes are suspected

carcinogens, but do not have established slope factors. Dimethylformamide and carbon black have been determined by IARC to possibly be carcinogenic to humans (IARC Group 2B). Dimethylformamide is used by at least one supplier in the electroless copper process. Carbon black is used in the carbon and conductive ink processes. Two proprietary chemicals used in the graphite and electroless copper processes, cyclic ether and alkyl oxide, have cancer slope factors. Another proprietary chemical used in the electroless copper process, trisodium acetate amine B, is possibly carcinogenic to humans but does not have an established slope factor.

An ecological hazards assessment was performed based on chemical toxicity to aquatic organisms. Concern concentrations (CCs) were estimated for MHC chemicals using an established EPA method. A CC is an acute or chronic toxicity value divided by an assessment factor (AsF). AsFs are dependent on the amount and type of toxicity data contained in a toxicity profile and reflect the amount of uncertainty about the potential effects associated with a toxicity value. Concern concentrations were determined for aquatic species (e.g., *Daphnia*, algae, and/or fish). The lowest CC is for copper sulfate, based on fish toxicity data.

Chemicals were also ranked for aquatic toxicity concern levels using established EPA criteria (high, moderate, and low concern) based on the available toxicity data. The number of chemicals with a high aquatic hazard concern level include nine in the electroless copper process, two in carbon, two in conductive ink, none in conductive polymer, three in graphite, three in non-formaldehyde electroless copper, and nine in the tin-palladium process, and two in the organic palladium process.