The Carcinogenicity of Formaldehyde

Annex 2

Toxicological profile for formaldehyde

CAS No: 50-00-0
EC No: 200-001-8
Formula: HCHO
Vapour pressure: 470 kPa @ 22 °C
Boiling point: -19.2 °C
Melting point: -92 °C
Conversion factor: 1 ppm = 1.23 mg/m³ @ 25 °C
MW: 30.03
Classification: Carc Cat 3; R40: T; R23/24/25 : C; R34 : R43

Toxicokinetics

Formaldehyde is an essential metabolic intermediate in all cells, produced during the normal metabolism of serine, glycine, methionine and choline and also by the demethylation of N-, S- and O-methyl compounds. Formaldehyde produced within the body via such normal biochemical processes is then oxidised to formate and then the carbon atom is further oxidised to carbon dioxide or incorporated into purines, thymidine and amino acids via tetrahydrofolate-dependent one-carbon biosynthetic pathways.

The toxicokinetics of exogenously administered formaldehyde after inhalation, oral and dermal exposures has been investigated in a number of species. A similar profile has emerged in each. Following inhalation and oral exposures, exogenous formaldehyde in the lumen of the respiratory and gastrointestinal
tracts rapidly and extensively passes into the site-of-contact tissues. In contrast, uptake into the skin following dermal application is very poor.

Once within the site of contact tissues, formaldehyde either reacts directly with biological molecules (proteins, nucleic acids) or, following reaction with glutathione, is rapidly metabolised by glutathione-dependent formaldehyde dehydrogenase and S-formylglutathione hydrolase to form formate. Formaldehyde dehydrogenase is widely distributed in mammalian tissues.

Formate is either excreted in the urine, primarily as formic acid; or incorporated via normal metabolic pathways into the one-carbon pool of the body; or further oxidised to carbon dioxide and exhaled (ATSDR, 1999; IARC, 1995; DECOS, 2003). Neither formaldehyde nor formate accumulate to any significant extent in the body.

Recent work using a PBPK model for formaldehyde has suggested that in humans very little unchanged formaldehyde reaches the blood following inhalation exposures of up to 10 ppm (Franks, 2004).

**Acute toxicity**

In humans, the clinical features arising from a single exposure to evidently harmful levels of formaldehyde range from irritation damage to the mucous membranes at the site of contact (respiratory or gastrointestinal tract) to coma and convulsions (DECOS, 2003). Serious ulceration and damage of the gastrointestinal tract have been found after ingestion of formaldehyde (45 ml of a 37 % solution) or a gulp of a 40 % solution (OECD, 2002).

In the rat, oral LD$_{50}$ values of 600 – 800 mg/kg and a 4 h inhalation LC$_{50}$ of 0.6 mg/l (480 ppm) are reported. Irritation of the eyes, nose, throat and lungs, as well as cellular changes in the upper respiratory tract are observed following acute inhalation exposure in experimental animals. A dermal LD$_{50}$ value of 270 mg/kg is reported in the rabbit (OECD, 2002).
**Irritation**

In humans, sensory irritation of the eyes and respiratory tract occurs at levels above 0.3 - 0.5 ppm, with eye irritation being the more sensitive endpoint. Moderate irritation of the eyes, nose and throat occurs at 2 - 3 ppm.

In animals, formaldehyde produces irritation of the skin, eyes and respiratory tract (OECD, 2002; DECOS, 2003).

**Sensitisation**

In humans, skin contact has been shown to cause allergic contact dermatitis. In animals, strong positive sensitisation responses have been reported in the guinea pig maximisation test, the Buehler test and the local lymph node assay (DECOS, 2003).

HSE has previously looked at the evidence for the potential for formaldehyde to induce occupational asthma (HSE, 1997). The available evidence indicates that although formaldehyde has induced asthma in some individuals, the numbers of such cases are extremely low in relation to the overall numbers of people exposed. Consequently, formaldehyde should not be regarded as a significant cause of occupational asthma.

**Repeat dose toxicity**

In humans, repeated exposure to formaldehyde under occupational or residential conditions has led to symptoms associated with irritation of the upper respiratory tract and eye at concentrations between 0.1 - 3 ppm. Studies investigating the effect of repeated formaldehyde exposure on pulmonary function in humans show little or no convincing evidence of an effect, certainly when exposures are less than about 1 ppm (ATSDR, 1999). In studies reporting changes in pulmonary function, the changes have been small (e.g. less than 5 - 10% compared with reference values); exposures in these studies range from less than 1 ppm to about 3.5 ppm (ATSDR, 1999).

A few studies have undertaken histopathological examination of the nasal epithelium (biopsy specimens) in workers exposed to formaldehyde. These
studies have consistently reported increases in the occurrence of mild nasal epithelial lesions (loss of ciliated cells, goblet cell hyperplasia, mild dysplasia) in exposed workers compared with unexposed controls. Mean formaldehyde exposures were in the region 0.2 - 2 ppm (ATSDR, 1999; DECOS, 2003).

A large number of repeat dose inhalation studies have been conducted in rats, mice and monkeys. In studies in which exposure duration varied between 3 days and 13 weeks, damage to and increased cell proliferation in the nasal epithelium is reported. The histopathological changes, seen in all species, range from slight hyperplasia and squamous cell metaplasia of the ciliated and non-ciliated respiratory epithelium at concentrations of 2 - 3 ppm, to severe rhinitis, necrosis and extensive hyperplasia and metaplasia of the nasal epithelium at concentrations of 6 ppm and above. The NOAELs for these studies are in the range 1 - 2 ppm. In the one study available in monkeys, exposure to 6 ppm (the only dose level used) for 6 hours/day, 5 days/week for 1 or 6 weeks, produced histopathological changes (no further details available) and increased epithelial cell proliferation in the upper respiratory tract. The effects were more severe after 6 weeks compared with 1 week.

Longer-term inhalation studies (up to 28 months) have also been performed in rodents. Non-neoplastic effects observed in these studies range from a minimal degree of hyperplasia and squamous cell metaplasia of the nasal respiratory epithelium (reported at concentrations between 0.3 - 2 ppm) to rhinitis, necrosis and extensive restorative hyperplasia and metaplasia of the nasal respiratory epithelium at concentrations of 6 - 15 ppm. The NOAELs in these studies are generally in the range 1 - 2 ppm (DECOS, 2003).

In a 2-year drinking water study, male rats were administered formaldehyde at up to 82 mg/kg/d and female rats up to 109 mg/kg/d. Hyperkeratosis, hyperplasia and ulceration of the forestomach epithelium, focal atrophic gastritis, glandular hyperplasia, erosions/ulcerations and submucosal inflammatory inflammation in the glandular stomach were reported at the top dose. No signs of systemic toxicity were reported. The NOAELs were 15 and 21 mg/kg in males and females, respectively (OECD, 2002; IARC, 1995).
Overall, these repeat dose studies indicate that formaldehyde exerts its toxicity locally at the site of initial contact following exposure, in a manner characteristic of direct-acting irritant/corrosive chemicals.

**Mutagenicity**

Formaldehyde is clearly genotoxic *in vitro*. It induces mutations and DNA damage in bacteria. DNA-protein cross-links, DNA single-strand breaks, chromosomal aberrations, sister chromatid exchanges and gene mutations are induced in human and rodent cells.

The mutagenic potential of formaldehyde has been well-studied *in vivo*, with data available from both humans and animals. The profile that emerges is consistent with formaldehyde acting as a site-of-contact mutagen. Overall, the animal studies show negative results in studies of systemic tissues (bone marrow, spleen, leucocytes, spermatocytes) but positive results in studies investigating mutagenicity at the site of contact (increased incidences of chromosomal aberrations in cells from the lung and GI tract). Inhalation of formaldehyde leads to the formation of DNA-protein cross-links in the nasal respiratory mucosa of rats and monkeys.

In humans, increased incidences of micronuclei are reported in the cells of the buccal cavity and respiratory epithelium, but no increases in chromosome aberrations in lymphocytes and no changes in sperm morphology are reported.

Overall, the available data indicate that formaldehyde should be considered as a site-of-contact mutagen *in vivo*. This is consistent with its toxicokinetic profile (IARC, 1995; DECOS, 2003).

**Carcinogenicity**

Formaldehyde is clearly an experimental animal carcinogen, at least in rats, producing nasal tumours that are both exposure duration- and concentration-dependent. In 2-year inhalation studies in rats, no such tumours have been seen with exposure to 2 ppm but clearly increased incidences of
tumours were seen at 10 ppm and above. Signs of nasal epithelium inflammation were apparent soon after exposure began. The incidence and severity were exposure duration- and concentration-dependent, with such effects seen at concentrations down to 0.3 ppm for 24 months. Any carcinogenic potential of formaldehyde is less evident in mice and hamsters. In mice, 2/120 males showed nasal tumours following 2-year exposure to 14 ppm formaldehyde (103/240 tumours detected in male and female rats under the same exposure conditions) whilst no such tumours were seen in 88 male hamsters exposed to 10 ppm for a lifetime.

No toxicologically significant increases in tumour incidence are reported in reliable oral studies in rats or in a dermal study in mice (OECD, 2002).

Overall, the animal carcinogenicity data on formaldehyde and the available background knowledge of other substances that have one or both of the properties of site-of-contact genotoxicity and chronic inflammatory potential suggest that the nasal tumours in rats most probably arise as a consequence of pronounced chronic irritation of the respiratory tract in association with genotoxicity at this site. By extrapolation, a combination of these circumstances in humans would be of concern in relation to cancer.

Data in humans are available in the form of a large number of epidemiology studies and meta-analyses of groups of studies. At different times in the past (most recently in 2003), various different regulatory authorities and bodies have assessed the available epidemiological database (e.g. DECOS, 2003; IARC, 1995; IPCS, 2002). Consistently, each has reached a similar conclusion: namely that although some individual studies are suggestive of formaldehyde possibly having caused nasopharyngeal or nasal cancer in exposed populations, the overall strength of evidence has fallen short of showing a clear and causal association with formaldehyde exposure. In addition, all acknowledge the biological plausibility that formaldehyde could produce cancer of the respiratory tract under circumstances of sustained cytotoxicity at the site of contact. There has been no convincing evidence for an association between formaldehyde exposure and cancer of any other sites; in this respect, for sites distant from the region of initial contact any apparent association is less biologically plausible.
These reviews cover the available epidemiological data published up to 2000. Since then, a number of new epidemiology studies have been reported that provide further evidence in relation to formaldehyde exposure and cancer of the upper respiratory tract; the authors of some of these studies have also raised questions about a possible association with leukaemia. In 2004, IARC reappraised its position on the carcinogenic potential of formaldehyde, taking these new studies into consideration. IARC concluded that there was ‘sufficient evidence’ that formaldehyde has caused nasopharyngeal cancer in humans, ‘strong but not sufficient evidence’ for a causal association between formaldehyde exposure and leukaemia, and ‘limited evidence’ that formaldehyde has caused sinonasal cancer in humans. The available evidence did not support a causal role for formaldehyde having caused cancer at any other sites, including the lung.

A study-by-study appraisal by HSE of the studies considered by IARC in relation to nasopharyngeal cancer is provided as a separate annex (Annex 3) within this package. HSE’s overall interpretation of the data from these studies is that they justify increased concern for the carcinogenic potential of formaldehyde in humans (specifically in relation to nasopharyngeal cancer), but that this falls short of providing conclusive evidence that formaldehyde exposure has caused nasopharyngeal cancer in humans; there is an inconsistent pattern to the findings of the most prominent new studies which lacks a clear explanation.

A number of reviews that specifically address the apparent association seen in some studies between formaldehyde exposure and leukaemia were published in 2004. All reach the conclusion that formaldehyde is not a causative agent for leukaemia (Collins and Lineker, 2004; Heck and Casanova, 2004; Cole and Axten, 2004; Marsh and Youk, 2004); based on an assessment of the evidence and also on biological plausibility, HSE agrees with this position.

Reproductive toxicity

Although no fertility studies on formaldehyde have been conducted, repeat dose studies have revealed no adverse effects to the reproductive organs.

There is no evidence that formaldehyde adversely affects foetal development when administered by inhalation, orally or dermally. Most recently, no
developmental toxicity has been reported in two inhalation studies in which rats were exposed to formaldehyde up to 40 ppm 6 hours/day on days 6 - 20 of gestation or up to 10 ppm 6 hours/day on days 6 - 15 of gestation (DECOS, 2003; IARC, 1995).

Overall, formaldehyde is not considered to be a reproductive toxicant.

References


OECD (2002). SIDS Initial Assessment Report (SIAR). Available at:

http://www.chem.unep.ch/irptc/sids/OECDSIDS/FORMALDEHYDE.pdf