Formaldehyde

Toxicological overview

Key Points

Kinetics and metabolism

- Formaldehyde is readily absorbed following inhalation and ingestion, but poorly absorbed following dermal exposure
- Formaldehyde is rapidly metabolised at the initial site of contact into formate prior to reaching the systemic circulation
- Negligible amounts of inhaled or ingested formaldehyde reach the systemic circulation
- It is eliminated either by urinary excretion as formic acid or exhaled as carbon dioxide

Health effects of acute exposure

- Acute inhalation exposure to formaldehyde results in irritation and burning of the mucous membranes of the nose, mouth and upper respiratory tract
- Severe inhalation may cause weakness, headache, nausea, vomiting, pneumonia, dyspnoea, wheezing, coughing, laryngeal and pulmonary oedema, bronchospasm, respiratory depression, laryngeal spasm, CNS depression, convulsions and coma
- Acute ingestion will cause irritation, ulceration, burns and haemorrhage to the gastrointestinal tract, as well as metabolic acidosis, tachypnoea, jaundice and acute renal failure
- Formaldehyde is corrosive and can cause irritation and burns to the skin and irritation of the eyes. Ocular exposure may result in permanent vision alterations or blindness

Health effects of chronic exposure

- Chronic exposure to formaldehyde causes irritation of the mucous membranes tract as observed following acute exposure and may be associated with temporarily decreased lung function
- Chronic dermal exposure can lead to skin irritation and may cause skin sensitisation (allergic contact dermatitis)
- Formaldehyde is a human carcinogen

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Toxicological Overview

Summary of Health Effects

Formaldehyde is readily absorbed from the respiratory tract following inhalation, and from the gastrointestinal tract following ingestion, but is poorly absorbed following dermal exposure [1, 2]. Ingestion of formaldehyde is not a common route of exposure to formaldehyde in humans and much of the data relating to the adverse effects of oral ingestion are from case reports of acute poisoning incidents [1].

The predominant effects following an acute inhalation exposure to formaldehyde is irritation and burning of the mucous membranes of the nose, mouth and upper respiratory tract [2]. Some adverse effects following acute exposure to large amounts of formaldehyde may include weakness, headache, nausea, vomiting, pneumonia, dyspnoea, wheezing, coughing, laryngeal and pulmonary oedema, bronchospasm, laryngeal spasm, respiratory depression, obstructive tracheo-bronchitis, central nervous system depression, convulsions and coma [2, 3]. The onset of pulmonary oedema may be delayed for 24-48 hours post exposure and may be fatal [3, 4]. Acute ingestion of formaldehyde will lead to irritation and burns of the mouth and throat and burns and ulceration of the gastrointestinal tract, chest or abdominal pain, nausea, vomiting, diarrhoea, gastrointestinal haemorrhage and renal failure [2, 5].

Formaldehyde is corrosive and can cause irritation and burns to the skin and irritation of the eyes [1-3]. Ocular exposure to formaldehyde may result in permanent alterations to vision or blindness [6].

Repeated or prolonged occupational exposure to formaldehyde causes irritation of the mucous membranes tract similar to that observed following acute exposure [1]. Occupational exposure to formaldehyde vapour has been associated with temporary reversible decreases in lung function [3].

Repeated or prolonged dermal exposure to splashes of solutions containing formaldehyde can lead to skin irritation and may also cause skin sensitisation (allergic contact dermatitis) [2].

Formaldehyde is not considered to be a reproductive or developmental toxicant at exposures below those which result in significant maternal toxicity [7].

The International Agency for Research on Cancer has evaluated that there is sufficient evidence for the carcinogenicity of formaldehyde both in humans and in experimental animals. Formaldehyde is therefore considered to be carcinogenic to humans (group 1) [7].

Kinetics and metabolism

Formaldehyde is readily absorbed from the respiratory tract following inhalation, and from the gastrointestinal tract following ingestion, but is poorly absorbed following dermal exposure [1, 2]. Studies involving human volunteers and experimental animals have demonstrated that inhalation exposure to formaldehyde resulted in only local absorption in the upper respiratory tract, with any absorbed formaldehyde rapidly undergoing metabolism prior to reaching the systemic circulation [1].

Formaldehyde is metabolised at the initial site of contact into formate, by formaldehyde dehydrogenase [1]. Formaldehyde is naturally a metabolic intermediate produced in all cells during the metabolism of serine, glycine, methionine and choline [1]. Neither formaldehyde or its metabolites accumulate in any of the body tissues to any appreciable extent. However, the elimination of formate is slower than its formation from formaldehyde [2]. Formaldehyde is eliminated mainly by urinary excretion as formic acid or exhaled as carbon dioxide [1-3].

Sources and route of human exposure

The major source of exposure to exogenous formaldehyde is from occupational exposure, since it is produced and used in large quantities industrially. Formaldehyde is used in the manufacture of many permanent adhesives such as those used to produce plywood, fibreboard, particle board and carpet adhesives [1-3]. Small amounts of formaldehyde may be released into the environment by off-gassing from such materials [2, 3]. Formaldehyde in solutions of approximately 5% in water is also used as a disinfectant and fumigant in hospitals [1-3].

Small amounts of formaldehyde occur naturally in the environment and may also be present in the emissions from the combustion of organic materials such as wood and tobacco smoke, and automobile emissions [1-3]. However, the amounts of formaldehyde present from such sources are likely to be smaller than may be found in an occupational setting [2]. In occupational settings the level of formaldehyde in the air should be controlled to the occupational exposure standard (2 ppm in the UK) by adequate ventilation, if this cannot be achieved breathing protection should be used [4]. Adequate personal protective equipment is also recommended to protect against skin contact from splashes of formaldehyde solutions [4].

The major routes of occupational exposure to formaldehyde are by inhalation of vapour or by dermal contact with splashes of formaldehyde solutions. However, ingestion of formaldehyde is not a significant occupational hazard [1-3].

Health Effects of Acute / Single Exposure

Human Data

General toxicity

Formaldehyde is toxic by inhalation and ingestion. Formaldehyde is also a severe irritant to the skin, eyes, mouth, nose and upper respiratory tract [1-4].

Inhalation

The predominant effects following an acute inhalation exposure to formaldehyde is irritation and burning of the mucous membranes of the nose, mouth and upper respiratory tract [2]. Acute inhalation exposure to large amounts of formaldehyde may also give rise to weakness, headache, nausea, vomiting, pneumonia, dyspnoea, wheezing, coughing, laryngeal and pulmonary oedema, bronchospasm, laryngeal spasm, respiratory depression, obstructive tracheo-bronchitis, central nervous system depression, convulsions and coma [2, 3]. Inhalation of significant amounts of formaldehyde may be fatal due to the onset of pulmonary oedema or respiratory failure [2].

Ingestion

Acute ingestion of solutions of formaldehyde is not likely to be a significant route of occupational exposure. Much of the data relating to the adverse effects of oral ingestion of formaldehyde in humans are from case reports of acute poisoning incidents [1]. Acute ingestion of formaldehyde will lead to irritation and burns of the mouth and throat and burns and ulceration of the gastrointestinal tract, chest or abdominal pain, nausea, vomiting, diarrhoea and gastrointestinal haemorrhage [2, 5]. Formaldehyde ingestion may also result in metabolic acidosis, tachypnoea, jaundice, proteinuria, haematuria and acute renal failure [5].

Dermal / ocular exposure

Exposure to either gaseous formaldehyde or splashes of solutions containing formaldehyde are corrosive and can cause irritation and burns to the skin and irritation of the eyes [1-3]. Ocular exposure to formaldehyde may result in permanent alterations to vision or blindness [6].

Delayed effects following an acute exposure

Following an acute inhalation exposure of formaldehyde, the onset of pulmonary oedema which may be delayed for 24 to 48 hours post-exposure [3, 4].

Animal and In-Vitro Data

General toxicity

The acute toxicity of formaldehyde in experimental animals appears similar to that observed in humans, with local irritation being the most common adverse effect [1, 2].

Inhalation

The LC_{50} for formaldehyde in rats following a 4-hour exposure is 578 mg m^{-3} (471 ppm), whilst in mice the 4-hour LC_{50} is 497 mg m^{-3} (405 ppm) [2]. Mice exposed to formaldehyde by inhalation at 0.6 mg m^{-3} (0.5 ppm) developed irritation of the eyes, nose and throat [2]. Severe irritation and damage to the epithelium of the nasal cavity has been observed in rats exposed to formaldehyde at concentrations above 2-6 ppm (2.5 – 7.4 mg m^{-3}) [1, 3].

Ingestion

The oral LD_{50} for formaldehyde in rats is 800 mg kg^{-1} body weight [2]. However, there is little data available relating to the adverse health effects of formaldehyde in experimental animals following acute oral exposure [1, 2].

Dermal / Ocular

Solutions of formaldehyde have been shown to produce mild to moderate skin irritation following a 4-hour application of a 37% solution [6]. Formaldehyde has been shown to be an eye irritant in rabbits [2].

Health Effects of Chronic / Repeated Exposure

Human Data

Inhalation

Repeated or prolonged inhalation exposure to formaldehyde as may be experienced in occupational settings causes irritation of the mucous membranes of the eyes, nose, mouth and upper respiratory tract similar to that observed following acute exposure [1]. Occupational exposure to formaldehyde vapour has been associated with temporary reversible decreases in lung function [3]. Chronic inhalation of formaldehyde does not lead to respiratory sensitisation but can cause symptoms of asthma in susceptible individuals due to respiratory irritation [3].

Dermal / Ocular

Repeated or prolonged dermal exposure to splashes of solutions containing formaldehyde can lead to skin irritation or allergic contact dermatitis and may also cause skin sensitisation [2]. Following sensitisation dermal contact with small amounts of formaldehyde will give rise to outbreaks of dermatitis which may spread from the hand and arms to the body and face [6].

Genotoxicity

There is some evidence to suggest that formaldehyde may be genotoxic in humans. Studies of workers occupationally exposed to formaldehyde showed increases in DNA-protein cross-links compared to non-exposed individuals [1, 7]. Another study of workers exposed to formaldehyde showed significant increases in chromosomal aberrations and chromosomal breakage compared to unexposed controls. However, in the same study, no differences were observed in the incidences of sister chromatid exchange and unscheduled DNA synthesis and repair [1].

The Committee on Mutagenicity (COM) considered a number of biomonitoring studies of genotoxicity in workers exposed to formaldehyde in a variety of occupations. They concluded that there was no convincing evidence regarding direct systemic mutagenic effects of formaldehyde from the available biomonitoring studies. They suggested that a secondary mechanism might be involved, with regard to the genotoxic effects documented in peripheral blood lymphocytes, in the biomonitoring studies reviewed [8].

The COM concluded that there was no reason to consider that direct systemic mutagenicity would be involved in the mechanism of formaldehyde-induced systemic mutagenicity. For occupational and environmental exposure to formaldehyde, the pattern of metabolism and distribution indicates that a threshold level for *in vivo* systemic mutagenicity is likely [8].

Carcinogenicity

The International Agency for Research on Cancer (IARC) has evaluated that there is sufficient evidence for the carcinogenicity of formaldehyde in humans, and has therefore concluded that formaldehyde is carcinogenic to humans (group 1) [7].

Occupational exposure of workers to formaldehyde has been associated with a significant increase in mortality due to nasopharyngeal cancers compared with the US national population [7]. The results from the largest and most informative cohort of industrial workers in the USA, supported by largely positive findings from other studies, provide sufficient evidence that formaldehyde causes nasopharyngeal cancer in humans. There was only limited epidemiological evidence that formaldehyde causes sinonasal cancer in humans [7]. There is strong but not sufficient evidence for a causal association between leukaemia and occupational exposure to formaldehyde. Increased risk for leukaemia has consistently been observed in studies of professional workers and in 2 of 3 of the most relevant studies of industrial workers. These findings fall slightly short of being fully persuasive because of some limitations in the findings from the cohorts of industrial and garment workers in the USA and because they conflict with the non-positive findings from the British cohort of industrial workers [7].

Reproductive and developmental toxicity

There have been relatively few studies investigating the reproductive and developmental toxicity of formaldehyde. One study noted an increased incidence of menstrual disorders, anaemia, toxaemia and low birth weight of offspring in female workers exposed to urea-formaldehyde [2]. Of these studies there is insufficient evidence to determine whether formaldehyde causes reproductive toxicity, due to limitations such as small sample sizes, no information of confounding factors, self-reporting and a lack of information regarding concurrent exposure to other potentially harmful compounds [2, 3]. Formaldehyde is not expected to cause reproductive or developmental toxicity at exposures below maternally toxic doses [7].

Animal and In-Vitro Data

Inhalation

The chronic toxicity of formaldehyde has been investigated in male rats exposed by whole-body inhalation to concentrations up to 15 ppm (18.4 mg m^{-3}) for 6 hours day^{-1}, 5 days $week^{-1}$ for 6 weeks. At doses above 6 ppm (7.4 mg m^{-3}), a dose dependent increase in lesions of the nasal passages was observed, in addition to a significant increase in cell proliferation in the nasal cavity [3]. Mice exposed to formaldehyde by inhalation at concentrations up to 40 ppm (49.1 mg m^{3}) for 6 hours day^{-1}, 5 days $week^{-1}$ for 13 weeks displayed a marked reduction in body weight, laboured breathing, listlessness, hunched posture and loss of coordination at concentrations of 20 ppm (24.6 mg m^{-3}) and above. In this study, damage to the trachea and larynx were also noted at 20 and 40 ppm formaldehyde [3].

Ingestion

Male and female Wistar rats exposed to formaldehyde in drinking water for up to 2 years displayed a significant reduction in body weight compared to the controls at 82 mg kg^{-1} body weight day^{-1} for the males and 109 mg kg^{-1} body weight day^{-1} in the females. The body weight reduction was associated with a decrease in food and water intake, with terminal weights approximately 10 – 15% lower than the control animals [1, 6]. In this study, gastrointestinal lesions including papillomatous hyperplasia and hyperkeratosis, chronic atrophic gastritis, focal ulceration in the forestomach and hyperplasia in the glandular stomach were first observed at the same concentrations after 53 weeks [1]. An increase in

renal papillary necrosis was also observed in this study in both male and female rats at 82 mg kg^{-1} and 109 mg kg^{-1}, respectively, which in the female rats was also accompanied by a relative increase in kidney weight [1].

Dermal

Hairless mice dermally exposed to 0.2 ml of a 10% aqueous solution of formaldehyde, 2 times $week^{-1}$ for 60 weeks, developed epidermal hyperplasia and some mice developed cutaneous ulcers [1, 6].

Studies in guinea pigs, using the guinea pig maximisation test and the Beuhler test, and in mice using the local lymph node assay, have confirmed that repeated dermal exposure to formaldehyde causes skin sensitisation [1, 6].

Genotoxicity

The potential of formaldehyde to induce genetic mutations has been extensively studied *in vitro* in the Ames test using strains of *Salmonella typhimurium* both with and without metabolic activation with liver S9 fraction. Both positive and negative results have been obtained [2, 3, 6].

Formaldehyde has been found to be positive for mutations in many mammalian culture systems in the absence of metabolic activation. An increase in sister chromatid exchanges was reported in cultured human lymphocytes treated with formaldehyde [2]. Positive results have also been obtained for unscheduled DNA synthesis and chromosomal aberrations in the absence of metabolic activation [2, 3]. These data suggest that formaldehyde does possess significant direct acting mutagenic potential *in vitro*.

In-vivo studies in rats and monkeys exposed to formaldehyde by inhalation at 6 ppm (7.4 mg m^{-3}) have reported positive results for DNA-protein cross-links in the nasal mucosa [3, 7]. Positive results for chromosomal aberrations have also been obtained in lung cells of rats exposed to 15 ppm (18.4 mg m^{-3}) formaldehyde by inhalation [3]. Studies of the potential for formaldehyde to induce sister chromatid exchange in the bone marrow of mice exposed by inhalation have however, proved to be inconclusive. These studies suggest that formaldehyde has direct acting mutagenic potential *in vivo*.

The available *in-vivo* tests for mutagenicity using the well established bone marrow assays for chromosome aberrations or micronuclei induction, using either the inhalation or the intra-peritoneal route were predominantly negative [2, 7, 8]. They also considered the reported positives for a dominant lethal effect in *in-vivo* germ cell assays using this endpoint and concluded that it was unlikely that the effects resulted from a systemic mutagenic effect of formaldehyde [8].

The mode of action regarding the induction of nasopharyngeal tumours in rats following inhalation is consistent with formation of formaldehyde DNA protein cross links with a similar dose-response to the formation of nasal tumours, with consequent marked local effects on cytotoxicity, cell proliferation and local site of contact mutagenic events being key elements. The magnitude of the formaldehyde induced local site of contact proliferation was emphasised [8].

Overall, formaldehyde has been investigated for its genotoxic potential using both *in-vitro* and *in-vivo* studies. Based on these results, formaldehyde is considered to be mutagenic at the site of contact.

Carcinogenicity

Evidence of the carcinogenicity of formaldehyde was observed in several studies of rats exposed by inhalation, particularly by the induction of squamous cell carcinomas in the nasal cavities [7]. Similar studies in hamsters showed no evidence of carcinogenicity, and studies in mice either showed no effect, or were inadequate to allow evaluation [3, 7]. Studies in rats exposed to formaldehyde in drinking water have also shown evidence of carcinogenicity. A study in male rats demonstrated an increase in forestomach papillomas. A further study in both male and females rats showed an increase in gastrointestinal leiomyosarcomas, particularly in the females, whilst another study identified an increased incidence in the male rats of malignant tumours, lymphomas, leukaemias and testicular interstitial-cell adenomas [7].

Overall, IARC has concluded that there is sufficient evidence for the carcinogenicity of formaldehyde in experimental animals [7].

Reproductive and developmental toxicity

Studies of the reproductive and developmental toxicity of formaldehyde in rats, mice, rabbits and dogs following inhalation, ingestion or dermal exposure have not identified any embryotoxic, fetotoxic or teratogenic effects at doses below those causing significant maternal toxicity [2, 6, 7]. Therefore formaldehyde is not considered to be a reproductive or developmental toxicant.

References

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