



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 to formate at the initial site of contact
- negligible amounts of inhaled or ingested formaldehyde reach systemic circulation
- formaldehyde is eliminated by exhalation as carbon dioxide or by urinary excretion

Health effects of acute exposure

- sore throat, rhinitis, nasal irritation, bronchospasm and breathlessness are common features following exposure by inhalation
- in severe cases, laryngeal and pulmonary oedema, pneumonitis and acute respiratory distress syndrome may occur
- ingestion of formaldehyde may cause ulceration and burns, pain, nausea, vomiting, diarrhoea, gastrointestinal haemorrhage, hypotension, shock and metabolic acidosis
- formaldehyde is corrosive and can cause irritation and burns to the skin and eyes; ocular exposure may result in permanent alterations in vision

Health effects of chronic exposure

- chronic exposure to formaldehyde causes irritation and may cause the development of histopathological lesions in the nasal mucosa
- formaldehyde is a known skin sensitiser in humans, causing allergic contact dermatitis
- formaldehyde is a human carcinogen

Summary of Health Effects

Formaldehyde is readily absorbed from the respiratory tract following inhalation and from the gastrointestinal (GI) tract following ingestion. It is poorly absorbed following dermal exposure. Ingestion of formaldehyde is not a common route of occupational 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. The effects following formaldehyde exposure are expected to be largely at the site of contact.

Irritation of the mucous membranes and respiratory tract may occur following an acute inhalation exposure to formaldehyde; in severe cases laryngeal and pulmonary oedema, pneumonitis and acute respiratory distress syndrome (ARDS) have been observed. The onset of pulmonary oedema may be delayed for 24-48 hours post exposure and may be fatal. Following the perception of odour, individuals may report effects of subjective sensory irritation at levels below those at which formaldehyde is thought to cause adverse health effects.

Ingestion of formaldehyde in solution can cause damage throughout the GI tract; in severe cases this may lead to circulatory collapse, acute renal failure, respiratory failure and death.

Formaldehyde is corrosive. Exposure to dilute solutions will cause irritation to the skin and eyes, while more concentrated solutions may cause blisters, fissures, urticaria and permanent damage to the eye.

Repeated or prolonged exposure to formaldehyde causes irritation of the mucous membranes and histopathological lesions of the nasal mucosa have been reported in occupational studies. Formaldehyde is a known skin sensitiser in humans, causing allergic contact dermatitis; anaphylaxis and urticaria have also been reported.

There is no conclusive evidence as to whether exposure to formaldehyde can cause reproductive or developmental toxicity below concentrations at which significant maternal toxicity is expected.

The International Agency for Research on Cancer (IARC) has concluded that there is sufficient evidence for the carcinogenicity of formaldehyde in both humans and in experimental animals. Formaldehyde causes cancer of the nasopharynx and leukaemia. Formaldehyde is therefore considered to be carcinogenic to humans (group 1).

Kinetics and Metabolism

Formaldehyde is endogenously produced in humans; it is an essential intermediate in the production of purines, thymidine and some amino acids. It is produced in all metabolically active cells, levels in blood range from 2-3 mg/L [1].

Following exposure, exogenous formaldehyde is rapidly and almost completely absorbed to the site of contact following inhalation and ingestion; but not following dermal contact [1, 2]. Dissolution into and reaction with the mucus of the nasal epithelium and subsequent mucocilliary clearance act as a barrier to formaldehyde exposure at low concentrations; though mucostasis has been observed in rodents exposed to 18.5 mg/m³ (15 ppm) formaldehyde [3].

Formaldehyde reacts rapidly with primary and secondary amines, thiols, hydroxyls and amides, forming methylol derivatives at the site of contact. It may also react with DNA, RNA and protein to form adducts or cross-links. Studies in experimental animals suggests that DNA-protein crosslinks do not accumulate with repeated exposure [1].

Formaldehyde is rapidly metabolised to formate, mainly by formaldehyde dehydrogenase, at the initial site of contact [1, 2]. Formate may be further oxidised to form carbon dioxide or may be used in the one carbon biosynthetic pathways to form purines, thymidine and some amino acids [4]. Following ingestion of formaldehyde solution, formate levels are seen to rise within 30 minutes and peak within an hour [5, 6].

Studies involving human volunteers and experimental animals have demonstrated that exposure to exogenous formaldehyde (acute or chronic) by dermal contact or inhalation does not significantly raise levels in the blood beyond those seen as a result of endogenous production and does not increase urinary excretion of formate. Furthermore, intravenous administration of formaldehyde in experimental animals has resulted in no accumulation in the blood [1]. This is thought to be because formaldehyde is water soluble, highly reactive and rapidly metabolised; therefore the effects of exposure are expected to be limited to the site of contact [1, 7].

Formaldehyde is primarily eliminated by exhalation as carbon dioxide; urinary excretion as various metabolites is a lesser route [1, 2, 5].

Sources and Route of Human Exposure

Formaldehyde is a high-production-volume chemical (produced at levels greater than 1,000 tonnes per producer/importer per year) with major uses as a chemical intermediate and in the manufacture of a number of resins. Formaldehyde resins are used as adhesives and binders in a range of industries producing wood products, pulp and paper, synthetic fibres, plastics and coating, and textiles [3]. Formaldehyde-urea foam has been widely used as an insulating material in construction [7]. Formaldehyde may be present in, or released from commercially available woods, textiles (including clothing and carpets), other furniture and furnishings, adhesives, paints, varnishes and lacquers, various detergents/cleaning agents

and waxes [1, 7]. It may also be used under restriction in the EU as a preservative in cosmetics and in nail hardening products [8]. Formaldehyde and formalin, an aqueous formaldehyde solution, have uses in the fields of veterinary hygiene (e.g. disinfection and fumigation), in embalming and in taxidermy [2, 5, 9]. Formalin is typically composed of 37-50% formaldehyde, 10-12% methanol (to prevent polymerisation of formaldehyde) and may include various metallic impurities [6, 10].

Formaldehyde is ubiquitous in the environment as a result of a number of natural and anthropogenic processes. Notable natural sources of formaldehyde include the decomposition of organic material, forest and bush fires, and volcanic emissions [1]. Photochemical oxidation of volatile organic compounds is a secondary source of formaldehyde in the atmosphere [7]. Anthropogenic sources of formaldehyde include industrial emissions, fuel combustion (including vehicle exhaust) and other combustion processes [1].

Formaldehyde does not persist in the environment; when released to air the majority of it degrades (with a half-life of around one hour, depending on conditions), while a smaller portion moves into water where it is broken down [1, 7]. Levels of formaldehyde in ambient air are generally below 0.01 mg/m^3 ; they may reach 0.02 mg/m^3 in urban or industrial areas [1].

Formaldehyde is considered to be an indoor air pollutant, as indoor levels are generally far higher than ambient levels. Indoor sources of formaldehyde include combustion processes (such as tobacco smoking, cooking and incense burning), consumer products and building materials. Levels of formaldehyde in the home appear to vary depending on a number of factors including, the age of the home (levels decrease with time), temperature and relative humidity, the air exchange rate, and the season. The average level in homes is 0.05 mg/m^3 , however concentrations may reach 0.2 mg/m^3 in homes which are new, renovated, or with new furnishings, or during hot and humid times of year [1].

Formaldehyde is considered to be mobile in soil and would not be expected to adsorb to soil particles [7].

The general public may be exposed to exogenous formaldehyde from contact with consumer products which contain it or from a range indoor air sources (see above). Indoor air has been estimated to contribute to 98% of total inhalation exposure [1]. While formaldehyde is not persistent in the environment, environmental exposure may still occur where release is continuous. Certain foods that naturally contain formaldehyde (e.g. some fruit and marine fish) are also potential sources for the general public [7].

Exposure to formaldehyde by dermal contact or inhalation may occur in a range of industries. For example, individuals who work with phenol or urea formaldehyde resins may be exposed to vapours (or particles carried on wood dust) and those who work with formalin may be dermally exposed [7, 11]. Workplace exposure limits (WELs) are enforced to protect workers from the harmful effects of formaldehyde; in the UK the long-term WEL is 2.5 mg/m^3 (2 ppm) and the short-term WEL is 2.5 mg/m^3 (2 ppm) [12].

Health Effects of Acute/Single Exposure

Human data

General toxicity

The effects of formaldehyde are expected to be largely site of contact. It is a severe irritant to the skin, eyes, mouth, nose and upper respiratory tract [2, 5, 13].

Inhalation

Inhalation of formaldehyde causes irritation of the mucous membranes and respiratory tract. Sore throat, rhinitis, nasal irritation, bronchospasm and breathlessness are common features following exposure by inhalation. In severe cases laryngeal and pulmonary oedema, pneumonitis and ARDS may occur [14].

The available data suggest that there is a wide range of individual variation in susceptibility to formaldehyde induced irritation [3]. The odour of formaldehyde may be detected by some individuals at concentrations below those thought to cause adverse effects. The perception of this odour may lead individuals to report subjective sensory irritation (including features such as headache and nausea); however this is not considered to be a toxic effect of formaldehyde. According to the World Health Organisation the threshold for subjective sensory irritation is 0.38 mg/m^3 (for 4 hours exposure) while the threshold for objective irritation (trigeminal stimulation of the eyes indicated by increased blink frequency) is 0.63 mg/m^3 [1].

Occupational exposure studies indicate that the lung function of workers is affected at formaldehyde concentrations greater than 1.23 mg/m^3 (1 ppm) in the workplace. However, no such effects were reported in both healthy and asthmatic individuals exposed to up to 3.69 mg/m^3 (3 ppm) formaldehyde in controlled human studies [8].

Ingestion

Much of the data relating to the adverse effects of ingestion of formaldehyde in humans are from case reports of acute poisoning incidents, many of which involve formalin. The effects of formaldehyde and methanol following formalin ingestion can be difficult to differentiate [4].

Formaldehyde solutions (such as formalin) are corrosive to the GI tract; burns and ulceration throughout the tract, chest and abdominal pain, nausea, vomiting, diarrhoea, GI haemorrhage, hypotension, shock and metabolic acidosis are common features following ingestion. Circulatory collapse, acute renal failure, ARDS, pleural effusion, respiratory failure and death have been reported in severe cases [6].

One study on outcomes following ingestion of formalin reported that 7 in 26 cases rapidly developed circulatory collapse, one developed respiratory failure and overall 8 patients died (one of an unrelated cause). The fatal dose for formalin ingestion is thought to be 60-90 mL. Death can occur within 30 minutes post ingestion [6].

Dermal/ocular exposure

Dermal contact with formaldehyde solutions of 1-2% may cause irritation [7]. Exposure to higher concentrated formaldehyde solutions may cause blisters, fissures and urticaria [6].

The eyes are highly sensitive to formaldehyde [14]. Solutions at low concentrations may only cause minor irritation while higher concentrations may cause permanent corneal clouding and loss of vision [6].

Formaldehyde in air may cause eye irritation and concentrations above 61.5 mg/m^3 (50 ppm) may cause severe lacrimation [14].

Delayed effects following an acute exposure

The irritant effects of formaldehyde are transient and would be expected to subside on cessation of exposure. However, following an acute inhalation exposure to formaldehyde, the onset of pulmonary oedema may be delayed for 24 to 48 hours [13]. From 2-8 weeks following the ingestion of formaldehyde solution, up to 20% of patients have developed strictures of the GI tract [6].

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 [2, 5]. As the effects of formaldehyde are predominantly site of contact, it should be noted that rodents are obligate nose breathers, while monkeys (and humans) are oronasal breathers [7].

Inhalation

Mice appear to be notably more sensitive to the irritant effects of formaldehyde than rats [3]. The LC_{50} in rodents range from 497 mg/m^3 in mice to 984 mg/m^3 in rats [7].

Dyspnoea, vomiting, hypersalivation, muscle spasms and death have been observed in animals following a single exposure to over 120 mg/m^3 of formaldehyde in air [7].

Mice exposed to formaldehyde by inhalation at 1.2 mg/m^3 developed irritation of the eyes, decreased respiratory rate, increased airway resistance and decreased compliance [5]. Severe irritation and damage to the epithelium of the nasal cavity has been observed in rats exposed to formaldehyde at concentrations above $2.5\text{-}7.4 \text{ mg/m}^3$ (2-6 ppm) [2]. Values of between 12.3 and 36.9 mg/m^3 (10 and 30 ppm) have been given for the concentration at which respiration rate is reduced to 50% in rats, while in mice values of between 3.69 and 6.15 mg/m^3 (3 and 5 ppm) are reported [3].

Neurobehavioral effects such as altered learning, memory and motor activity have been observed in animals on both acute and repeated dose exposure to formaldehyde. Rats and mice inhaling up to 6.4 mg/m^3 (5.2 ppm) for two hours in open field behaviour studies showed decreases in exploratory behaviours and spontaneous motor activity [4].

Ingestion

There are limited data available relating to the adverse health effects of formaldehyde in experimental animals following acute oral exposure [2, 5]. The oral LD₅₀ for formaldehyde in rats is 800 mg/kg body weight [5].

Dermal/ocular exposure

Solutions of formaldehyde have been shown to produce mild to moderate skin irritation following a 4-hour application of a 37% solution [15]. Formaldehyde has been shown to be an eye irritant in rabbits [5].

Health Effects of Chronic/Repeated Exposure

Human data

Inhalation

Repeated or prolonged inhalation exposure to formaldehyde causes irritation of the mucous membranes of the eyes, nose, mouth and upper respiratory tract similar to that observed following acute exposure [2]. Histopathological lesions of the nasal epithelium have been observed in workers chronically exposed to formaldehyde, such effects have been seen below 1.23 mg/m^3 (1 ppm) [3, 7]. Changes in lung function in individuals chronically exposed to formaldehyde have not been consistently observed [4].

Atopic eczema but not respiratory allergy was associated with exposure to higher indoor levels (a median of 0.030 mg/m^3 and a peak of 0.164 mg/m^3) of formaldehyde in a prospective study of 998 pregnant women. Similarly eczema but not allergic respiratory effects were reported in a study on Finish metal workers exposed to formaldehyde (amongst other chemicals). Of 143 students exposed to 3.0 mg/m^3 , two students (one of whom was atopic) developed skin reactions to a 1% formaldehyde solution [1].

There is uncertainty surrounding the role of formaldehyde in respiratory sensitisation. There are many reports of individuals reacting to bronchial challenge with formaldehyde; however these results are often not accompanied by the detection of formaldehyde specific IgE antibodies. Reports of allergic (immunological) asthma are infrequent and where IgE is detected this does not correlate with the extent of exposure, severity of symptoms or the concurrent presence of skin reactions [16]. Studies on airway sensitisation in children have also been inconclusive [1, 2].

Dermal/ocular exposure

Formaldehyde is a known skin sensitiser in humans, causing allergic contact dermatitis [8]. Anaphylaxis and urticaria have also been reported in some cases following dermal exposure to formaldehyde. Sensitivity is routinely assessed in patch tests; approximately 2% of the European population may react to a 1% formaldehyde solution, while reactions to concentrations as low as 0.015% have been reported [16]. Elicitation of already sensitized individuals has been reported at 0.003% in solution and 0.006% in consumer products [8].

Genotoxicity

Please refer to the Genotoxicity section in “Animal and in-vitro data” for more details.

A number of studies have reported an increase in the incidence of micronucleus formation in the nasal or oral mucosa of formaldehyde exposed humans including industrial workers, pathologists, other laboratory workers and students [17, 18]. These studies suggest that formaldehyde may have a site of contact mutagenic effect in human cells. In 2012 the EU Committee for Risk Assessment (RAC) stated that although the positive data indicate a potential mutagenic effect at the site of contact, the majority of the results were not completely reliable due to methodological shortcomings (e.g. large variations in the

background frequencies of micronuclei in control populations, variety of staining procedures, no consideration of co-factors) [18].

There are several reports of an increase in the incidence of micronucleus formation in peripheral blood lymphocytes of humans exposed to formaldehyde via inhalation [18]. Inconsistent results have been reported for sister chromatid exchange (SCE) and chromosomal aberrations in human peripheral blood lymphocytes [2, 17]. Studies of workers occupationally exposed to formaldehyde showed increases in DNA-protein crosslinks in peripheral blood lymphocytes compared to non-exposed individuals [2, 18, 19].

In 2007 the Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM) reviewed the available evidence for systemic mutagenicity of formaldehyde. The Committee considered that the available biomonitoring studies of genotoxicity in workers exposed to formaldehyde in a variety of occupations were of poor quality. 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 reviewed studies. The Committee also considered data from toxicokinetic studies in both humans and animals and concluded that the amount of formaldehyde systemically available following inhalation exposure at the occupational standard would be negligible. The COM concluded that there is no reason to consider that direct systemic mutagenicity would be involved in the mechanism of formaldehyde induced systemic tumourigenicity. 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 [19].

Similarly in 2012 the EU RAC stated that systemic effects are not expected as formaldehyde exposure does not result in an increase of blood formaldehyde concentrations. The Committee considered that the results from human biomonitoring studies were inconsistent. In addition, the positive findings from the human studies were not supported by the in vivo mutagenicity studies in experimental animals. The Committee concluded that there is not sufficient evidence to conclude that formaldehyde induces systemic genotoxicity in humans [18].

Carcinogenicity

The IARC has classified formaldehyde as carcinogenic to humans (group 1). IARC states that formaldehyde causes cancer of the nasopharynx and leukaemia, and that a positive association has been observed between exposure to formaldehyde and sinonasal cancer [17].

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. 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. Case control studies have shown positive associations between formaldehyde exposure and sinonasal cancer,

these findings however are not supported by industrial cohort studies. In the case controlled studies wood dust exposure is strongly associated with sinonasal cancer. Uncontrolled confounding to wood dust could explain the reported associations in these studies. Local effects in nasal tissues, genotoxicity and cell-proliferation rate are considered to be key determinants in the nasal carcinogenicity of formaldehyde [17].

Consistent reporting of increased leukaemia risk in proportionate mortality studies, elevated risk in a nested control study and 2 large industrial cohort studies suggest a causal association between formaldehyde and leukaemia. However, a large high quality study on British industrial workers showed no excess mortality for leukaemia. The IARC note in their 2012 evaluation that full agreement was not reached within the working group in regards to formaldehydes role in leukaemia. The majority believed the evidence for causality to be sufficient while a minority believed the evidence to be limited [17].

In 2012 EU RAC reviewed the available evidence on the carcinogenicity of formaldehyde and concluded that formaldehyde should be classified as Carc.1B (may cause cancer) according to Classification, Labelling and Packaging regulations. The Committee considered that there was limited evidence of carcinogenicity in humans and this data was mainly from a positive association of nasopharyngeal tumours in industrial cohorts. However, there was sufficient evidence of carcinogenicity in experimental animal studies [18].

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, toxemia and low birth weight of offspring in female workers exposed to urea-formaldehyde. From 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 [5].

A retrospective cohort study on birth outcomes in pregnancies where paternal exposure to formaldehyde had occurred suggested an increased rate of spontaneous abortion. However, as a retrospective study this finding could be subject to recall bias [20].

A meta-analysis of epidemiological studies showed a slightly elevated but non-significant risk of spontaneous abortion amongst formaldehyde exposed female workers, though after data adjustments to control for bias were made, the elevated risk was lost. A more recent meta-analysis utilising many of the same studies demonstrated a significant increased risk; however when self-reported studies were removed from analysis significance was lost [20].

The UK Teratology Information Service followed up prospective (22) and retrospective (3) cases of formaldehyde/formalin exposure during pregnancy. Amongst the prospective cases the rate of congenital malformations in live born infants was not significantly higher than background. Data from the retrospective cases did not show any patterns in pregnancy outcomes for maternal formaldehyde exposure [20].

The evidence regarding a potential increase in the risk of congenital malformations and spontaneous abortions following exposure to formaldehyde during pregnancy is inconclusive. Data is both limited and conflicting and as such, an increased risk cannot be ruled out [20].

Animal and in-vitro data

Inhalation

Inhalation studies in various animal species demonstrate that the nasal epithelium is the most sensitive target for inhaled formaldehyde [4]. Rhinitis and histopathological changes of the upper respiratory tract (most notably the nasal cavity), including metaplasia, hyperplasia and rhinitis have been observed in a number of species following chronic exposure to formaldehyde [3, 7]. Additionally, studies in experimental animals have suggested that formaldehyde may also enhance sensitivity to inhaled allergens [7].

Neurobehavioral effects which include altered motor activity and impaired learning and memory have been observed in numerous animal studies. Mice exposed to 2.46 mg/m³ (2 ppm) for 3 hours a day, 5 days a week for 2 weeks showed reductions in spontaneous motor activity. In another study rats were trained in water mazes and then exposed to formaldehyde via inhalation for 2 hours a day, for 10 days, re-running the maze each day [4]. The rats were exposed to 0, 0.12, 0.62 or 6.64 mg/m³ (0, 0.1, 0.5 or 5.4 ppm) formaldehyde; mean swimming time increased at 0.62 and 6.64 mg/m³ while error frequency increased at all doses [4].

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 bw/day for the males and 109 mg/kg bw/day 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 [2, 15]. 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. An increase in renal papillary necrosis was also observed in this study in both male and female rats at 82 mg/kg and 109 mg/kg, respectively, which in the female rats was also accompanied by a relative increase in kidney weight [2].

Dermal

Hairless mice dermally exposed to 0.2 ml of a 10% aqueous solution of formaldehyde 2 times a week for 60 weeks developed epidermal hyperplasia and some mice developed cutaneous ulcers [2, 15].

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 [2, 15].

Genotoxicity

Formaldehyde has produced positive results in bacterial mutagenicity assays, with and without metabolic activation. Chromosomal aberrations, increased micronucleus formation and SCE have been observed in cultured human cells and cultured mammalian cells treated with formaldehyde. Positive results have also been reported for DNA strand breaks, unscheduled DNA synthesis and DNA-protein crosslinks [5, 17, 18]. These data suggest that formaldehyde does possess significant direct acting mutagenic potential in-vitro.

In vivo studies have demonstrated genotoxic effects in somatic cells at the site of contact in animals exposed to formaldehyde [18, 19]. DNA protein crosslinks were induced in the nasal turbinates of monkeys (≥ 0.7 ppm (≥ 0.861 mg/m³)) and the nasal mucosa of rats (≥ 0.3 ppm (≥ 0.369 mg/m³)) exposed to formaldehyde by inhalation [18].

However, in-vivo tests for micronucleus induction and chromosome aberrations in the bone marrow of rodents exposed to formaldehyde by inhalation or intraperitoneal administration were predominantly negative [19]. Formaldehyde did not induce DNA protein crosslinks, SCE or micronuclei in the peripheral blood cells of rats exposed via inhalation [18].

The mode of action for formaldehyde induced nasal tumours in rats is considered to involve increased cell proliferation due to formaldehyde induced cytotoxicity. The increase in cell proliferation increases the number of DNA replications and therefore increases the probability of DNA-protein crosslink initiated replication errors, resulting in mutations. This suggested mechanism is based on evidence of a consistent dose-response relationship for cell proliferation, DNA protein cross links and tumours [7, 19, 21].

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 [17, 18]. 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 female 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 [17].

Overall, IARC and the EU RAC have concluded that there is sufficient evidence for the carcinogenicity of formaldehyde in experimental animals [17, 18].

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 [5, 15, 20].

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