Risiken erkennen – Gesundheit schützen

Toxicological Assessment of Formaldehyde

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Formaldehyde is manufactured on a large scale industrially and is to be found in numerous (consumer) products. Furthermore, it is formed during the cell metabolism of humans and other living organisms. At present, the substance is classified as “possibly carcinogenic” (C 3). Mid 2004 after a consultation with experts, the International Agency for Research on Cancer (IARC) announced that formaldehyde was deemed to be a human carcinogen following a reassessment (sufficient evidence that formaldehyde causes nasopharyngeal cancer in humans). It has not yet published its reasons.

In conjunction with a reassessment of formaldehyde, BfR has undertaken a hazard assessment. It contains the data needed to assess the human carcinogenicity of formaldehyde as well as a proposal for the classification and labelling of the substance on the European level. BfR proposes only classifying formaldehyde as a human carcinogen in respect of uptake from respiratory air.

Based on the hazard assessment BfR undertook a toxicological assessment. This assessment draws on a concept that postulates a so-called “practical threshold” below which a significant carcinogenic risk is no longer to be feared. In the past a “simplified approach” was used to assess substances whose carcinogenic effects are triggered by a change in genetic information. Each amount was deemed to be harmful and no threshold value was established. In the case of formaldehyde, however, tumour formation is linked to two biological mechanisms of action which develop joint action from a specific concentration upwards: first, a cytotoxic effect which triggers reactive cell proliferation and second, a change in genetic information. Based on animal data on cell proliferation as well as on human data on sensory irritation of the upper respiratory tract, a tolerable air concentration was, therefore, established for formaldehyde, a so-called safe level of 0.1 ppm (parts per million).

Investigations are currently underway to determine whether a tolerable dose should also be established for oral intake. The Indoor Air Hygiene Committee of the Federal Environmental Agency (UBA) is also examining grounds for an indoor air guide value.

1 General Considerations

Risk assessment of formaldehyde is focussed on the most important endpoint for adverse effects on human health, namely carcinogenicity.

Data have been described and thoroughly assessed in BfR’s report on the assessment of the carcinogenicity of formaldehyde (Schulte et al., 2006). According to the hazard assessment, there is sufficient evidence that formaldehyde causes tumors of the upper respiratory tract in humans, based on epidemiological data and on mechanistic considerations. Hence, risk assessment is performed for tumors in the upper respiratory tract.

In epidemiological studies an association has also been observed between formaldehyde exposure and leukemia in humans. However some facts cast doubts on a causal relation between formaldehyde exposure and leukemia. First, inhalation of formaldehyde (1.9 parts per million (ppm) for 40 minutes (min] in humans, 6 ppm for 6 hours (h) in monkeys, 14.4 ppm for 2 h in rats) does not increase the systemic concentration of formaldehyde and it can be assumed that there is no increased formaldehyde concentration in the bone marrow, the

target tissue for inducing leukemia, after formaldehyde exposure in the concentration range described (Casanova et al., 1988, Heck et al., 1985). Furthermore, inhaled formaldehyde does not increase protein adducts or DNA-protein cross links in bone marrow of rats (up to 15 ppm) or rhesus monkeys (up to 6 ppm) and does not induce chromosomal aberrations in rat bone marrow (up to 15 ppm) (Heck and Casanova, 2004) indicating that formaldehyde related effects cannot be demonstrated in the target tissue. It can be concluded that inhaled formaldehyde reacts at the site of entry and therefore will not reach relevant target cells in the bone marrow via the blood stream. It has been speculated that stem cells circulating in the peripheral blood could be targeted by formaldehyde when passing the lung or tissues in the upper respiratory tract. However, no experimental evidence has been provided to support this hypothesis. Hence, there is no biologically plausible mechanism which could explain the epidemiological findings. In summary, it is concluded that at the present state of knowledge the epidemiological findings describe an association rather than a causal relationship between leukemia and formaldehyde exposure. This is why risk assessment is referred at present to the induction of tumors in the upper respiratory tract and does not take leukemia into consideration.

There are two main approaches to perform risk assessment. In the margin of exposure (MOE) approach the relevant no observed adverse effect level (NOAEL) is compared with the exposure level and the distance between the two levels is assessed with respect to the safety of human health. In the safe level approach, the NOAEL (used as “point of departure”) is usually divided by two safety factors. One accounts for the difference between animal and man, the other for the variability among humans. If the NOAEL can be derived from human data it may be appropriate to use modified safety factors or even no safety factor at all.

Formaldehyde is acting at the site of entry and concentration is the relevant metric for the exposure. As formaldehyde is a chemical with a variety of use categories and use patterns the safe level approach is more appropriate than the MOE approach. It allows the comparison of the measured concentration in the air (which is the relevant measure with regard to the exposure eliciting a local effect) with the defined safe level. It is thus possible to elaborate management options suited to the individual exposure scenario.

In other contexts, acceptable exposure to formaldehyde is restricted to concentrations at which no odor is perceived. However, the perception of odor as such is judged not to be an adverse effect on human health (see: European Methodology for producing Acute Exposure Threshold Levels, 2006) and hence, in risk assessment, odor perception is not an appropriate health endpoint.

In this section, a safe level is derived with regard to the induction of tumors in the upper respiratory tract including the pharyngeal region. The “point of departure” is cytotoxicity in rats and sensory irritation as a surrogate for this in man. It takes into consideration the dose-response relationship and mechanistic information of relevant steps in the development of formaldehyde induced tumors in this anatomical region.

2 Mechanistic Aspects

Understanding the mechanisms underlying tumor induction by formaldehyde is critical for determining whether risks observed in animal experiments are of relevance to humans. Mechanistic considerations may also be used to define a practical threshold. A chemical agent can increase the risk of cancer either by damaging DNA or by increasing the number of cell replications, or both. Cell replication can rise due to increased cell division (by mitogenesis), due to inhibited apoptosis or by regeneration processes following cytotoxicity.

Whether genotoxicity is caused by an endogenous process or due to exogenous exposure leading to genetic changes, DNA replication is required to fix the genetic errors permanently. Thus, DNA replication not only provides more opportunities for errors, but also fixes the errors into a permanent genomic alteration. An increased DNA replication can lead to an increased risk of cancer. Even for genotoxic chemicals, the dose response for tumor incidence is essentially dependent on cell proliferation. Increased cell proliferation is by itself the basis for carcinogenicity induced by non-genotoxic agents. For non-genotoxic chemicals, particularly those acting by non-receptor dependent mechanisms, a threshold phenomenon will usually be involved, in many cases associated with cytotoxicity.

With respect to the induction of nasal tumors by formaldehyde it has to be considered

1) whether genotoxic events play the determining role or
2) whether the increased incidence of tumors is secondary to recurrent cytotoxicity only or
3) whether a combination of both processes may be involved.

2.1 Cell proliferation and histopathological effects

Increased cellular proliferation as a consequence of epithelial cell toxicity is a most significant determinant of uncontrolled cell growth. Formaldehyde induces irritation and cytotoxicity at the point of contact. An interaction of the carbonyl atom as the electrophilic site with amino groups in cellular proteins and nucleic acids is believed to be related to the germicidal properties of formaldehyde. The same reaction may also be responsible for its irritating and cytotoxic effects. Toxicity occurs when intracellular levels of formaldehyde saturate formaldehyde dehydrogenase activity, overwhelming the natural protection against formaldehyde and allowing the intact molecule to damage cell membranes, cytoplasmic or nuclear components, as well as DNA. Therefore, high doses of formaldehyde are cytotoxic resulting in degeneration and necrosis of mucosal epithelial cell layers. A prevalent and constant observation in inhalation studies is the appearance of non-neoplastic lesions in different grades of severity and incidences. They have been observed in low severity grade but statistically significant at concentrations down to 2 ppm.

Overall the results support the well-established pathogenesis that epithelial hyperplasia may precede squamous metaplasia which in turn may become a dysplasia known as precursor lesion of squamous cell carcinoma. In determining the extent of damage to the respiratory epithelium the relationship between concentration and total dose has been studied in experiments where rats were exposed to a range of concentrations for various duration of time so that the total inhaled dose was constant. It was concluded that formaldehyde concentration in the inspired air might be more important than exposure duration (Wilmer et al. 1987, 1989). Nevertheless, the development of nasal squamous cell carcinoma is likely to require repeated and prolonged damage to the nasal epithelium. A single high dose (40 ppm) for short duration is probably not sufficient to induce squamous cell carcinoma cancer (Bhalla et al., 1991, Monteiro-Riviere and Popp 1986).

The effect of formaldehyde exposure on cell proliferation within the respiratory epithelium of rats has been examined in a number of short-, medium-, and long-term studies and an extensive data set is available in the F344 rat (Swenberg et., 1986; Wilmer et al., 1987, 1989; Zwart et al., 1988; Monticello et al., 1991, 1996; Casanova et al., 1994). Rats inhaled formaldehyde (0, 0.7, 2.0, 6.0, 10 and 15 ppm) 6 h/day, 5 days/week for up to 2 years. The dose response for regenerative cell proliferation was non-linear, with the proliferation rates at 0.7 and 2 ppm not significantly different from control, but showed even lower values. At higher concentrations (6, 10 or 15 ppm) increasing rates of cell turnover were seen

(Monticello et al., 1991; Connolly et al. 2002). Also in another study the no-effect level in rats was approximately 2 ppm (2.4 mg/m3) given for 6 h/day for 9 days (Swenberg et al., 1983). In addition, the relative increase in proliferative response is dependent on the specific site within the nasal cavity and not always directly related to the duration of exposure. The extent of the carcinogenic response following exposure to formaldehyde is correlated to the size of the target cell population within specific regions of the nasal cavity (Monticello et al., 1996).

To illustrate more precisely a non-monotonic dose response relationship Gaylor et al. (2004) analyzed the cell proliferation data from the study of Monticello (1996) with Fisher 344 rats exposed to formaldehyde by inhalation at concentrations of 0, 0.7, 2.0, 6.0, 15 ppm for 6 h per day, 5 days per week, for up to two years. At the time of sacrifice of an animal, measurement of the labeling index was obtained for several sites of the nasal respiratory epithelium. In this analysis a statistically significant departure from a monotonic dose response was demonstrated for time-weighted average labeling indices with an estimated zero equivalent dose at a formaldehyde concentration of 5.4 ppm, with a lower 95 % confidence limit of 2.7 ppm. For cancer risk assessment, the data supports the hypothesis that the threshold-type dose response for nasal tumor incidence is the result of minor genotoxicity at low doses which is superimposed by a non-linear dose response for cell proliferation at cytotoxic dose levels.

Increased epithelial cell proliferation (respiratory and olfactory epithelia) within the upper respiratory tract has also been observed in monkeys exposed to airborne formaldehyde (Monticello et al., 1989; Casanova et al., 1991). Although comparable data in humans are not available it can be assumed that similar responses will occur in the respiratory epithelium of humans.

2.2 Genotoxicity

In rats and monkeys formaldehyde induces DNA-protein-crosslinks (DPX) at the anatomical site of exposure. In the rat, these lesions are detected mainly in the mucosa of the lateral meatus in the nasal turbinates after inhalation of a concentration as low as 0.3 ppm formaldehyde (Casanova et al., 1989). In monkeys, these alterations are found predominantly in epithelial cells of the middle turbinate mucosa beginning at an air borne concentration of 0.7 ppm. For concentrations up to 2 ppm formaldehyde, a linear dose-response-relationship is seen. At concentrations above 2 ppm, when the cellular content of glutathione becomes saturated, cytotoxicity influences the yields of DPX, resulting in an increased DPX formation rate and finally a non-linear dose response curve. The available results lead to the conclusion that it is not possible to derive a defined exposure concentration below which DPX formation may not be induced. Therefore a NOAEL cannot be established for the generation of DPX.

As DPX have not been measured in human studies, a model for species extrapolation was developed according to which DPX yields in humans are lower than in monkeys, and in monkeys much lower than in rats (Casanova et al., 1991). In human studies evidence has been most consistent for effects at the site of contact with an increased incidence of micronucleated cells of humans occupationally exposed to formaldehyde. In spite of methodological insufficiencies the results can be interpreted as showing that formaldehyde can express its genotoxicity in directly exposed cells. However, a dose-effect relationship cannot be derived from these studies.

With regard to a mechanistic model it is important to consider whether DPX are pre-mutational lesions able to produce neoplasia (by initiating DNA replication errors resulting in

mutations), or are most probably events leading to cell death or are effectively repaired. Induction of DPX in parallel with mutation endpoints, such as micronuclei and so-called small colonies in the mouse lymphoma assay, indicative of clastogenic effects (Merk and Speit 1998; Speit et al. 2000), give some evidence of a close relationship between the genotoxic endpoints. This finding is interpreted as being in line with the assumption that cross links act as adducts which impair replication of DNA, leading to DNA strand breaks and chromosomal aberrations. Although the interpretation that formaldehyde induced DPX represent premutagenic events, is in need of further corroboration, presently the possible causal relationship between DPX and mutations should be considered as a crucial factor in tumor induction by formaldehyde.

The generation of DPX depends on the concentration of formaldehyde present in the cell which in turn is related to the airborne concentration and the capacity of the cell to metabolize formaldehyde and to unspecific covalent binding of the chemical. Toxicokinetic modeling suggests that at concentrations up to 6 ppm approximately 93 % of formaldehyde in the rat nasal respiratory mucosa is eliminated via metabolic pathways, the capacity of which can be saturated at high concentrations, 7 % is eliminated by non-saturable pathways other than formation of DPX (e.g. covalent binding to mucous proteins) and only 7×10^{-6} % is covalently bound as DPX (Heck et al., 1994; Heck and Casanova, 2004). In rhesus monkeys, results were obtained at several sites of the upper respiratory tract (middle turbinates, lateral wall septum and nasopharynx) which were similar to the findings in rats (Casanova et al., 1991). In addition, after exposure of rhesus monkeys to 6.0, 2.0 and 0.71 ppm 14C-formaldehyde for 6 h, formation of DPX could also be demonstrated in other tissues of the upper respiratory tract (larynx, trachea, carina, and major pulmonary airways) at exposure concentrations of 2 ppm and 6 ppm. As formaldehyde is “detoxified” involving GSH-dependent oxidation by formaldehyde dehydrogenase, the generation of DPX will sharply increase at formaldehyde concentrations exceeding the intracellular capacity of glutathione. This will result in a non-linear concentration-effect relationship of airborne formaldehyde and DPX generation with a disproportional increment when formaldehyde concentrations exceed 2 ppm.

2.3 Other effects relevant for tumor formation

As has been pointed out, based on data in rats, cytotoxicity does play a critical role in the process of cell proliferation which contributes to tumor formation. Whereas for the rat a NOAEL can be derived concerning cytotoxicity, dose-response data in humans are not available for the whole range of concentrations. In humans effects at low formaldehyde concentrations are related to sensory irritation of mucous membranes of eyes, nose and throat. According to Doty et al. (2004) airborne chemicals may elicit sensory irritation by stimulation of free nerve endings, particularly those on readily exposed mucous membranes of eye, nose, and the upper respiratory tract. Sensory correlates are sensations such as stinging, burning or irritation whereas physiological correlates include release of mediators such as substance P and calcitonin gene-related peptide and even inflammation as has been described for acetone (Matshushita et al., 1969; Morgott, 2001). Given the physiological correlate to inflammation, we feel that it is justified to use sensory irritation as a surrogate for cytotoxicity.

Clinical studies and cross-sectional surveys in humans are sources for concentration-effect relationship concerning sensory irritation on eyes, nose, and throat. There is some variability among the results of different studies. This is partly because of variation in individual responses to formaldehyde. However, exposure conditions (temperature, humidity, duration

and co-exposure to other irritants) are also likely to influence response levels in well-conducted studies (Bender, 2002).

Several short-term studies have been reported concerning irritation (Kulle et al., 1987,1993). Analysis of the studies allows the conclusion that a LOAEL (lowest observed adverse effect level) for mild and moderate eye irritation of 1.2 mg/m^3 (1 ppm) and for nose/throat irritation of 2.5 mg/m^3 (2 ppm) can be derived. The NOAEL in the studies was 0.6 mg/m^3 (0.5 ppm). In their review Paustenbach et al. (1997) calculated from numerous studies that about 50 % of chamber-exposed individuals will report eye irritation at 2 ppm formaldehyde, 25 % at 1 ppm and few, if any, will report eye irritation at 0.5 ppm. They concluded that no irritation should occur at 0.3 ppm or less even with exposure for 8 h/d. In another study, eye irritation was reported in 3 out of16 (19 %) volunteers exposed to 0.24 ppm formaldehyde for 5 h (Andersen and Molhave, 1983).

From a long-term exposure study a LOAEL of 0.26 mg/m^3 (0.21 ppm) and a NOAEL of 0.09 mg/m^3 (0.08 ppm) can be established. The critical effects refer to nasal and eye irritation and nasal obstruction (Wilhelmsson and Holmström, 1992)**.** Another study describes mild damage to nasal epithelium as well as mild irritation of the eyes and the upper respiratory tract at a level of 0.3 mg/m^3 (0.25 ppm) (Holmström et al. 1989).

2.4 Dose-response relationship for tumors in the upper respiratory tract

The majority of inhalation studies in rats show that significant tumor rates were obtained at exposure levels greater than or equal to 6 ppm. There is firm correlation between the most frequent tumor type (squamous cell carcinoma) and the predominant target epithelium for exposure and their anatomical localization in the nasal cavity. Results from inhalation studies in mice confirm the nasal cavity and the respiratory epithelium as the target site for tumor response.

Considering all human data from cohort studies including the recent updates by Hauptmann et al. (2004), there is evidence for a causal relationship between the exposure to formaldehyde and the generation of tumors in the naso-pharyngeal regions of humans. An almost twofold excess of death due to naso-pharyngeal cancer was observed in workers exposed to high peak and high cumulative amounts compared to non-exposed controls suggesting that tumor related death depends on concentration/exposure levels. In the human studies the concentration-response relationship which could be assessed is limited to the relatively small range between 1 and 5 ppm. There are no data in humans for concentrations above 6 ppm, the concentration at which the animal experiments show clear increase in tumor rate. As the exposure analysis is retrospective and the exposure matrix expressed on categorial exposure scale there are some difficulties to apply a concentration-response model to the data. It can be concluded from the data in the cohort studies that the relative risk for naso-pharyngeal cancer was significantly increased when the exposure concentration was equal to or greater than 4 ppm (repeated peak exposure category).

In conclusion:
DPX cross-links and tumors clearly show a dose-response relationship in various species. Cross-links have been observed at low exposure concentrations, with significantly increased rates at concentrations above 2 ppm and a dose-response relationship has also been demonstrated for tumors with statistically significant increases at exposure concentrations higher than 6 ppm in the rat and 4 ppm in man.

2.5 The mechanistic model for tumor induction

2.5.1 Genotoxic mechanisms

The mechanisms by which inhaled formaldehyde induces nasal tumors are understood in the essential steps. Basically the induction of mutations, for which DPX are considered as precursors, is one factor in inducing carcinogenicity. When discussing the role of inhalation exposure to formaldehyde it should be considered that formaldehyde is formed endogenously by catabolism of the amino acids glycin and serin. In its activated form formaldehyde is physiologically essential, e.g. for the synthesis of purin bases. Formaldehyde concentrations are approximately 100 µmol/l in the blood of several species, such as rats, monkeys and humans. Concentrations of 200 - 400 µmol/l were determined in livers or nasal mucosa of rats (Heck et al., 1982). Hence, there is “internal” exposure by endogenous formaldehyde levels to which all tissues in the body are exposed. The question is whether there are genotoxic effects arising from physiological formaldehyde exposure. Studies with various cell lines show that formaldehyde concentrations in the range mentioned above (100 – 400 µmol/l) are able to induce DNA damage (e.g. DNA single strand breaks, micronuclei). In spite of the difficulty of extrapolating these results to the in vivo situation, one has to consider the possibility that endogenous formaldehyde may contribute to "spontaneous" base-line level of DPX.

2.5.2 Cytotoxicity

Nasal tumors are rare among control rats and mice. Their incidence is well under 1 % and in humans ~10^{-6} . The basal tumor rate might be due, for example, to DNA-damage, which remain unrepaired, or a spontaneous random infidelity in DNA replication. Normally the rates of DNA synthesis and mitosis in the adult nasal epithelium are low and similar in rodents and humans. There is considerable evidence that a sustained increase in epithelial cell regenerative proliferation resulting from formaldehyde-induced cytotoxic events is a prerequisite for the induction of nasal tumors. Regenerative cell proliferation increases the number of DNA replications and thus increases the probability of a DPX initiated DNA replication error resulting in a mutation. This proposed mode of action could be consistent with the observed point mutations at the GC base pairs in the p53 cDNA sequence in 5 of 11 squamous cell carcinomas from rats exposed to 15 ppm formaldehyde for up to 2 years (Recio et al.,1992). However, it is not clear whether this kind of mutation is primarily an initiating event or whether it is induced in a later stage e.g. in the progression stage of tumor formation.

2.5.3 Dose-response relationship

Given the internal exposure to endogenous formaldehyde and the experimental results it is not feasible to derive an exposure concentration without DPX formation. However, there is evidence that a relevant increment of DPX formation is linked to intracellular glutathione depletion at higher exposure concentrations, which leads to a non-linear increase of intracellular formaldehyde, and to sustained cell proliferation due to cytotoxic effects. The proposed mode of action is based on observations of consistent, parallel dose-response relationships for all three endpoints (sustained cell proliferation, generation of DPX and tumors) and on the concordance of the incidence of these effects across various regions of the nasal passages of the rat. While exposure to formaldehyde leads to both genotoxic effects and irritation/cytotoxicity, neoplastic transformation is observable only if certain concentrations in the target cells are reached or exceeded, leading to a non-linear dose-response relationship which is mainly determined by regenerative hyperplasia. The

concentration-response-relationships for DPX formation, cytotoxic effects, proliferative response and tumors are highly non-linear, with a significant increase of the slopes at concentrations of around 4 ppm, a concentration at which glutathione-mediated metabolism is saturated (Casanova and Heck 1987). According to data from Swenberg et al. (1983) and Casanova et al. (1994), increased epithelial cellular proliferation, histological changes and DPX formation are more closely related to exposure concentration than to total cumulative exposure. This finding is in line with the analysis of exposure matrices in the epidemiological studies where the observed tumors were related to peak exposure (Hauptmann et al., 2004).

2.5.4 The “safe” level

As the concentration-effect relationship of epithelial cellular proliferation is non-linear, a linear extrapolation of the tumor incidence from high to low dose exposure would markedly overestimate the risk at low exposure and is therefore inappropriate. Given a non-linear concentration-effect relationship and considering the background DNA damage and its variability, it is assumed that at lower concentrations the cancer incidence caused by formaldehyde cannot be distinguished from background incidence. In those circumstances, a “safe” level is defined as the concentration at and below which there is no increased risk above background risk. As formaldehyde increases the incidence of tumors in the upper respiratory tract only at concentrations which also induce cytotoxicity, a “practical” threshold is marked by this effect. Any risk in the concentration range at and below the so defined “safe” level is extremely low and cannot be distinguished from the background risk, and is, therefore, “practically” non-existent.

2.5.5 Interspecies comparison

The proposed underlying mechanism for the induction of tumors by formaldehyde and its biological plausibility is derived from animal data, mainly in rats. There are no arguments that the chain of events does not apply to the situation in humans. Interspecies comparison shows that cells lining the nasal airways of F344 rats and rhesus monkeys are comparably sensitive to the cytotoxic effect of inhaled formaldehyde. Hence, there seems to be no great interspecies difference (Kimbell et al., 2001). Although not sufficient in itself as a basis for inferring causality, direct evidence on histopathological lesions in the nose of humans exposed primarily to formaldehyde in the occupational environment is consistent with a qualitatively similar response of the upper respiratory tract in humans and experimental animals to formaldehyde. However in rats exposed to moderate levels of formaldehyde, histopathological changes, increased epithelial cell proliferation, and DPX formation are restricted to the nasal cavity while in formaldehyde exposed monkeys (with a similar anatomical situation of the upper respiratory tract to man, serving as surrogates) effects have been observed deeper within the respiratory tract. As the anatomy of the upper respiratory tract in rhesus monkeys is similar to the situation in man it can be assumed that human cells will react in the same way as the monkey’s cells, resulting in a sensitivity which is comparable to monkey.

In summary, from all the evidence available, it can be concluded that inhalation of formaldehyde presents a carcinogenic risk to humans at concentrations leading to irritation/cytotoxi-city. At irritating/cytotoxic concentrations inflammatory reactions and regenerative processes become the dominant risk factors, by promoting formaldehyde induced genotoxic events (DPX), increasing DNA damage and thus promoting malignant cell transformation. In the absence of cytotoxicity and regenerative processes, the theoretical increase in tumor incidence caused by formaldehyde is practically non-relevant.

3 Derivation of a "safe" level

3.1 Choice of endpoint and point of departure

Direct derivation of a “safe” level from epidemiological studies is not feasible as the availability of data in particular those describing the exposure parameters is limited, as is the number of tumor cases. The extrapolation to low concentrations based on a statistical model has a high degree of uncertainty because the result is determined more by the choice of the model than by the observed concentration response data (Edler, 2005).

Therefore, an alternate approach has been chosen, based on mechanistic considerations described under sub-section 2.5. As pointed out irritation/cytotoxicity is the most important step in the chain of events. Hence, the NOAEL for this effect has been used as point of departure for the derivation of the “safe” level. As for humans the available data do not allow deriving a NOAEL for cytotoxicity, sensory irritation is selected as a surrogate which selection has been justified in sub-section 2.3. The concentration at which no sensory irritation is observed is taken as point of departure. Supportive evidence is provided using data in rats and the concentration at which no cytotoxicity has been observed in animal studies serves as point of departure. The “safe” level is derived by applying appropriate safety factors to the NOAEL in animals.

3.2 Human data

From the short-term studies a LOAEL can be derived for mild and moderate eye irritation of 1 ppm and for nose/throat irritation of 2 ppm. A NOAEL of 0.5 ppm is reported by Kulle et al. (1987; 1993). Based on the analysis of Paustenbach et al. (1997) and considering additional subjective data it cannot be excluded that even at concentrations of 0.2 - 0.3 ppm some individuals respond with sensory irritation after short-term exposure.

In long term studies (10 years average) also LOAELs in the range of 0.2 - 0.3 ppm were observed and from the available data a NOAEL of about 0.1 ppm may be derived. The critical effect refers to nasal and eye irritations, which we use as surrogates for cytotoxic effects (Holmström et. al, 1989; Wilhelmsson and Holmström, 1992). The derivation is in agreement with the evaluation of WHO (2002) that only a very small proportion of the population experience symptoms of irritation following exposure to 0.1 ppm formaldehyde.

An evaluation of acute sensory irritation data in humans has recently been made by Arts et al. (2006). Their final assessment on the level at which no marked effect is noted is based on a benchmark analysis of the data. Their model is characterized by a background incidence without formaldehyde exposure and a 10% response over a background response as the relevant effect size. The modeling approach of the authors results in a value of 1 ppm as the concentration without any relevant risk. However the interpretation of the results of the modeling approach as a “safe” level is not very convincing considering the assumptions surrounding the background response and the selected (10%) relevant effect size.

As the point of departure for deriving the “safe” level is based on human data, no interspecies safety factor is needed. The level of 0.1 ppm is more than 10 times lower than a threshold for cytotoxic damage to the nasal mucosa. Hence, we conclude that a safety factor accounting for intraspecies variability is not necessary. Given the described mechanism of action for tumor formation, the formaldehyde concentration of 0.1 ppm represents an exposure level at which there is practically no risk of upper respiratory tract cancer in humans.

3.3 Animal data

The derivation of a safe level of 0.1 ppm is supported by analysis of relevant animal data. In animals, cytotoxic response is observed at 2 ppm and cell proliferation is increased at 2.7 ppm (Gaylor et al., 2004) whereas the steep increase in DPX formation is seen at concentrations above 2 ppm (Monticello et al., 1991; Swenberg et al., 1983). In the analysis of animal data by Arts et al. (2006) 1 ppm is the level in rats without producing nasal irritation which we selected as appropriate effect to derive the “safe” level. The “safe” level in humans is calculated by applying safety factors to the NOAEL in rats.

Regulatory bodies have discussed the appropriate choice of safety factors and results are presented in several scientific publications. Two recent documents are the result of international consensus (IPCS, 2006; ACUTEX Project, 2006). Two safety factors have to be considered when extrapolating from animal data. First, a factor which accounts for differences between animal and man (interspecies factor) and second, a factor which accounts for the variability among the human population (intraspecies factor). According to the documents, the default **interspecies** factor for systemic effects is 10 divided into a sub-factor accounting for differences in systemic metabolism and a sub-factor accounting for differences in toxicodynamics. When extrapolating from rat to man, the sub-factor accounting for differences in systemic metabolism is 4 according to allometric scaling. As formaldehyde is acting locally, no systemic metabolism has to be considered, thus reducing the interspecies factor from 10 to 2.5 is appropriate. As has been demonstrated in the experimental studies, there is no great difference in sensitivity between the species (Kimbell et al., 2001). This finding allows further to reduce the interspecies sub-factor accounting for the toxicodynamics from 2.5 to 1. Hence, the resulting total interspecies safety factor is 1. According to the documents cited above, the default **intraspecies** factor of 10 is also divided into a sub-factor accounting for variability in systemic metabolism and a sub-factor accounting for variability in toxicodynamics. Both sub-factors are set at default values of 3.2 (3.2 x 3.2 = 10).

With regard to formaldehyde systemic metabolism does not play a role because formaldehyde is acting locally. Hence, the sub-factor need not be taken into consideration. Thus an intraspecies default factor of 3.2 remains which accounts for the variability in the toxicodynamics. From the short-term and long-term human studies a formaldehyde specific intraspecies/interindividual factor can be derived for the variability in toxicodynamic. According to the experimental data, the interindividual variability of the NOAEL can be characterized by a factor of 4, and the interindividual variability of the LOAEL is characterized by a factor of 5. Hence, the intraspecies variability for the toxicodynamic factor is greater than the default value of 3.2. To be on the safe side, we selected the higher intraspecies factor of 5 for the derivation of the “safe” level. The resulting total intraspecies safety factor is 5. Starting with a concentration of 1 ppm and dividing by a safety factor of 5 results in a concentration of 0.2 ppm. Children, in particular small babies, are a special subpopulation with respect to inhalation exposure. However, the special sensitivity of children is related to the respiration rate and the immature metabolism leading to a higher internal exposure (Abraham et al., 2005a, Abraham et al., 2005b). There is, however, no indication that a higher sensitivity is present for locally acting substances at the portal of entry, in particular when the effect is related to the concentration, as it is the case for formaldehyde.

We are also aware of a study by Naya and Nakanishi (2005) on risk assessment of formaldehyde for the general population in Japan. They recommend a reference concentration of 10 ppb in outdoor atmosphere for the general population in Japan.

Atmospheric (outdoor) concentrations of formaldehyde in Japan were determined to be 2.5 to 3.2 ppb between 1998 and 2003.

3.4 Other derivations

Further evidence supporting that a level of 0.1 ppm would be safe comes from a study in which a modeling approach has been used to analyze experimental data. Key elements of this approach were:

1) the use of a three-dimensional computer reconstruction of the rat nasal passages and computational fluid dynamics (CFD) modeling to predict regional dosimetry of formaldehyde;
2) association of the flux of formaldehyde into the nasal mucosa, as predicted by the CFD model, with formation of DPX and with regenerative cellular proliferation;
3) the use of a two stage clonal growth model to link DPX and proliferation rates with tumor formation.

Based on the model structure, the prediction of the tumor dose response was extremely sensitive to cell kinetics. The raw dose-response data for proliferation rates are J-shaped, and use of these data led to a predicted J-shaped dose response for tumors, notwithstanding a concurrent low-dose-linear directly mutagenic effect of formaldehyde mediated by DPX (Connolly et al., 2003). This modeling approach was extended to humans. Regional dosimetry predictions for the entire respiratory tract were obtained by merging a three-dimensional CFD model for the human nose with a one dimensional typical path model for the lower respiratory tract. In other respects, the human model was structurally identical to the rat model. Additional risks of respiratory tract cancer were predicted to be negative up to about 1 ppm when the raw regenerative cellular proliferation data from the rat were used. When a hockey stick shaped model was fit to the rat cellular proliferation data, positive maximum likelihood estimates (mle) of additional risks were obtained. These mle estimates were lower, for some comparisons by as much as a factor of 1000, than mle estimates from previous cancer dose-response assessments for formaldehyde. Breathing rate variations associated with different physical activity levels did not markedly influence the predicted additional risks. In summary, this analysis of the human implications by modeling the experimental data indicates that - if the J-shaped predictions are accurate - the respiratory tract carcinogenicity of formaldehyde is not a human health concern below about 1 ppm. Furthermore from the modeling approach the predicted cancer risk associated with inhalation of formaldehyde is calculated to be below 10^{-6} at concentrations lower than 0.2 ppm. The authors conclude that protection from the irritant effects of formaldehyde on the eyes, nose and throat should be sufficient to protect also from its carcinogenic effect (Connolly et al., 2004).

4 Conclusion

The analysis of the available data leads to the assessment that formaldehyde exposure is carcinogenic in humans leading to tumors in the upper respiratory tract. The conclusion is based on epidemiological data and mechanistic considerations, confirming a plausible mechanism of action for the site of entry.

Results from epidemiological studies also suggest a relation between formaldehyde exposure by inhalation and leukemia. However, at present a biologically plausible mechanism how formaldehyde exposure could be related to leukemia is not available.

Therefore at the present state of knowledge the epidemiological findings describe only an association rather than a causal relationship.

Concerning the tumors in the upper respiratory tract, the steps in the induction of tumors are understood and include non-genotoxic mechanisms, which in the low concentration range are the most critical events. Hence, it seems well founded that a safe level can be derived despite the fact that genotoxicity also plays a role in tumor formation. Our analysis of the available **human data** suggests that a level of 0.1 ppm formaldehyde is “safe” for the general population. The proposed level of 0.1 ppm is 2 fold lower than the level derived from **animal data** by applying appropriate safety factors. In the literature, a physiologically based model has been reported which has been applied to the animal data. From the reported calculations and their extrapolation to the human situation a level of 1 ppm, 10 times the level proposed by us, was considered to be safe. Therefore, the recommended level of 0.1 ppm seems to be a conservative estimate. The level is in good agreement with the MAK value of 0.3 ppm which has been derived to protect humans at the working place (DFG, 2000).

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