FormaCare
The formaldehyde sector group of cefic

SCIENTIFIC FACT SHEET
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Formaldehyde - Occurrence and Uses

- Formaldehyde is a **naturally occuring organic substance** present in most life forms, including humans. On the biological level, all normally functioning cells in humans, animals and plants produce and use formaldehyde as a normal constituent of metabolism.
- The **formation** of formaldehyde in the environment results mainly from the photochemical oxidation of methane that is naturally present in the atmosphere, as well as the natural decomposition of Volatile Organic Compounds (VOC). Formaldehyde is also present in many foodstuffs such as fruits, meat and vegetables, sometimes in significant doses.
- Formaldehyde occurs as a **by-product** of all combustion processes. Furthermore, it is a large volume industrial chemical with a broad range of applications.
- Formaldehyde **does not accumulate in the environment** because it is broken down in air within a few hours by sunlight or by bacteria present in soil or water. Formaldehyde metabolizes quickly, so it **does not accumulate in the body**.
- Formaldehyde is an important **industrial chemical used in a wide range of production processes. Main applications for formaldehyde based products include** building materials, furniture, paints and coatings, textiles and pharmaceuticals. It would be nearly impossible to imagine life today without products made using formaldehyde.

Scientific Data

- It has been known for already 25 years that formaldehyde at highly irritating concentrations may lead to **nasal tumours in rats**. Tumour development was confined to concentrations leading to strong cytotoxic irritation and increased cell proliferation in the nose of rats. Such effects are today considered to be the prerequisite for later tumour formation.
- **Over 50 epidemiological investigations** on possible cancer development in formaldehyde exposed workers have been carried out. These studies have been reviewed periodically by different authorities and scientific organisations. **Up to 2003 the general conclusion** was that the overall strength of **evidence has fallen short of showing a clear and causal association** between formaldehyde exposure and tumour development in humans. This also was the conclusion of repeatedly convening expert working groups at IARC[1] in 1982, 1987 and 1995.
- In **2004** (as published in 2005) a **new expert group of IARC** concluded that there is sufficient evidence of carcinogenicity in humans. This was mainly based on the recent epidemiological updates of the **three largest cohort studies** in formaldehyde exposed workers, comprising in total nearly 50,000 workers with exposures dating back up to 1937.
- Two tumour types were of major concern for IARC:
  - **Nasopharyngeal cancer**: This is a very rare tumour type. In one of the three cohort studies, the one that evaluated 25,500 workers, ten cases of nasopharyngeal cancer were found. Two of them occurred in workers not exposed to formaldehyde, eight in the formaldehyde exposed workers. In conjunction with positive findings from other studies, the IARC working group concluded that this "provided sufficient

[1] IARC: International Agency for Research on Cancer

epidemiological evidence". It should be noted that most of the cancer cases came from **one specific plant** while no such increase was noted in any of the other nine plants of this investigation. A detailed analysis of this one plant led another investigator to the conclusion that factors (occupational or non-occupational) other than formaldehyde exposure might have caused this increased tumour incidence. In addition, the other two epidemiological updates comprising in total approximately 25,000 workers did not show an increase in nasopharyngeal tumours.

- **Leukaemia**: IARC concluded that "there is strong but not sufficient evidence for a causal association (with) occupational exposure to formaldehyde". In some studies an increase in leukaemia has been observed in professional workers like embalmers, pathologists or anatomists. In addition, there was a statistically significant increase for workers exposed to high levels of formaldehyde in the update of the large study with 25,500 workers, but not in the other two recent updates.

- There are many studies clarifying the mechanism of **tumour formation in experimental animals**. The following conclusions are now generally accepted:
  - **Inhalation** of formaldehyde may lead to tumour development in the upper respiratory tract (i.e. the nose of rats) only at concentrations with severe local irritation leading to cell death followed by an increase in cell proliferation and damage to the genetic material.
  - Due to the rapid detoxification, formaldehyde after inhalation will not reach distant sites in the body apart from the upper respiratory tract. Thus, formaldehyde does **not** act as a **systemic carcinogen** and **formation of leukaemia is highly improbable**.
- If – as stated by IARC – there is a causal relationship between formaldehyde exposure at the workplace and development of nasopharyngeal cancer, the risk should be considered very small. Within the formaldehyde exposed group of the 25,500 industrial workers eight cases of this tumour type were found vs. four expected. Taking all three larger studies together, nine cases of nasopharyngeal cancer were observed in those workers exposed to formaldehyde vs. seven expected. In addition, the results of all of these epidemiological studies reflect formaldehyde exposure concentrations of decades ago as the worker populations date back up to 1937. A large part of the workers were exposed to an average of above 1 or 2 ppm with peak exposures frequently above 4 ppm. Nowadays workplace concentrations typically are in the range of 0.3 -0.5 ppm and indoor exposures of the general population below 0.1 ppm (rarely reaching 0.05 ppm).
- In consideration of the **mechanistic data** the German MAK[2] Commission assigned formaldehyde to Category 4 of carcinogenic substances which means that under the conditions of the **MAK value "no significant contribution to human cancer risk is expected"** at the workplace. The workplace exposure limit has been set by the MAK commission at 0.3 ppm. Furthermore, a biological/mathematical model was developed using the mechanistic data and the airflow in the upper respiratory tract of different species. By this model the cancer risk for a continuous life-time exposure (80 years) to formaldehyde at 0.1 ppm was calculated to be approximately five additional tumour cases for one million smokers or three additional tumour cases for 10 million non-smokers.

In conclusion, under today's exposure conditions no increased cancer risk is to be expected neither at the workplace nor for the general population.

[2] MAK Value: "Maximale Arbeitsplatzkonzentration", German occupational exposure level developed by the respective German expert commission.

The need for further scientific studies

Industry is aware of the scientific evidence put forward so far. However, it is crucial to have further scientific data in order to come to a **balanced view** on the inherent characteristics of the substance. Therefore, FormaCare has initiated **two lines of research** focusing on the two most relevant cancer endpoints alleged by IARC to be related to formaldehyde, namely nasopharyngeal cancer in the upper respiratory tract and possibly leukaemia. In addition, a study on sensory irritation in human volunteers is sponsored. This **Scientific Research Programme** encompasses the following:

- **Study focussing on Nasopharyngeal Cancer:** Start is foreseen in Q 4/2005 for a duration of 1.5 years.

The site of nasopharyngeal cancer in humans (nose/mouth-breathing) might resemble the nasal cancer site in rats (obligatory nose-breathing). For the rat a close parallelism has been demonstrated between cell destruction, increased cell proliferation[3], DNA-protein cross-link formation[4] and tumour development in the nose after formaldehyde inhalation. One major yet unsolved question is whether formaldehyde induced DNA-protein cross-links may lead to true mutations in the nasal epithelium of rats. And if this is the case, what is the dose-response-relationship for the induction of DNA-protein cross-links and true mutations? In other words, will cross-links or mutations occur first with increasing formaldehyde exposure concentrations?
In order to answer these questions, rats will inhale increasing formaldehyde concentrations and the micronuclei[5] formation in the nasal epithelium will be determined. The dose-response-curve thereby obtained will be compared to that from previous studies for DNA-protein cross-link formation. Although a clear threshold has not been shown for the formation of DNA-protein cross-links, the hypothesis is that for induction of mutations such a threshold does exist.

These in vivo studies will be supplemented by mechanistic in vitro investigations. The in vitro dose-response-curves for induction of mutations and DNA-protein cross-links will be investigated with different cell lines. Special emphasis will be placed on the steepness of the dose-response-curve, indications for a threshold and finally the interrelationship of both of these effects. In addition, the time course of the repair of DNA-protein cross-links will be investigated. There is good evidence that these cross-links will be repaired quite rapidly while micronuclei formation is an irreversible effect.

A third part of this project focuses on the question whether formaldehyde inhalation may lead to micronuclei formation in the mouth (buccal cells) of humans. There are some reports in literature claiming formation of micronuclei in buccal cells of humans after exposure to formaldehyde, while other investigators did not find such effects. But the methods employed had several insufficiencies and were poorly standardized. Meanwhile a group of experts has developed a standard procedure, which will be used to investigate buccal cells from human volunteers exposed to formaldehyde (see below).

These investigations are carried out in close cooperation with researchers at the universities of Ulm and Stockholm.

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[3] Proliferation is a rapid reproduction of tissue.
[4] DNA-protein cross-links are unnatural chemical links produced by a chemical between the DNA and surrounding proteins.
[5] Micronuclei are fragments of chromosomes generated by chromosomal damage, a mutagenic event.

- **Study focussing on Leukaemia:** Start is foreseen for Q 4 / 2005 for a duration of 1.5 years.

While according to IARC the epidemiological studies have given an indication for leukaemia formation in humans, inhalation studies in rats, mice and hamsters did not show such an effect. In a well designed drinking water study in rats there was no indication for induction of leukaemia, but another study did report such effects. However, in this latter investigation major methodological problems and inconsistencies were noted by the IARC working group.
In order to systematically check for leukaemia formation in animal experiments, industry intends to systematically evaluate materials still available from animal studies for indications of leukaemia. This histopathology investigation will be carried out by an international group of highly recognized pathologists.

- **Human Sensory Irritation study**:
  Started in September 2005, first results in April 2006.

There is broad scientific consensus that cytotoxic irritation with cell destruction and cell replication is a prerequisite for tumour formation in the upper respiratory tract. Such cytotoxic irritation can be tested in experimental animals but not in humans. Therefore, as a surrogate for humans, sensory irritation will be investigated well knowing that sensory irritation will occur at lower exposure levels than cytotoxic irritation. Although there are many reports on the effects of formaldehyde inhalation in human volunteers, a study is missing defining unambiguously the threshold for sensory irritation. In cooperation with the University of Heidelberg such an investigation is initiated to define the threshold for sensory irritation in volunteers. In the course of this study possible micronuclei formation in human buccal cells will also be investigated (see above).

Apart from these studies, there is also an epidemiological update being carried out by the US National Cancer Institute NCI[6]:

- **NCI epidemiology update**: Start Q4 / 2005, results end of 2006.

The large epidemiology study on 25.500 workers that was pivotal for the IARC decision only analysed mortalities up to 1994. The US National Cancer Institute will carry out a follow-up study investigating cause of death occurring up to the years 2004/05. This will add mortality data of another 10 more years to the former study and any conclusion on possible tumour formation by formaldehyde will then be on a much more solid ground.

[6] NCI : National Cancer Institute

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Industry Position

- The scientific argumentation brought forward by both IARC and the French INRS[7] **does not warrant a reclassification**
  - There still is considerable uncertainty whether the human evidence for naso-pharyngeal cancer used by IARC for their Group 1 classification is really related to formaldehyde exposure and whether this is sufficient for a regulatory decision in the EU.
  - The epidemiological data have not changed substantially since the last IARC evaluation in 1995 not reaching the conclusion for Group 1.
  - A final decision on a possible upgrade of the classification within the EU to cat. 1 should wait for the update of the NCI epidemiology, the results of which are to be expected by end of 2006.
  - Basically the animal data with regard to carcinogenicity have not changed since the EU classified formaldehyde as a Category 3 carcinogen in the early 1980's. In contrast, new mechanistic data have strengthened the position of formaldehyde being a threshold carcinogen with low potency.
  - Irrespective of the animal and epidemiological data a classification should consider the low potency of formaldehyde for tumour formation in relation to chronic cytotoxic irritation and sustained cell proliferation as well as its threshold action.
- Therefore it is proposed that the **present classification** (Category 3) in the EU is appropriate and **should not be changed.**

Contact us

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[7] INRS : Institut National de Recherche et de Sécurité