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Statement made by an ECETOC Working Group

European Chemical Industry
Ecology and Toxicology Centre

Avenue Louise 250 Bte 63
B - 1050 Brussels - Belgium

SUMMARY OF RESULTS PRESENTED AT THE CIIT CONFERENCE ON FORMALDEHYDE TOXICITY ON 20 - 21st NOVEMBER 1980

The CIIT Conference covered various aspects of the toxicity of formaldehyde. This statement is confined to considerations of the aspects related to the carcinogenic potential of formaldehyde. As written abstracts or papers were not available, this summary is based on the oral presentations of the investigations. Since some of the experiments are still in progress, final conclusions could often not be drawn. Thus, only a preliminary statement can be given and changes might become necessary when further data are available.

As yet incomplete results of a CIIT study in which mice and rats were exposed to formaldehyde vapour 6 hours a day, 5 days a week for 24 months showed a significant number of squamous cell carcinomas in the nasal cavity of rats (F 344) exposed to 15 ppm (95 rats out of 220) and 6 ppm (3 rats out of 204), and in mice (C3HB6F1) exposed to 15 ppm (2 mice out of 85). No such tumours were found in control animals, in rats exposed to 2 ppm formaldehyde vapour, or in mice exposed to 2 ppm or 6 ppm. These findings indicate that inhalation of formaldehyde vapour is carcinogenic in rats and mice. Squamous metaplasia and dysplastic epithelium were observed in the nasal cavities of rats at all dose levels, and of mice exposed to 6 and 15 ppm after 24 months. However, data from animals maintained for 3 months after the 24-month exposure period showed some evidence for regression of the metaplasia, particularly in the mice

In another inhalation study (Bio-Dynamics Inc.) in which rats, hamsters and monkeys were exposed to 0.2, 1 and 3 ppm formaldehyde vapour 22 hours a day, 7 days per week for 26 weeks, squamous metaplasia in the nasal epithelia was found at six months in rats and monkeys exposed to 3 ppm.

No tumours were detected in any of the animals exposed at any level but it should be emphasised that the design and duration of the experiment do not permit an assessment of carcinogenicity.

Formaldehyde is a known weak mutagen for bacteria and Drosophila and it is negative in the Ames test. Data presented at the CIIT conference showed that formaldehyde induced forward mutations in mouse lymphoma cells, sister-chromatid exchanges in Chinese hamster ovary cells, and cell transformation in balb c/3T3 cells and BHK cells, while an in vitro cytogenetic test with chinese hamster ovary cells was negative. Formaldehyde alone did not transform C3H/10 T½ cells, but was active in the presence of the tumour promotor tetradecanoylphorbol acetate (TPA). In vivo, the dominant lethal test was negative and data on the induction of sister-chromatid exchanges in mouse bone-marrow cells was equivocal.

Further investigations of the mode of action of formaldehyde are being performed and the results available from these studies indicate that many different processes are involved in the tumour development. It was shown that mice were more sensitive than rats to respiratory irritation by formaldehyde. Thus, reduction of the minute volume on inhalation of formaldehyde was much more marked in mice than in rats, leading to a better physiological defense mechanism in mice. It was also shown that radio-labelled formaldehyde was mainly retained in the nasal mucosa following inhalation. This suggests that tumour induction is a local effect. When the dose received after exposure to 15 ppm was related to the surface area of the nasal epithelium, the values calculated for mice were about half of those calculated for rats. Therefore the amounts of formaldehyde actually effective per unit area in mice exposed to 15 ppm were similar to those of rats exposed to 6 ppm, which is in accordance with the tumour

incidence in these two groups. Thus, mice and rats appear to be equally susceptible to the carcinogenic effects of formaldehyde when related to the actually effective amounts.
This also indicates that the action of formaldehyde depends not only on the atmospheric concentration but also on the local dose in the respiratory tract which is influenced by various factors such as mode of breathing, minute volume, defence mechanism, etc.

Although it has been demonstrated that formaldehyde has a very short half-life in blood, the half-life of the total radioactivity after intravenous administration of labelled formaldehyde was shown to be relatively long. Toxicokinetic studies showed that formate and formaldehyde behaved very similarly. This indicates that the radioactivity from the formaldehyde which remained within the animals was the result of metabolic incorporation, and most probably not of the alkylation of macromolecules which is thought to be one of the steps necessary for tumour formation.

Inhalation of formaldehyde vapour in a high dose (15 ppm, 6 hr/day over 4 days) results in a marked increase in cell replication within the nasal mucosa, probably due to cell replacement since formaldehyde was shown to be extremely cytotoxic. This irritation, if continued for a long period of time, could lead to metaplasia which in turn could result in tumour formation. Formaldehyde can also react with DNA, but only with the single stranded form.
Thus rapid cell proliferation induced by a cytotoxic dose may facilitate this reaction as suggested by several mutagenicity studies. Furthermore, the rapid cell replication may overcome the effectiveness of DNA-repair which may well give sufficient protection at non-cytotoxic doses.

Therefore, when evaluating the carcinogenicity of formaldehyde it is essential to consider the interrelationship of the different processes involved, e.g. cellular uptake, physiological compensation (breathing rate depression, increased mucous secretion) metabolic inactivation, local irritation, cell replication,

mutagenic activity, DNA repair and regression of the metaplasia. It should also be borne in mind that formaldehyde is a normal metabolic product. Finally, it should be stressed that the experimental results suggest that the metaplastic change is at least in part reversible. A full evaluation of the findings presented at the CIIT Conference must await completion of the studies. However, if chronic irritation is taken as a prerequisite for tumour development, then it is possible that no tumours would develop at sub-irritant concentrations. To date, the results of limited epidemiological studies have not indicated any increased tumour incidence in exposed human populations.

CIIT also reported low dose extrapolations in which various mathematical models were applied to the animal data. Extrapolations based on multi-stage models indicated that concentrations in the range 1-2 ppm and 0.1-1 ppm could result in one additional tumour per 10^5 and 10^8 exposed, respectively. Extrapolation with a linear model, resulted in concentrations several orders of magnitude lower for the same levels of risk. The estimates from the multi-stage model correspond to the threshold for sensory irritation in man. All data so far support the hypothesis that tumour formation results from a multi stage process, and that any extrapolations must consider every single process and not only the final event (tumour formation) as such.

At the end of the meeting the President of CIIT Dr. L. Golberg stated that a final evaluation of the animal studies with regard to human risk assessment should be postponed until all relevant data are available.

This statement must be considered as a whole, and may not be cited in part.
