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ECETOC Summary Review: Recent Findings Relevant to the Carcinogenicity of Fomaldehyde

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ECETOC SUMMARY REVIEW : RECENT FINDINGS RELEVANT TO THE CARCINOGENICITY OF FORMALDEHYDE

A. Introduction

ECETOC has reviewed information relevant to the toxicology of formaldehyde in animals (ECETOC, 1981a and 1982) and in humans (ECETOC, 1981b and 1982).In 1982 the International Agency for Research on Cancer (IARC, 1982) concluded that there was sufficient evidence for the carcinogenicity of formaldehyde in rats but inadequate evidence to assess the carcinogenicity to humans.

Since the above publications appeared the results of many additional animal and epidemiological studies have been reported. The purpose of this short review is to assess the significance of these in relation to ECETOC's earlier conclusions concerning the carcinogenic risk associated with the exposure of humans to formaldehyde.

B. Experimental Data

A key study reviewed in the ECETOC (1981a and 1982) reports was that of the US Chemical Industry Institute of Toxicology (CIIT), in which an excess incidence of tumours of the nasal cavity was found in rats, and to a much lesser extent in mice, exposed to formaldehyde by inhalation. (Kerns et al., 1983). Most of the subsequent work has clarified the reasons for the

differences in response to formaldehyde between species, and has led to a better understanding of the significance to man of the findings from animal studies.

1. The localised nature of the effects of formaldehyde.

   The effects of formaldehyde at the site of first contact are considered to be of major importance in the proposed mechanism of its carcinogenic activity in animals (ECETOC, 1981a and 1982). All recent inhalation studies in animals (see many of the following references) confirm that the effects of formaldehyde are confined to the nasal cavity, i.e. the site of initial contact, and that it consistently failed to produce systemic effects at sites distant from this. This lack of systemic effects may be explained by the findings of Heck et al. (1985). They demonstrated that after the administration of formaldehyde to rats and humans, by inhalation, the concentrations of formaldehyde in the blood did not increase above the endogenous levels.

   Minini (1985) found DNA-protein cross-linking in rats to which formaldehyde was administered by gavage. However, only at a high concentration (750 mg/kg, representing about 3/4 of the LD_{50} of formaldehyde to the species used) was cross-linking observed, and this was at the site of administration, i.e. the stomach and the beginning of the small intestine.

   In skin-penetration studies with radio-labelled formaldehyde in rats, rabbits and monkeys, the fraction penetrating the skin was very small (Jeffcoat, 1983; Robbins et al.,1984; and Bartnik, 1985).

   In studies by Sprangler et al. (1983) and Krivanek et al. (1983), only a very weak, questionable promoting effect of formaldehyde was detected in initiation-promotion studies on mouse skin.

   There is also more evidence to support the view that tissue damage, which is necessary for the subsequent tumour development, recovers when exposure ceases. This has now been demonstrated by experiments with both short- and long-term inhalation exposures in various species. Thus, Marshall et al. (1981-1982) exposed guinea pigs to 0.8 and 9 ppm of formaldehyde, by inhalation, and found that the initially-observed

elevation of mucous flow, and the appearance of foci of squamous metaplasia in the respiratory epithelium, had largely reversed 30 days after cessation of the 8-week exposure, there being only slight residual hyperkeratosis in the 9 ppm group. Schreiber et al.(1979) exposed golden hamsters to up to 250 ppm of formaldehyde (15 exposures of 1 h/d) and found that the observed effects (dysplasia and squamous metaplastic foci) were fully reversible. Kerns et al.(1983) also found that these same two effects were reversible in mice exposed for 24 months to 2, 5.6 and 14.3 ppm of formaldehyde, and in rats similarly exposed to 2 and 5.6 ppm.

2. Species differences in response for formaldehyde

The difference in response between various species exposed to formaldehyde, noted in the earlier ECETOC reports, has been confirmed by several studies :

a) Dalbey et al.(1982) observed no excess incidence of tumours in golden hamsters after a lifetime exposure to 10 ppm by inhalation;

b) Rush et al.(1983) reported differences in susceptibility with respect to the development of squamous metaplasia of the nasal epithelium in rats, monkeys and hamsters exposed to formaldehyde;

c) Chang et al.(1983) exposed rats and mice to formaldehyde, by inhalation, and found that the dose available for deposition in the nasal cavity was less in mice than in rats, mainly because mice are able to reduce their respiratory minute-volume by about 40-70%, whereas rats cannot. This corresponds to the lower nasal toxicity in the mouse.

The work of Chang et al.(1981,1983) and Kerns et al.(1983) has shown that rats and mice respond to respiratory irritants in different ways, which explains why the magnitude of the irritant response and the excess incidence of tumours in mice exposed to formaldehyde are significantly less than in rats exposed to the same concentrations.

3. Dose-response relationships

In the study by Kerns et al.(1983), the dose-response curve of tumour incidence in rats was steep and non-linear, suggesting that there is a threshold concentration below which tumours would not develop. This suggestion is supported by the subsequent work of Starr and Gibson (1984) who found that in rats exposed to 0.5, 2, 6 and 15 ppm of formaldehyde in

air, mucociliary clearance was completely stopped at 15 ppm, was slightly reduced at 6 and 2 ppm, but was unimpaired at 0.5 ppm. (The mucociliary apparatus of the nose acts as a defence barrier against inhaled formaldehyde which is either absorbed by, reacts with, or is eliminated in, the mucous). The existence of a threshold is also indicated by the work of Rush et al. (1983) who found that continuous exposure, by inhalation, to 1 ppm of formaldehyde did not cause tissue damage in rats, hamsters or monkeys.

The inhalation of formaldehyde by rats caused DNA-protein cross-linking in the nasal respiratory epithelium (but not in the olfactory epithelium or bone marrow) at concentrations of 2 ppm and above (Casanova-Schmitz and Heck, 1983; Casanova-Schmitz et al.,1984). Later work showed that there was no such cross-linking at 0.9 ppm (Casanova-Schmitz and Heck, 1985). Once again, the dose-response curve was very steep, as in the CIIT carcinogenicity study.

Grafstrom et al. (1984) and Fornace et al. (1984) found that DNA-protein cross-links caused by formaldehyde in human cells were rapidly removed. In mice, the half-life of such cross-links was less than 4 h (Ross et al., 1980). Swenberg et al.(1983) administered formaldehyde to rats by inhalation (concentration range 3-12 ppm; duration 3-12 days) and showed that its cytotoxicity depended on the concentration rather than the cumulative dose, i.e. the product of concentration and time. The overloading of protective mechanisms such as mucociliary clearance, metabolic detoxification and DNA repair, and stimulation of the proliferative response by tissue injury, are probably responsible for the fact that in the CIIT study (Kerns et al.,1983) less than 1 in 100 rats exposed to 5.6 ppm of formaldehyde developed tumours, whereas 50 times this number developed tumours when exposed to 14.3 ppm.

4. Mutagenicity

A number of recent studies confirm that positive results are found only in systems with prokaryotes and eukaryotic cells in culture, generally at concentrations which lead to toxic effects (Basler et al., 1985; Brusick, 1983; Goldmacher, 1983; Ross et al., 1980; Martin et al., 1978; Grafstrom et al., 1983; and Plesner et al., 1983). Sister-chromatid exchanges (SCE) were induced in vitro in V79 cells, but in the presence

of an exogenous metabolising system (S9 mix, primary rat hepatocytes) the frequency of SCEs decreased almost to that in the control experiment (Basler et al., 1985). None of the recent results alter the strong indications that formaldehyde reacts only with single-stranded DNA, i.e. during a period of DNA-replication within a cell. The latest studies confirm that there are no mutagenic effects on mammals in vivo, although it is noted that in most of the work the effects were sought in tissues remote from the site of primary contact with formaldehyde (Fleig et al., 1982; Fontignie-Houbrechts, 1981; Kligerman et al., 1984; Natarajan et al., 1983; Thomson et al., 1984; and Ward et al., 1984).

C. Data on Humans

The results of numerous epidemiological studies and some papers in which they are assessed have become available since the ECETOC documents were published (Acheson et al., 1984; Almgren, 1983; Bierre et al., 1981; Brinton et al., 1984; Brunner et al., 1985; Coggon et al., 1984; Fayerweather et al., 1983; Harrington et al., 1984; Hayes, 1984; Krieger, 1983; Levine, 1982 and 1984; Liebling et al., 1984; Marsh, 1983; Möller-Jensen et al., 1982; O'Berg, 1985; Olsen et al., 1984; Rush, 1985; Stayner et al., 1985; Wong, 1983; Tola et al., 1980; and Walrath et al., 1983;). Although in individual studies slight increases in the incidence of tumours of the colon, prostate, kidney, lymphopoietic system, buccal cavity, skin and brain were found, there was no consistent association from one study to another between the organs affected and exposure to formaldehyde. In the light of all that is known about the disposition and metabolism of formaldehyde it is highly improbable that it causes tumours at sites remote from its point of initial contact.

None of the above studies demonstrate a causal relationship between formaldehyde exposure and nasal cancer although the authors of two of the studies (Hayes, 1984 unpublished; Olsen, 1984) suggested that there might be a weak association detectable from the results of their case-control studies. However, both studies suffer from a number of deficiencies.

Olsen analysed 754 cases of carcinoma of the nasal cavity, paranasal sinuses and nasal pharynx taken from the Danish Cancer Register for the period 1970-1982. No quantitative data on the levels and duration of exposure to

formaldehyde were given and even the qualitative assessment of exposure was based on extremely incomplete and weak occupational data. Smoking habits were not taken into account although smoking is a confounding factor. Moreover, when the tumour incidence in the group exposed to formaldehyde was corrected for concurrent exposure to wood dust, which is known to be related to nasal cancer, it was not statistically significantly higher than expected.

Hayes studied 112 cases of cancer of the nose and nasal sinuses recorded in the Netherlands between 1978 and 1981. Exposure to formaldehyde was not substantiated by quantitative data but was only qualitatively assessed ("none", "low" and "high") by two independent groups. There were marked discrepancies between the assessments of the two groups, resulting in no statistically-significant elevation of relative risk in one assessment and a slight increase in risk in the second. The use of 90% confidence limits for the calculated relative risk, instead of the usual 95%, increases the uncertainty in the interpretation of the risk as significantly elevated. Concurrent exposure to wood dust, and smoking habits, which are confounding factors, were inadequately taken into account. The number of persons assessed as having been exposed to formaldehyde was small.

In view of the deficiencies in both of these studies they are not considered to have demonstrated an association between exposure to formaldehyde and nasal cancer.

D. Conclusions

The work reviewed here reinforces the conclusions reached in the previous ECETOC documents regarding the toxicity of formaldehyde to animals and man.

1. Tumours produced in rats and mice exposed to formaldehyde arise from sustained and extensive tissue damage at the site of initial contact. The marked response in rats probably arises from the overwhelming of defence mechanisms, which are more effective in other, less susceptible, species such as the mouse and hamster.

2. The effects of exposure to formaldehyde are localised, stemming from action at the site of initial contact, i.e. the respiratory tract or

skin. These local effects depend on the concentration to which tissues are exposed, but not on the cumulative dose. They are reversible, even after repeated exposure for long periods to doses which produce cytotoxic effects and tissue destruction.

3. The dose-response relationships for the cytotoxic/irritant action of formaldehyde and the occurrence of localised DNA-protein cross-linking, support the proposal that there is a threshold for its toxic action.

4. Formaldehyde is mutagenic in many in vitro systems, including mammalian cells, but is not mutagenic in vivo.

5. The numerous epidemiological studies available, in most of which the levels of exposure to formaldehyde were higher than those at present, do not demonstrate that there is a causal relationship between exposure to formaldehyde and the occurrence of an excess incidence of tumours in humans.

6. Consideration of the above epidemiological studies, and the fact that the animal studies which demonstrate that formaldehyde is a carcinogen were carried out under conditions which cannot appropriately be extrapolated to humans, leads to the conclusion that at current levels of exposure formaldehyde presents no significant risk of cancer to humans.

E. Bibliography

- Acheson E.D., Barnes H.R., Gardner M.J., Osmond C., Pannett B. and Taylor C.L. (1984). Lancet, March 17, 611-616.

- Almgren K.G. (1983). Dept. of Occupational Health, Perstorp, Sweden, Report F I 24.I.198, no. 14.

- Bartnik F.G., Gloxhuber C. and Zimmermann V. (1985). Toxicol. Letters, 25, 167-172.

- Basler A., Hude W.V.D. and Scheutwinkel-Reich M. (1985). Arch. Toxicol., 58, 10-13.

- Bierre T.H., Tunnicliff K.J. and Darby F.W. (1981). Dept. of Health, New Zealand (report of Dec. 1981; no further details of reference are available).

- Brinton L.A., Blot W.J. and Becker J.A., (1984). Am. Epidemiol. J., 119, 896-906.

- Brunner P. and Warich W., (1985). Pathologe, 6, 43-45.

- Brusick D.J. (1983). In : Formaldehyde Toxicity, ed. Gibson. J.E., Hemisphere Publ. Corp., New York, 72-84.

- Casanova-Schmitz M., Starr T.B. and Heck H. d'A. (1984). Toxicol. and Appl. Pharmacol., 76, 26-44.

- Casanova-Schmitz M. and Heck H. d'A. (1985). Toxicologist, 509, 128.

- Chang J.C.F., Steinhagen W.H. and Barrow C.S. (1981). Toxicol. and Appl. Pharmacol., 61, 451-459.

- Chang J.C.F., Gross E.A., Swenberg J.A. and Barrow C.S (1983). Toxicol. and Appl. Pharmacol., 68, 161-176.

- Coggon D., Pannett B. and Acheson E.D. (1984). JNCI, 72, 61-65.

- Dalbey W.E. (1982). Toxicology, 24, 9-14.

- ECETOC (1981-a). Technical Report no. 2, 18 May.

- ECETOC (1981-b). Technical Report no. 1, 13 May.

- ECETOC (1982). Technical Report no. 6, Sept.

- Fayerweather W.E., Pell S. and Bender J.R. (1983). In : Formaldehyde, ed. Clary J.J., Gibson J.E. and Waritz R.S., Marcel Dekker Inc., New York and Basel, 47-127.

- Fleig I., Petri N., Stocker W.G. and Thiess A.M. (1982). J. Occup. Med., 24, 1009-1012.

- Fontignie-Houbrechts F. (1981). Mut. Res., 88, 109-114.

- Fornace A., Lechner J.F., Grafstrom R.C. and Harris C.C. (1982). Carcinogenesis, 3, 1373-1377.

- Grafstrom R.C., Fornace J., Autrup H., Lechner J.F. and Harris C.C. (1983). Science, 220, 216-218.

- Grafstrom R.C., Fornace A. and Harris C.C. (1984). Cancer Res., 44, 4323-4327.

- Goldmacher V.S. and Thilly W.G. (1983). Mut. Res., 116, 417-422.

- Harrington J.M. and Oakes D. (1984). Brit. J. Indust. Med., 41, 188-191.

- Hayes R.B., Raatgever J.W. and Bruyn A.E. de (1984). Technical Report, Dept. of Public Health and Social Medicine, Erasmus University, Rotterdam.

- Heck H. d'A., Casanova-Schmitz M., Dodd P.B., Schachter E.N., Witek T.J. and Tosun T. (1985). Am. Ind. Hyg. Assoc. J., 46, 1-3.

- IARC (1982). IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Vol. 29, 352-389.

- Jeffcoat A.R. (1984). Research Triangle Inst. Report RT1-2009-00-01F, North Carolina, August.

- Kerns W.D., Pavkov K.L., Donofrio D.J., Gralla E.J. and Swenberg J.A. (1983). Cancer Res., 43, 4382-4392.

- Kligerman A.D., Phelps M.C. and Erexson G.L. (1984). Toxicol. Letters, 21, 241-246.

- Krieger N. (1983). Can. Med. Assoc. J., 128, 244.

- Krivanek N.D., Chromey N.C. and McAlack J.W. (1983). In : Formaldehyde, ed. Clary J.J., Gibson J.E. and Waritz R.S., Marcel Dekker Inc., New York and Basel, 159-171.

- Leibling T., Rosenman K.D., Pastides H., Griffith R.D. and Lemeshow S. (1984). Am. J. Indust. Med., 5, 423-428.

- Levine R.J., Dallorso R.D., Blunden P.B. and Battigelli M.C. (1984). J. Occup. Med., 26, 91-98.

- Marsh G.M. (1982). Brit. J. Indust. Med., 39, 313-322.

- Marshall T.C., Hahn F.I., Henderson R.F., Silbaugh S.A. and Hobbs C.H. (1981-1982). Annual Report, Lovelace Biomedical and Environm. Res. Inst., Albuquerque, LMF-102, UC-48, pp. 423-427.

- Martin C.N., McDermid A.C. and Garner R.C. (1978). Cancer Res., 38, 2621-2627.

- Minini U. (1985). Dissertation, Eidgenössischer Techischen Hochschule, No.7763, Zürich.

- Möller-Jensen O. and Kruger-Andersen S. (1982). Lancet, April 17, 913.

- Natarayan A.T., Darroudi F., Bussmann C.J.M. and Kesteren-van-Leeuwen A.C.
(1983). Mut. Res., 122, 355-361.

- O'Berg M. (1985). Advances in Chemicals Series, Am. Chem. Soc., 210, 289-295.

- Olsen J.H., Jensen S.P., Hink M., Faurbo K., Breum N.O. and Jensen O.M. (1984). Int. J. Cancer, 34, 639-644.

- Plesner B.H. and Hansen K. (1983). Carcinog., 4, 457-459.

- Robbins J.D., Norred W.P., Bathija A. and Ulsamer A.G. (1984). J. Toxicol. Environ. Health, 14, 453-463.

- Ross W.E. and Shipley N. (1980). Mut. Res., 79, 277-283.

* - Roush G., Walrath J., Stayner L., Kaplan S. and Blair A. (1985). (Have we a full reference ?).

- Rusch G.M., Clary J.J., Rinehart W.E. and Bolte H.F. (1983). Toxicol. Appl. Pharmacol., 68, 329-343.

- Schreiber H., Bibbo M., Wied G.L., Saccomano G. and Nerheim P. (1979). Acta Cytologia, 23, 496-503.

- Spangler F. and Ward J.M. (1983). In : Formaldehyde, ed. Clary J.J., Gibson J.E. and Waritz R.S., Marcel Dekker Inc., New York and Basel, 147-158.

- Starr T.B. and Gibson J.E. (1984). Trends Pharmacol. Sci., 5, 477-480.

- Stayner L., Smith A.B., Reeve G., Blade L., Elliott L., Keenlyside R. and Halperin W. (1985). Am. J. Indust. Med., 7, 229-240.

- Swenberg J.A., Barrow C.S., Boreiko C.J., Heck H.d'A, Levine R.J., Morgan K.T. and Starr T.B. (1983). Carcinogenesis, 4, 945-952.

- Thomson E.J., Shackleton S. and Harrington J.M. (1984). Mut. Res., 141, 89-93.

- Tola S., Hernberg S., Collan Y., Linderborg H. and Kortab M.L. (1980). Int. Arch. Occup. Environ. Health, 46, 79-85.

- Walrath J. and Fraumeni J.R. (1983). Int. J. Cancer, 31, 401-411.

- Ward J.B., Hokanson J.A., Smith E.R., Chang L.W., Periera M.A., Whorton E.B. and Legator M.S. (1984). Mut. Res., 130, 417-424.

- Wong O. (1983). In : Formaldehyde Toxicity, ed. Gibson J.E., Hemisphere Publ. Inc., New York, 256-271.

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