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No 1

Assessment of Data on the Effects of Formaldehyde on Humans

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ECETOC

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ASSESSMENT OF DATA ON THE EFFECTS OF FORMALDEHYDE ON HUMANS

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CONTENTS

A. SCOPE AND OBJECTIVES

Recent animal experiments at the Chemical Industry Institute of Toxicology (USA) have shown that formaldehyde causes gross destruction of the nasal epithelium, and provokes squamous cell carcinomas in the nose of rats exposed to 6 and 15 ppm, and in mice exposed to 15 ppm (1). There is apparently no evidence of damaged lung tissue at the levels of exposure studied. Epithelial damage of the nose is followed by increased tissue regeneration, hyperplasia, metaplasia and in some cases neoplasia. Data from animals maintained for 3 months after the 24-month exposure period showed some evidence of regression of the epithelial dysplasia and hyperplasia. Recovery in rats occurred in the 6 ppm group and in mice in the 15 ppm group.

The question therefore arises - is formaldehyde a carcinogen for man, and if so under what circumstances ? ECETOC in its Monograph n°2 (2) has defined a *Proven Human Chemical Carcinogen* as "a substance for which a causal relationship has been established between previous exposure and the occurrence of malignant neoplasms in man". To classify the status of formaldehyde it was thus vital to review the evidence available concerning the effects of formaldehyde on humans. An ECETOC Formaldehyde Human Exposure Working Group (see list of members in I) was therefore set up to determine what studies relating human exposure to formaldehyde with possible carcinogenic effects have been done in the past, are underway, or are planned for the future, and to make recommendations for any further studies necessary to clarify the above relationship.

As the animal experiments showed an effect of formaldehyde only in the nasal epithelium, it was important to search for human epidemiological studies which could have shown similar effects in the nose of man, and of course any effects on the respiratory tract had also to be considered.

For an assessment of the health effects of formaldehyde on man about 200 or so papers were studied and evaluated. Only 66 were of sufficient scientific relevance to be further considered. In the study of the potential carcinogenicity of formaldehyde the possible formation of bis-chloromethyl ether (BCME) is a confusing but relevant factor, since formaldehyde can react with hydrochloric acid to yield the carcinogen BCME. The question is whether BCME can be formed from formaldehyde and hydrochloric acid at concentrations comparable with the occupational exposure levels.

Because of limitations in the epidemiological data presently available, the working group has made some recommendations for future work.

B. CONDITIONS OF HUMAN EXPOSURE

Formaldehyde is a normal metabolite of the cell, and participates in the one-carbon pool. It is readily oxidized to formic acid. Numerous enzymes catalyzing this reaction have been identified in liver preparations and erythrocytes (3). In the earth's atmosphere the photochemical oxidation of methane is known to be a major source of formaldehyde.

Formaldehyde was discovered in 1859. In 1888 formaldehyde was introduced as a disinfectant. This means that for about 100 years people have been exposed to man-made formaldehyde. At present, formaldehyde is a significant commodity chemical, with a worldwide consumption of about 5 million tons annually. The major production route as well as the main uses are described in Appendix A.

Unfortunately only a very few reports of health effects of formaldehyde on humans provide information about the ambient air-concentration. It is therefore difficult to establish a clear dose-response relationship for the effects on humans. The following data, recorded in the literature may however give a reasonable estimate of the concentrations to which men have been exposed in certain circumstances.

Sources of exposure of the public to formaldehyde include cigarette smoke, automotive exhaust, photochemical smog, incinerators, and release from urea-formaldehyde products. Automotive exhausts have been reported to contain formaldehyde in the range of 29-43 ppm (4). Outdoor-air in Los Angeles, as a result of photochemical smog formation, contained formaldehyde at 0.05 - 0.12 ppm over the course of 26 days of measurement (5). Approximately 13% of the daily maxima exceeded 0.1 ppm, and the highest measured concentration was 0.16 ppm.

Cigarette smoke contains as much as 40 ppm of formaldehyde by volume and it has been reported (6,7) that when 5 cigarettes were smoked in a 30 m^3 climatic chamber the concentration of formaldehyde reached 0.23 ppm (8).

Inside buildings, one of the possible sources of formaldehyde is the particle board used in furnishing, fixtures and fittings. Although in time the concentration decreases, the levels of formaldehyde in new flats in Denmark (9) and German schools (10) were occasionally found to be 0.35 - 0.59 ppm and 0.3 - 0.9 ppm respectively.

In America there has been a large number of complaints claimed to involve formaldehyde arising from the plywood and particle-board of mobile homes (11).

The use of urea-formaldehyde foam for thermal insulation is another potential source of formaldehyde, especially when not properly installed. Thus, in certain apartments in Chicago urea-formaldehyde insulation was, responsible for room air concentrations of between 0.8 and 0.95 ppm of formaldehyde (11).
A review of the regulatory guidance on permitted workplace levels in different countries shows that exposure limits vary between 1 and 5 ppm in 1980 (see Appendix B). In Germany (BRD) the time-weighted-average standard (MAK) was reduced from 5 ppm to 1 ppm in 1971. While the time-weighted-average standard for the UK was still 10 ppm in 1946, it was

reduced to 5 ppm in 1948. In 1963, 5 ppm was taken as a ceiling limit, and this was lowered in 1973 to 2 ppm.

Over the 100 years of exposure to formaldehyde there seems no doubt that some people were exposed to levels significantly higher than the present atmospheric limit values.

Medical personnel have historically been extensively exposed to formaldehyde, but few data exist about the present levels. It was reported that in the dissecting rooms of two German University Medical Schools, where human bodies were treated with formaldehyde, the air concentrations of formaldehyde varied between 0.31 and 1 ppm in one school (12)and between 0.31 and 0.57 ppm in a second school (13). Formaldehyde levels were also measured in German clinics and institutes , and 42 samples of air containing formaldehyde were examined. Only four of fifteen samples of room air containing formaldehyde were found to be statistically below the target level of 0.1 ppm viewed from the aspect of hospital hygiene. The remaining eleven samples were in the control range i.e. 0.025 ppm and 0.25 ppm. Ten out of seventeen samples of room air containing formaldehyde, taken from working places in hospitals and institutes, exceeded statistically the maximum working place concentration of 1.00 ppm, whereas the remaining seven varied at random between 0.25 and 2.5 ppm (14).
In Appendix C,methods are listed for the measurement of formaldehyde concentrations in air,and for biological monitoring.

C. EPIDEMIOLOGICAL STUDIES

A review of morbidity and mortality studies is given in Appendix D. Those epidemiology studies which are now terminated did not identify one single case of nasal cancer. The respiratory-tract cancer rate was not different from the rate in the general population.

Dr. Matanoski (15) reported an excess of primary liver cancer and lung cancer in pathologists when compared with radiologists. Oral and pharyngeal cancers were lower in the pathologists,who were more likely to be exposed to formaldehyde than were radiologists. The study was not originally planned for the detection of formaldehyde-induced effects.

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Although not published, the following information which was presented at the Nov. 1980, CIIT Formaldehyde Toxicity Conference is of importance (1).

- J. Walrath performed a proportional mortality analysis of 1,106 deceased morticians. These were exposed between 1902 and 1979 to embalming liquids which apart from formaldehyde contain a variety of chemicals such as phenol, arsenic,creosote, etc. The overall proportional mortality rate for all cancers wa not significantly different from the US male population. As in all epidemiological studies there did appear to be an increased incidence of certain disease processes. In this group there was an increased incidence of skin, brain and kidney cancers but there was no proportionate excess of deaths from respiratory cancer, and no deaths from cancers of the nose or nasal sinuses were observed.

- Dr. Marsh (Pittsburgh-University) studied 2500 formaldehyde workers and found no nasal cancers and no dose-response relationship between formaldehyde exposure and respiratory and other cancer. Mortality rates for formaldehyde exposed workers were "generally similar to those for unexposed workers".

- Dr. Wong of TOMA studied 2,026 workers at the largest U.S. formaldehyde manufacturing plant and found no nasal cancers nor any excess of respiratory cancer. Of the 136 deaths reviewed in this study, 4 deaths were attributed to cancer of the prostate when 1.36 were expected from the national average. He concluded that the overall mortality of workers potentially exposed to formaldehyde was less than expected.

Dr. Jensen of the Danish Cancer Institute (16) has reported that during the period 1943-76 three cases of cancer in nasal cavities, sinuses and nasopharynx were notified among Danish doctors. None of these people had ever worked in a pathology department or as an anatomist. The author concludes that "Although of limited significance, this report indicates that the carcinogenic risk of formaldehyde to man, if there is one, is not likely to be important".

It should also be stressed that nasal cancer is a rather rare type of tumour. Informal data suggest that in the United Kingdom 140 cases of nasal and related cancer deaths per year are recorded. The results of a case-control study on 1,000 nasal cancers in the period of 1965 to 1970 is being prepared for publication by Prof. Acheson (Univ. Southampton, UK).

It should be noted that the exposure levels were not precisely quantified in any of the reported epidemiological studies. Large cohort studies are going on in the United States and Europe according to better-defined protocols.

The total number of reported cases of formaldehyde-associated asthma appears to be small, and (if factual) the cause of bronchospasm remains uncertain (25). Formaldehyde comes under suspicion as a possible promotor of bronchospasm since it is a known skin-sensitising agent, and some experts believe that a material which has this effect on the epithelium of skin will act in a similar manner if it comes into contact with pulmonary epithelium. As an irritant, formaldehyde may cause its bronchoconstrictive effects by initiating release of histamine from mast cells in the lungs, or merely by stimulating irritant receptors which in turn cause a sequential response in the bronchial tree (26).

Whether the occurrence of bronchospasm is the result of an immune reaction, or of a deeper penetration of formaldehyde in the respiratory tract, is at present not clear. However, the adverse effects of low-molecular-weight compounds in general is poorly understood. Animal studies have shown that formaldehyde does not penetrate in the lower regions (1).
At this point it should be emphasised that man, contrary to the rat, may breathe through his mouth as well as through the nose.
The variable responses of people to formaldehyde, as observed in industry and the home, indicate that some groups of people may be more susceptible to formaldehyde than others.

2. SKIN EFFECTS OF FORMALDEHYDE

In the literature, formaldehyde is mainly associated with effects on the skin. Contact with weak solutions may cause allergic contact dermatitis, and eczematous lesions appear on exposed areas.

It is a skin irritant and sensitiser (27). Strong, irritating solutions on the skin coagulate the protein and produce necrosis. Although sensitisation occurs mainly through contact with solutions of formaldehyde, contact of exposed areas of the skin with formaldehyde vapours may also be a cause of a sensitising reaction

There are reports from the USA that families exposed to formaldehyde in the home have experienced numerous complaints of the upper respiratory tract, gastro intestinal tract and central nervous system (e.g. headaches) (22). These symptoms appear to differ from known industrial experience where some habituation and job selection can occur.

Formaldehyde at levels of 0.3 - 2.00 mg/m³ caused no change in airway resistance in 16 healthy male subjects. There was however some reduction of mucous secretion and reduced ciliary activity in the mucous membrane of the nasal tract (23).
Of these 16 healthy young men voluntarily exposed for 5 hr. to formaldehyde, 3 complained at 0.3 mg/m³, 5 at 0.5 mg/m³, 15 at 1.0 mg/m³ and 15 at 2.0 mg/m³, mainly about conjunctival irritation and dryness in the nose and throat.

It has been reported (24) that some workers from a cohort of 200 exposed to formaldehyde for 1 to 15 years, at levels which could be higher than the present UK TLV of 2 ppm ,have occasionally experienced slight nose bleeding. As these workers were specifically encouraged to report this effect it is difficult to know whether the number of cases is statistically higher than in other groups of workers who may not have reported nose bleeding.

There are a number of references in the literature to adverse respiratory symptoms believed to be associated with formaldehyde. The cases are mostly vaguely described as bronchospasm. The exposure levels are not given in detail, but are reported as "high and prolonged".

A report from Eastern Europe states that no grave health problems were found in a group of formaldehyde workers exposed to levels of 5 ppm, but in one subject pulmonary challenge with acetylcholine showed a positive bronchoconstrictive response.

The present available data do not show any evidence that formaldehyde is "a proven human chemical carcinogen" (ECETOC Definition (2)).

D. EVIDENCE OF ADVERSE HUMAN EFFECTS

The epidemiological evidence concerning the carcinogenicity of formaldehyde to man, provides no proof of a causal relationship between previous exposure and the occurrence of malignant neoplasms in man. However, recent evidence has emerged which links exposure to formaldehyde with nasal tumours in rats and mice. In this case it is provisionally believed that irritation of, and then damage to, epithelial cells is a prerequisite for tumour development. When the detailed animal study results are available, it will be necessary to assess what significance they have for man.

Evidence about toxic effects other than carcinogenicity is therefore surveyed by the WG in this section, because such evidence may clarify the situation.

In the general literature survey,special attention was given to the irritant effects in the respiratory tract. To get an overall toxicological profile, other health effects were also surveyed. An extensive literature survey and assessment is given in a US National Academy of Science report, March 1980. (17)

1. RESPIRATORY EFFECTS OF FORMALDEHYDE

Formaldehyde causes irritation of the upper respiratory tract and eyes. There is considerable variability in the levels at which effects have been reported (see Appendix E).

Estimations of the irritant threshold vary from 0.13 (18) to 1-2 ppm (19). Fassett (20) says that mild irritation of the upper respiratory tract occurs after 8 hr. exposure to 2-3 ppm, and Walker (21) gives 5 ppm as the throat-irritation threshold.

Allergic dermatitis is confirmed by positive patch-test reactions to formaldehyde (2% solutions) (28).
Formaldehyde sensitisation has been observed in association with the use of formaldehyde-based glues and disinfection procedures, and has been reported in the resin-finished textile industry, the formaldehyde-based plastics industry, the paper and wood industry, pathology laboratories and under nearly all professional or non-professional exposure conditions.

Skin effects were reported in the literature as early as 1926 (29), and thus awareness of possible effects of formaldehyde on the skin spread internationally early in this century. Despite extensive observations in all countries, and many different sectors of industry where formaldehyde exposure has occurred, there has been no evidence of cancer induction in the exposed skin.

J. Walrath ((1) and Appendix D) in her NCI study found four skin cancers in the face and neck in a group cohort of 1,106 New York morticians who were exposed to formaldehyde, phenol, arsenic, creosote etc. Two skin cancers were expected, but the excess of two cases was attributed to some aspect of life-style rather than occupational exposure.

3. OTHER HEALTH EFFECTS OF FORMALDEHYDE

Formaldehyde is a metabolite normally occurring in the human body, and it participates in the one carbon pool.
The lethal dose by mouth has been estimated at 30-60 ml of a 37% solution. Death has occurred from 30 ml, and recovery has occurred after 120 ml ingestion (30). Poisoning is rapid in onset. The signs and symptoms are those of many corrosives, and include necrotic gastritis, depression of the central nervous system, pallor, cyanosis, collapse, vertigo, headache, respiratory failure, renal damage, anuria, acidosis, coma and death (31) (32) (33) (34) (35).

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Electroencephalogram changes have been reported (36) with exposure to very low concentrations in air (0.04 ppm), and electrocardiogram changes with concentrations of 0.8 ppm (37). Helwig (38) says that electroencephalogram changes are inexplicable and not due entirely to formaldehyde.

Tests on 12 men exposed to 13.8 ppm for thirty minutes, showed no significant variation in blood pressure, pulse rate, respiratory rates, electro-cardiograph tracings or auscultatory screens (39).

Estimations of the odour threshold vary from 0.06 ppm (40) to 1 ppm (20). Dark adaptation is said to be affected by levels of 0.7 ppm (40). No effect on visual acuity, depth perception peripheral vision, accomodation, fixation, or colour vision was found in 83 workers exposed to 0.4 ppm (41).

Differences in skin temperature on opposite sides of the body are said to be affected by exposure to formaldehyde (42). The significance of this is not clear.

Many Russian authors report menstrual disturbances in female workers (in a multitude of occupations) but many authorities feel this is not surprising considering the heavy manual work some of these women perform. Schulmilina (43) suggests that exposure to urea-formaldehyde resin increases menstrual disturbance, pregnancy complications and the proportion of underweight children. As exposure to formaldehyde was only one of the parameters, no direct correlation can be established between the observed effects and formaldehyde exposure.

No evidence was found to suggest that formaldehyde caused abortion or miscarriage (22), or that it was teratogenic in humans.

Neshkov and Nosko (44) reported a high incidence of sexual dysfunction amongst males producing glass-fibre-reinforced plastic. However,most of the complaints were psychogenic and the men were exposed to many chemicals other than formaldehyde.
It should be emphasised that no information is given about the analytical methods used to obtain the Russian concentration data (cf sensitivity of the latest analytical methods in AppendixC).

In Appendix E the responses of man to various concentrations of formaldehyde vapour are summarized. The above assessment of the data available on the effects of formaldehyde on man gives no indication that the irritant effect, resulting from formaldehyde exposure, gives rise to malignant or benign tumour development in the respiratory tract. It should however be noted that so far no studies have been performed where the existence of metaplasia in the nose cavity of man was specifically sought.

E. POSSIBLE EFFECTS OF BIS-CHLOROMETHYL ETHER (BCME)

S.Z.M. Travenius (45) has stated that it is possible that the key to the carcinogenicity of formaldehyde in animals could be found (at least partly) in the formation of BCME. The main question is : can BCME originate from formaldehyde and hydrochloric acid at concentrations comparable with the threshold limit values; and can the carcinogenic action of formaldehyde be attributed to BCME formed at the same time. There is biological and chemical evidence that BCME does not play a major role in animal studies of the carcinogenicity of formaldehyde.

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1. CHEMICAL INVESTIGATIONS

Because detection of BCME in air at below 0.1 ppb is not well established, research on the reaction was carried out at relatively high concentrations of the reactants (20 - 10,000 ppm) (45) (46). It was thought that on the basis of kinetics and equilibria, the experimental results could be extrapolated to lower concentrations of reactants. However, the study of the kinetics and equilibrium of BCME formation has been made difficult by the polymerization of formaldehyde and other phenomena, difficult to understand. So it is impossible to calculate the chemical equilibrium constant from the experimental results in order to predict BCME-concentrations at low levels of hydrochloric acid and formaldehyde. To avoid these problems, the formation of BCME should by preference be measured at concentrations of formaldehyde (CH_2O) and hydrochloric acid(HCl), which are equal or close to industrially-occurring concentrations.

Nevertheless, it is attractive to get an idea of the BCME-concentrations to be expected at low reactant concentrations. For this purpose the WG tried to derive a mathematical expression of the data of Frankel et al (46) by linear regression analysis. The following relation was obtained between the formaldehyde and hydrochloric acid concentration on the one hand and the BCME-concentration on the other :

$$[BCME] = 0.005 [CH_2O]^{0.73} [HCL]^{0.73}$$

$[CH_2O]$ in ppm
$[HCl]$ in ppm
$[BCME]$ in ppb

This means, that a concentration of 2 ppm formaldehyde and 5 ppm hydrochloric acid would result in an average concentration of about 0.026 ppb of BCME. It should however be taken into account, that the relative humidity should be less than 100%.

The calculated concentration of 0.026 ppb is about 40 times smaller than the present TLV of BCME.

In the particle board and plywood industry, where formaldehyde and chloride-containing glues and resins are cured at elevated temperature, the evolved superheated steam will prevent the emission of BCME. Van der Ven and Venema (47) showed that when the vapour from glue heated during the manufacture of particle-board, was cooled and led through a Tenax-GC adsorption tube, the BCME decomposed. The BCME used as an internal standard was also decomposed in the adsorption tube by the released vapours.
Van der Ven and Venema (47) also tried to determine BCME in workroom air by the same method. The detection limit was 0·3 ppb and the internal standard of BCME in the adsorption tube was not decomposed by sucking workroom air through the tube. No BCME could be detected in workroom air.

2. BIOLOGICAL STUDIES

Reports are available about the carcinogenic effects in experimental animals exposed to BCME on the one hand, and to formaldehyde, or formaldehyde and hydrochloric acid, on the other. Exposure of Sprague-Dawley rats to 10.6 ppm of hydrochloric acid and 14.6 ppm of formaldehyde (6 hrs/day, 5 days/week ± 530 exposures over 814 days) induced an incidence of 25% of squamous cell carcinoma in the nasal cavity, but no tumours in the lung as would be expected from BCME (48). These results should be compared with the results given at the latest CIIT Conference (1) (49) on the exposure of rats to 2, 6 and 15 ppm of formaldehyde.

BCME itself, however, shows the following picture of carcinogenicity. Male Sprague-Dawley rats were subjected to 4, 8, 12, 16 and 20 weeks exposure to 0.1 ppm of BCME (6 hrs/day, 5 days/week). In the nose 17 esthesioneuro-epitheliomas, 1 ganglioneuro-epithelioma, 5 unclassified tumours, 1 adeno-carcinoma and only one squamous cell carcinoma were found in 170 treated animals. In addition 13 squamous cell carcinomas and 1 adeno-carcinoma were found in the lungs. In the control animals only one adeno-carcinoma was detected in the nasal cavity (50).

From this we may conclude that BCME-exposure induced a different carcinogenic effect from that found on exposure to formaldehyde, or to hydrochloric acid and formaldehyde at the same time. It therefore seems improbable that the carcinogenic effect induced by simultaneous exposure to formaldehyde and hydrochloric acid was caused by BCME, originating from these two chemicals. In addition, the BCME-concentration was measured in this rat experiment by Rusch (48) and amounted to about 0.1 ppb.

F. CONCLUSIONS

1. Formaldehyde is a natural metabolite in man and is normally present in the environment.
2. Although formaldehyde has been manufactured for almost 100 years, available epidemiological data do not indicate any causal relationship between previous exposure to formaldehyde and the occurrence of malignant neoplasms in man.
   In none of the studies were exposure concentrations well-defined, but it can be supposed that in the past men have been exposed to higher concentrations than the present limit values.

3. Adverse clinical symptoms (affecting eyes, lungs and skin) have been recognised for many years, but they were never associated with malignant degeneration and their magnitude was not comparable with the effects observed in long-term animal studies.
4. At the present, normally-existing,formaldehyde and hydrochloric acid levels in the atmosphere, bis-chloromethyl ether (BCME) will not be formed in an amount sufficient to pose a carcinogenic hazard.

G. RECOMMENDATIONS

Although no ultimate proof exists for non-carcinogenicity, recommendations can be made to give more weight to the preceding conclusions and/or to decrease the other health effects which may appear when people are exposed to formaldehyde.

1. To make future epidemiological studies valuable, exact information on the formaldehyde levels in the environment and in the workroom is necessary.
2. More data from extensive retrospective and prospective epidemiological studies on well-defined occupational and environmental cohorts should be acquired. Results with cohorts of tens-of-thousands would provide evidence of the validity or non-validity of results obtained from mathematical model extrapolations from animal data in the CIIT study.
3. Case control studies for nasal cancers should be performed where a correlation should be looked for with formaldehyde exposure.
4. Chemical companies and pathologists societies should be encouraged to publish or make available any evidence about the possible carcinogenic action of formaldehyde in occupational conditions.
5. For those exposed to occupational formaldehyde a relevant personal monitoring system should be developed.

6. The number of people who are occupationally-exposed should be monitored.

7. Consideration should be given to expanding the knowledge of the breathing behaviour of man, and the physiology and pathology of the nasal tissue in people exposed to formaldehyde, preferably with non-invasive techniques.

APPENDIX A - SUMMARY OF USES OF FORMALDEHYDE

Formaldehyde is produced in industry by the catalytic oxidation of methanol. It is marketed mainly in the form of aqueous solutions, partly under the common name of "formalin", normally containing 30% to 50% formaldehyde by weight.

Three main reactions characterise its uses, i.e. self-polymerization, oxidation-reduction and addition-condensation, chiefly with organic compounds.
The major use of formaldehyde is in the synthetic resin industry, in the production of urea -, phenolic -, polyacetal -, and melamine-formaldehyde resins, and in the manufacture of pentaerythritol and hexamethylene-tetramine.

Over half of the formaldehyde produced is used in the manufacture of urea-formaldehyde and phenol-formaldehyde resin. The former is, among other uses, applied as a foam for thermal insulation. The hardening and drying of the resin lasts up to 48 hours.

There are formaldehyde applications in a wide variety of industries, e.g. in the wood, plywood and particle board industry; in paper , textile , and dyestuffs manufacture; soil and seed treatment in agriculture to destroy micro-organisms; as a powerful bactericide, fungicide and fumigant; in medicine and analytical chemistry.

In medicine, formaldehyde solutions have been used for disinfection of the skin, for the treatment of warts on the palms of the hands and soles of the feet, in mouth-washes as an antiseptic, in dentistry for the treatment of pulp tissue and septic root canals, and in hospitals for the disinfection of rooms, blankets and bedding. Formaldehyde is also a component of cosmetics such as antiperspirants, shampoos, etc.

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APPENDIX B - EXPOSURE LIMITS IN THE WORKROOM ENVIRONMENT

Europe	ppm	mg/m³
BELGIUM		
TLV (1976)	2 (ceiling)	3 (ceiling)
BRD (GERMANY)		
MAK. (1971)	1 (ceiling)	1.2 (ceiling)
CSSR		
TLV (1976)	1.7	2
DDR (GERMANY)		
MAK (1976)	2	3
DENMARK		
TLV (1979)	1	1.2
proposal for (1983)	0.3	
proposal for new plants (1982)	0.3	0.4
FINLAND		
TLV (1976)	2 (ceiling)	3 (ceiling)
FRANCE		
TLV (1977)	No own standard, oriented towards US- and USSR standards.	
HOLLAND		
MAC (1976)	2 (ceiling)	3 (ceiling)
ITALY		
TLV (Hygiene) (1976)	1.25	1.5
TLV (ENPI) (1976)	1	1.2
NORWAY		
TLV	1	1.2
SWEDEN		
LV (1979)	1 (ceiling)	1.2 (ceiling)
proposal for new plants	0.5	0.6
SWITZERLAND		
MAC (1976)	1 (ceiling)	1.2 (ceiling)
UNITED KINGDOM		
TLV	2 (ceiling)	2.5 (ceiling)
USSR		
TLV (1976)	0.42 (ceiling)	0.5 (ceiling)
Outside Europe		
JAPAN		
TLV (1976)	5	6
USA		
OSHA Federal Standard:TWA (1974)	3; 5 (ceiling)	36; 6 (ceiling)
	10 (ceiling for once a day up to 30').	12 (ceiling for once a day up to 30').
NIOSH:TWA (1976 recommended)	1	1.2
ACGIH : TWA (1973)	2(ceiling)	3 (ceiling)

APPENDIX C 1 : EXPOSURE MEASUREMENTS OF FORMALDEHYDE IN THE AIR.

The measurement of formaldehyde by personal sampling, the preferred way of measurement for checking compliance with exposure standards, has not been practicised because no solid adsorbent exists with appropriate adsorption and desorption characteristics for measuring formaldehyde or its oxidation product formic acid.

All methods follow the same way of sampling. Air is sucked through a washing bottle, or an impinger, filled with an absorption liquid. After sampling, a colouring reagent is added and after a stable colour has been formed the absorbance is measured in a spectrophotometer or in a colourimeter at an appropriate wavelength. The method based on chromotropic acid (di-sodium-4,5-dihydroxy-2,7-naphthalenedisulphonic acid) as colouring agent, is most frequently mentioned in the scientific literature (51). Otherwise, the method with pararosaniline -tris-(4-aminobenzyl)-carbinol as colouring agent is used (52). Both methods have the advantage of being sufficiently specific for formaldehyde. The two methods are reliable only if carried out by experienced analysts.

A third method, with MBTH (3-methyl-2-benzothiazolon-hydrazon hydrochloride) as a colouring reagent, has the same sensitivity or better than the afore-mentioned methods and is easier to carry out (53). The reagent solutions are more stable and no special experience of the analyst is required. However, the disadvantage is its lower specificity, since other aldehydes are also determined, and aromatic amines and halogens interfere by increasing the absorbance.
However, the MBTH-method is useful, fast and reliable if no other aldehydes and interfering compounds are expected to be present. These conditions are often met in formaldehyde-containing resin, glue and particle board manufacturing plants.

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If compounds interfering with the MBTH-method are present, the pararosaniline or chromotropic acid method should be used. The choice of method should be made on the grounds of the available experience of the analyst.

The sensitivity of the above three methods is about the same. It depends on the amount of sampled air and the volume of the sampling liquid. Concentrations of 10μ g/m³ (0.008 ppm) can be reliably determined.

Many other methods are reported in the literature, but they lack the sensitivity and (apart from the MBTH-method) the specificity of the afore-mentioned methods.

RECOMMENDATION FOR MEASUREMENT STRATEGY

In view of the current concern about the animal carcinogenicity results, it is worthwhile to survey the time-weighted-average concentrations in formaldehyde processing industries to gain better information of actual personal exposure and not merely to check compliance with the present exposure standards. It is recommended to carry out measurements for determining formaldehyde concentrations starting from 0.1 ppm (= 120μg/m³). A minimum number of four measurements is recommended for every group of workers who have an approximately similar exposure. The method of sampling should, by preference, be personal and not local. Because only sampling methods with absorption of the formaldehyde into liquid are available, the use of spill-proof micro-impingers as described by Linch(54) is recommended. A battery-powered portable pump forces the sample air into the impinger and makes it possible to take time-weighted-average samples by personal monitoring.

2. EXPOSURE MEASUREMENTS OF FORMALDEHYDE BY BIOLOGICAL MONITORING METHODS.

An alternative approach to the assessment of exposure to industrial chemicals is available in the form of biological monitoring methods (55), which are already widely applied in the fields of Occupational Medicine and Industrial Toxicology. One such method is the measurement of formaldehyde level in blood, which has been used to monitor occupational exposure to formaldehyde. Workers exposed at air concentrations of ± 5.8 ppm showed blood levels of 0.6- 4 mg/l (56).

A more promising indicator of the exposure is determination of the urinary level of formic acid, a metabolic oxidation product of formaldehyde. It is an endogenous substance, being formed by the degradation of glycine (57). The elimination of formic acid is exponential in time and work has been carried out in a wide range of laboratory animals (58). In a study of humans (12) professionally exposed to formaldehyde at 0.93 - 1.19 ppm during an 8 hour period, the formic acid concentrations measured in urine showed increased levels (factors between 3 and 7) compared with 3 mg% in controls (59). Similar urinary formic acid levels were determined among workers who were exposed to formaldehyde at between 0.2 and 1.0 ppm at their work place (60). However, these results could not be confirmed by another research group (13) perhaps because of lower formaldehyde concentrations (0·32 - 0·57 ppm) and shorter (3h) exposure time of the individuals.

The urinary level of formic acid is measurable by gas chromatography (55) (57). Its modification in the form of headspace analysis enables the analysis of a score or more urine samples in the one batch (61). Formic acid and an internal standard, propionic acid, are extracted from acidified urine into ethyl acetate. The compounds are esterified with phenyldiazomethane reagent and analysed as the benzyl esters by flame-ionization gas chromatography.

Normal urine contains an average of 17 mg/l formic acid. Formic acid is a metabolite of methanol, formic acid esters and certain halogenated methane derivatives, as well as formaldehyde. Normal urine constituents do not interfere with the assay.

APPENDIX D - FORMALDEHYDE MORTALITY STUDIES - A REVIEW

PMR = Proportionate Mortality Ratios SMR = Standardised Mortality Ratios

Type of study	Investigator (reference)	Population	Exposure period	Exposure levels	Results
PMR	Pittsburgh Univ. (G. Marsch) (1)	2,500 Formaldehyde Workers (Mass)		estimated, but not given in ppm	No excess in cancer mortality;no nasal cancer.
PMR	NCI	medical technologists (California)	technologists licensed between 1947 & 1967		in progress
SMR	CIIT	embalmers (Ontario) 1,200 persons	embalmers licensed between 1914 & 1967	estimated, but not given in ppm.	in progress
PMR	NCI J. Walrath (1)	embalmers (New York) 1,106 persons		estimated, high and low exposure groups	no excess in cancer mortality; no nasal cancer.
SMR	Johns Hopkins Univ. Matonoski (1)	pathologists		not known	increased risks for lymphoma and possibility of liver and pancreas cancers
SMR	CIA-HIST-UK Prof. Acheson (pers. communication)	8,000 persons			start 1981
PMR	Perstorp (pers. communication)	Perstorp population	1950-1977	not known	mortality pattern similar to that of Oderljunga population
SMR	TOMA O. Wong (1)	2,026 Formaldehyde workers	1940-1977	estimated, but not given in ppm	no excess respiratory cancer mortality, no nasal cancers
SMR	Formaldehyde Institute/NCI	5 to 8,000 formaldehyde workers	> 15 years	workplace measurements and if possible individual exposure	start 1981

(Appendix D continued)

FORMALDEHYDE MORBIDITY STUDIES - A REVIEW

Type of study	Investigator	Population	Exposure period	Exposure levels	Results
Morbidity	NJ Dept. Health	residents of insulated homes	home insulated within last 6 months (as of March 1979)		in progress
Morbidity	Wisc.Dept.Hlth & Soc. Serv.	mobile home residents (65 mobile homes)			in progress
Morbidity	Univ.Washington	mobile home residents (334 mobile homes)		Q3 to 1.77 ppm	Most commonly reported complaints were eye and respiratory irritation
Morbidity	Oregon Dept.Dis. Monit.Control	300 mobile home residents		not known	in progress
Morbidity	Connect.Dept. Hlth Serv.	residents of insulated homes		mean:1.5ppm (range: 0 - 10 ppm)	interim results : eye, nose, throat, irritation headaches
Morbidity	NH Bur. Occup. Health	residents of insulated homes, businesses, schools		0 to 0.15ppm (max.: 2ppm)	
Morbidity	Univ.Minnesota			0.1 to 3.0ppm	Eye, nose, throat irritation, headaches. Diarrhea for newborn infants
Morbidity	Ciba-Geigy (Duxford) (pers. communication)	workers (200)	1 to 15 years	not known	increased incidence of dermatitis
Morbidity	CIIT R. Levine (1)	100 West Virginia Embalmers		estimated,high and low exposures with or without smoking histories	no formaldehyde related respiratory disease or symptomatology

APPENDIX E - RESPONSES OF MAN TO VARIOUS CONCENTRATIONS OF FORMALDEHYDE VAPOUR

Concentration ppm	Exposure Time	Response	Reference
0.01		Eye irritation threshold	(62)
0.04		E.E.G. changes	(36)
0.06		Odour threshold	(40)
0.06		Odour threshold in 7 out of 15 test subjects	(37)
0.07		Chronaximetric response threshold	(40)
0.08		Cortical reflex threshold	(40)
0.13-.45		Irritant threshold	(18)
0.17		Odour threshold	(63)
0.25		Odour threshold in 1/2 subjects	(38)
0.25-5.0		Irritant threshold	(31)
0.3-0.9		Eye irritation	(18)
0.5		Odour threshold	(31)
0.8		Slight irritation	(40)
0.8		Odour threshold. Irritation of upper respiratory tract and E.C.G. changes	(37)
0.9-1.6		Irritant threshold	(64)
1.0		Odour threshold	(20)
1-2		Irritation threshold	(19)
2.0-3.0	8 hr.	Tolerable; mild irritation of eyes, nose and posterior pharynx	(20)
4.0-5.0	10-30 min.	Intolerable to most people; mild lacrymation; very unpleasant	(20)
5		Intense irritation	(64)
5.0		Throat irritation threshold	(21)
2-10		Collapse, headache, nausea vomiting, dizziness	(65)
10.0	few min.	Profuse lacrymation	(20)

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(Appendix E continued)

Concentration ppm	Exposure Time	Responses	Reference
20.0	15-30 sec.	Lacrymation	(66)
20.0	30 sec.	Irritation of nose and throat	(66)
20.0	1-2 min.	Sneezing	(66)
50-100	5-10 min.	May cause very serious damage	(20)

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