459 - P35

Gezondheidsraad
P.O.Box 1052
2500BB Den Haag
The Netherlands

Tampere, 6 August, 2001

Dear Lady/Sir,

1625

Re: **Draft Document on Formaldehyde**

Thank you for the possibility to comment on this. The document has cited many articles, but still many – possibly relevant ones – have been omitted, too. In our national document for formaldehyde limit value from 1997 we had only 27 citations, and your document covers 9 (33%) of these. Lately, new interesting articles have been published. I will not deal in length with these older publications, however.

In 3.2 you give the vapour pressure of 0,2 kPa at 20 C. I wonder if this one is for a water solution of formaldehyde. At flash point you mention flammable gas, and to my knowledge the vapour pressure of the gas is several decades higher.

As for sensory irritation in animal experiments, you mention the Kane and Alarie study for RD50. Many more exist, like Chang,1981 (4,9 ppm) and DeCeaurritz,1981 (5,3 ppm).

The existing guidelines for working population tend to be outdated. This draft is no exception. In table 3, Sweden has also a note of carcinogenicity, and ACGIH a note of sensitisation. The Iceland standard is presently 0,3 ppm (Vinnueftirlit Rikisins, 1999).

The present Finnish limit values are 0,3 ppm (8 hr) and 1 ppm (ceiling). The year of adoption was 1998, and the present literature reference is 'Sosiaali- ja terveysministeriö, HTP-arvot 2000, Työsuojelusäädöksiä 3, 2000'.

I would like to point out few recent publications that might have relevance to limit value setting.

An article from Australia (Allergy 1999,54,330) pointed out that *the risk of atopy* was increased by 40% , if the formaldehyde concentration of bedrooms was at least 135 micrograms per cubic metre or the concentration of the whole apartment at least 145 micrograms per cubic metre.

An American study on *nasopharyngeal carcinoma* supported the hypothesis that formaldehyde but not wood dust increases the risk on NPC (Vaughan et al (2000): Occupational Exposure to Formaldehyde and Wood Dust and Nasopharyngeal Carcinoma, Occup. Environ. Med. 57, 376-384). There was a statistically significant risk for people exposed to more than 1,10 ppm –years. For 40 years this would mean 0,0275 ppm as 8 hr – if I calculate right.

Short- term effects of formaldehyde on *peak expiratory flow and irritant symptoms* of students dissecting cadavers was studied by Kriebel et al (Archives of Environmental Health 2001, 56, 11-18).

French researches reported recently on their study of ten workers exposed to formaldehyde. Using the *micronucleus assay* they reached results that suggested that exposure to formaldehyde induces chromosome aberrations on lymphocytes (Sari- Minodier et al (2001): le Test des Micronoyaux dans l'Evaluation du Risque Mutagene:Etude aupres de 10 Salaries Exposes au Formaldehyde, Arch. Mal. Prof. 62, 75-82).

Sincerely,

Asko Aalto (Finland)

Gezondheidsraad
Health Council of the Netherlands

mr A Aalto
Ministry of Labour
Occupational Safety and Health Division
PO Box 536
FIN-33101 Tampere
Finland

1,130328147195

Subject	: Comments on public draft 'Formaldehyde'
Your reference	: August 6, 2001
Our reference	: 1625/AvdB/459/N38
Enclosure(s)	: 1
Date	: January 27, 2003

Dear mr Aalto,

In 2001, the Dutch Expert Committee on Occupational Standards (DECOS) published a draft report on formaldehyde for public review. Your organisation used the opportunity to comment on the draft report. The committee thanks you for your comments, which were used in finalising the report. On behalf of the President of the Health Council of the Netherlands I herewith present you the DECOS' reaction to your comments.

The committee has updated the existing guidelines for the working population from other countries.

You suggested to include several additional studies in the report. The committee has reviewed all these studies and decided, however, not to include the animal studies of Chang and DeCeauritz because the HBROEL is based on human data only. In addition, the human study of Kriebel et al is not added to the report because the differences between the exposed groups and the controls is (although relevant and significant) limited.

The committee considered the human studies of Garret et al and Vaughan et al as important and of sufficient quality and these studies are therefore described in the final report. However, the committee concluded that, although a small number of studies produce limited evidence on nasal cancer, the total body of data doesnot support a causal relationship for a nasal cancer risk at the experienced exposure levels.

P.O Box 16052
NL-2500 BB Den Haag
Telephone +31 (70) 340 75 20
Telefax +31 (70) 340 75 23

Visiting Address
Parnassusplein 5
NL - 2511 VX Den Haag
email GR@gr.nl

Gezondheidsraad
Health Council of the Netherlands

Subject : Comments on public draft 'Formaldehyde'
Our reference :3113/AvdB/459-N38
Page : 2
Date : January 27, 2003

The final report was published on January 27, 2003. Enclosed you will find a copy.

Yours sincerely,

Ms dr ASAM van der Burght
scientific secretary DECOS

1,130328147196

P.O Box 16052
NL-2500 BB Den Haag
Telephone +31 (70) 340 75 20
Telefax +31 (70) 340 75 23

Visiting Address
Parnassusplein 5
NL - 2511 VX Den Haag
email: GR@gr.nl

SENATSKOMMISSION
DER DEUTSCHEN
FORSCHUNGSGEMEINSCHAFT
ZUR RRÜFUNG
GESUNDHEITSSCHÄDLICHER ARBEITSSTOFFE
VORSITZ PROF DR MED H GREIM
Dr. Heidrun Greim

TECHNISCHE
UNIVERSITÄT
MÜNCHEN

Kommissionssekretariat
Hohenbachernstraße 15-17
D-85350 Freising-Weihenstephan
Telefon 08161/ 71-5601
Telefax: 08161/ 71-5618
E-mail: heidrun.greim@lrz.tum.de

Dutch Expert Committee on
Occupational Exposure Standards (DECOS)
Health Council of the Netherlands
PO Box 16052

NL - 2500 BB Den Haag

Weihenstephan, 26. Juli 2001
(7/mak/DECO2307.doc HG/nk)

2,130325328070

Formaldehyde
Draft May 1, 2001

Dear Madam and Sirs,

The description of the MAK carcinogen category 4 in your draft document is not correct.
My suggestion would be to replace the second sentence of paragraph 3 on pagina 59 with :
"Formaldehyde is classified in carcinogen category 4, which contains substances with carcinogenic potential for which genotoxicity plays no or at most a minor part. No significant contribution to human cancer risk is expected provided the MAK value is observed. The classification is supported especially by evidence that increases in cellular proliferation or changes in cellular differentiation are important in the mode of action. To characterize the cancer risk, the manifold mechanisms contributing to carcinogenesis and their characteristic dose-time-response relationships are taken into consideration."

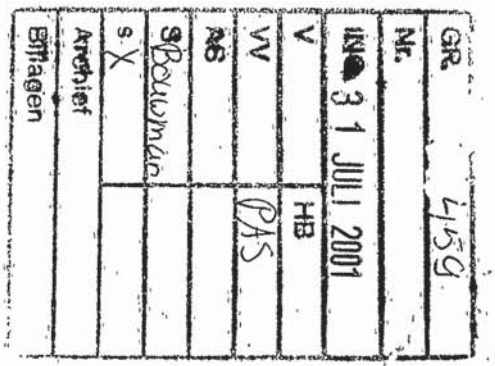
I would also suggest replacing the last line in the 3rd paragraph of pagina 5 with:
"and classified formaldehyde into carcinogen category 4 (genotoxicity playing no or at most a minor part)".

Further more, I would like to inform you that our commission has classified formaldehyde into germ cell mutagenicity category 5.

Yours sincerely

Dr. Heidrun Greim

01526



Gezondheidsraad
Health Council of the Netherlands

mrs dr H Greim
Senatskommission der Deutschen Forschungsgemeinschaft
Kommissionsekretariat
Hohenbachernstrasse 15-17
D-85350 Freising-Weihenstephan
Deutschland

1,130328147194

Subject	: Comments on draft 'Formaldehyde'
Your reference	: 7/mak/DECO2307.doc HG/nk
Our reference	: 01526/AvdB/459.038
Enclosure	: 1
Date	: January 27, 2003

Dear dr Greim,

In 2001, the Dutch Expert Committee on Occupational Standards (DECOS) published a draft report on formaldehyde for public review. Your organisation used the opportunity to comment on the draft report. On behalf of the President of the Health Council of the Netherlands I herewith present you the DECOS' answers to your comments.

DECOS has corrected the last line of the 3rd paragraph of page 5 according to your comments. In addition, the committee adjusted the desciption of carcinogen category 4 on page 59 as you suggested and added the classification of formaldehyde into germ cell mutagenicity category 5.

The final report was published on January 27, 2003. Enclosed you will find a copy.

Yours sincerely,

Mw dr ASAM van der Burght
Scientific Secretary DECOS

Bezoekadres
Parnassusplein 5
2511 VX Den Haag
Telefoon (070) 340 75 20
email: GR@gr.nl

Postadres
Postbus 16052
2500 BB Den Haag
Telefax (070) 340 75 23

Corporate Safety, Health, Environment & Manufacturing

Milieu & Productveiligheid

Het Overloon 1, 6411 TE Heerlen
Postbus 6500, 6401 JH Heerlen
Phone (045) 5782075, Fax (045) 5787112, Internet www.dsm.nl

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Dutch Expert Committee on Occupational
Exposure Standards,
Health Council of the Netherlands
P O. Box 16052,
2500 BB Den Haag

01504

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Your reference	Our reference	Dealt with by	Direct line
	WB034/CVM 7404 DMM	W.F. ten Berge	+31 45 5787128
Subject		E-mail	
Formaldehyde	19 July 2001	wil.berge-ten@dsm.com	

Dear Madam, Sir,

Herewith I send you as attachment my comments to the DECOS proposal for a Health-based recommended occupational exposure limit.

I look forward to your final evaluation.

Kind regards,

Wil ten Berge.

Enclosure: Comment to the proposal

Corporate Safety, Health, Environment & Manufacturing

Milieu & Productveiligheid

Your reference	Our reference	Direct line	Date
	WB034/CVM 7404 DMM	+31 45 5787128	19 July 2001

Comment to the proposal of the Dutch Expert Committee on Occupational Standards for a Health Based Recommended Occupational Exposure Limit of Formaldehyde

Author: W.F. ten Berge, DSM Heerlen, NL

Introduction

The Dutch Expert Committee on Occupational Standards has issued a draft health-based recommended occupational exposure limit for formaldehyde. The basis for the recommendation of 0.15 mg/m3 is based on cytotoxicity of formaldehyde of the nasal epithelium in rats and on eye irritation in volunteers. Both toxicological end points in relation to formaldehyde exposure and other environmental factors are considered in the text below in order to provide the complete information on the studies used by DECOS for setting an occupational standard for formaldehyde.

Cytotoxicity studies in rat nasal epithelium of rats

Zwart et al. (1988) exposed Wistar rats to 0, 0.3, 1 and 3 ppm formaldehyde vapour for 6 hours per day, 5 days per week during 3 days or 13 weeks, using in vivo [3H]thymidine labeling for cell proliferation studies and light and electron microscopy for detecting morphological effects. No difference in the nasal epithelium were found at 0, 0.3 and 1 ppm exposure by means of light and electron microscopy. Clear effects were seen at 3 ppm as loss of the cilia of the epithelial cells After 3 days a dose related increase in cell proliferation was observed in the posterior part of the incisor teeth region, which had disappeared after 13 weeks. This indicates an adaptation after prolonged exposure to formaldehyde for 13 weeks. In the anterior part of the incisor teeth region an increase of cell proliferation was seen only at 3 ppm. Three ppm was definitely an adverse effect level. The No Observed Adverse Effect Level appeared to be 1 ppm.

Reuzel et al. (1990) studied the interactive effects of ozone and formaldehyde on the nasal repiratory lining epithelium in rats. This study is interesting because of the exposure to only formaldehyde at levels of 0, 0.3, 1 and 3 ppm for 22 hours per day for 3 consecutive days. The pathology of nasal epithelium was studied by means of light microscopy and the cell proliferation was measured by counting by [3H-methyl] thymidine labeled cells at epithelium of the incisor teeth region. Treatment related histopathological changes and increased cell proliferation were only found at 3 ppm formaldehyde. The No Observed Adverse Effect Level was estimated to be 1 ppm.

Kamata et al. (1997) exposed groups of 32 male F-344 rats to formaldehyde levels of 0, 0.3, 2 and 15 ppm for 6 hours per day, for 5 days per week for 28 months. Nasal tumours were microscopically evident in the 15 ppm group from the 14th month and 8 of 32 rats bore such tumours at the 24th month. Histopathological examination revealed both squamous cell papillomas and carcinomas. No nasal tumours were observed in the lower exposure groups (0.3 and 2 ppm groups).

Cell infiltration, erosion and edema of the epithelium was observed in all groups. This points to a chronic inflammation of the upper respiratory tract. Epithelial hyperplasia with squamous cell metaplasia was found at the level of 0.3 ppm after 24 months and one isolated squamous metaplasia was seen after 18 months At 2 ppm 5 rats developed squamous metaplasia without hyperplasia and 7 rats developed epithelial cell hyperplasia with squamous metaplasia after month 18. One rat showed epithelial cell hyperkeratosis at spontaneous death in the 2 ppm group.

Interspecies variation in nasal epithelium cell proliferation due to formaldehyde exposure

Morgan (1997) has shown, that the effects in the monkey and the rat are more or less comparable at 6 ppm formaldehyde except that the extent of DNA-protein cross-linking due to formaldehyde is considerably higher in rats. He made his comparison only for one dose level, 6 ppm formaldehyde. He emphasises the need of exploring interspecies differences in nasal dosimetry and local metabolism over the full dose range. He states, that low concentration (< 2 ppm) extrapolation, where no tissue damage is observed, should be uncoupled from the responses at high concentration (> 6 ppm), where epithelial degeneration, regenerative cell replication and inflammation appear to be essential driving forces in formaldehyde carcinogenesis

Heck and Casanova (1999) studied the cytotoxicity of formaldehyde to the nasal epithelium on the basis of DNA replication at low formaldehyde exposure levels. DNA replication was measured by radioactive thymidine incorporation. On the basis of the data in both species it was concluded, that inhibition of DNA replication was less than 1 % after 6 hours exposure to 1 ppm of formaldehyde for the rat and 2 ppm formaldehyde in rhesus monkeys.

Interpretation of the cytotoxicity of formaldehyde for nasal epithelium

The study of Zwart et al. indicate a NOAEL of 1 ppm after 3 days and 3 weeks for 6 hours per day, 5 days per week under all conditions. The NOAEL was established via light microscopy, electron microscopy and measuring of cell proliferation in the most susceptible part of the rat nasal epithelium..

Rats exposed to 0.3 ppm and 1 ppm for 22 hours per day on three consecutive days did not show a clear effect on cell proliferation or changes in the nasal epithelium The nasal epithelium was slightly affected at 0.3 and 1 ppm formaldehyde compared to the control group, but there was no difference between the 0.3 and 1 ppm exposure groep. The effects observed were minimal to slight hyper/metaplasia in 1 of 10 rats at 0.3 ppm and in 2 of 10 rats at 1 ppm and minimal to slight rhinitis in 2 of 9 rats at 0.3 ppm and in 1 of 9 rats at 1 ppm. These are slight effects above background, not significantly different from the control group.

In the study of Kamata (1997) epithelial cell hyperplasia with squamous cell metaplasia was observed in the most susceptible region of the nasal epithelium in 4 of 32 to rats after 24 months of exposure to 0.3 ppm of formaldehyde Epithelial cell hyperkeratosis, a further degeneration of the epithelium, was not observed at 0 3 ppm, but only in 1 rat, dying

spontaneously, of the 2 ppm group. It is surprising, that the effect of squamous metaplasia with hyperplasia occurred so late in the study and that it was not earlier detected like in the studies of Zwart et al.(1988) and Reuzel et al. (1990). However, it might be that the susceptibility of the nasal epithelium was enhanced by chronic inflammation of the hasai epithelium. Ceil infiltration, erosion and edema in the nasal epithelium were evident in all groups, including the 0 ppm group and the Room Control group. This points to some widespread upper respiratory tract infection, which might have made the nasal epithelium more susceptible for the irritant action of formaldehyde. So the results of Kamata et al. (1997) might be flawed by the occurrence of chronic infection of the upper respiratory tract. An other shortcoming is the monitoring of the formaldehyde during the study. It was measured only twice per day by means of the acetyiacetone method, a method presently hardly used. This method was also not mentioned in section 3.3 of the DECOS report.

A few words should be spent to the severity of nasal metaplasia as a toxic effect of irritants. In the human population squamous metaplasia and hyperplasia are common findings in nasal epithelium due to virus infections or allergic rhinitis. With increasing age there is an increase in squamous epithlium of the nasal mucosa. In persons more than 40 years of age squamous epithelium was observed in more than one third (Boysen 1982). So squamous metaplasia and epithelial cell hyperplasia itself does not mean being predisposed to get nasal cancer.

In addition, one should consider that rats are obligate nose breathers. Man and monkey can change to mouth breathing in case of irritant vapours and this will diminish the deposition of formaldehyde in the nasal epithelium and so also damage of the nasal epithelium becomes less probable.

The study of Heck and Casanova (1999) indicates that at low exposure levels (1-2 ppm formaldehyde) monkeys are a factor 2 less sensitive than rats concerning increased cell proliferation in the nasal epithelium due to exposure to formaldehyde. Monkey is generally assumed to be a better model for man than the rat.

Our conclusion from the results of the studies presented is, that exposure of man up to 1 ppm formaldehyde for 8 hours per day is not expected to result in increased damage of the nasal epithelium of healthy workers. This is based on the following considerations:

- The studies of Zwart et al. (1988) and of Reuzel et al (1990) indicate, that exposure levels of 0.3 and 1.0 ppm do not result into histopathological damage of the nasal epithelium..
- Heck and Casanova (1999) showed that rhesus monkeys were a factor 2 less sensitive than rats concerning slight inhibition of cell proliferation. Monkeys are assumed to be a better model for nasal pathology than the rat.
- The study of Kamata is seriously flawed by upper respiratory tract infection and is not in agreement with the findings of Zwart et al. (1988) and Reuzel et al. (1990)

Your reference	Our reference	Direct line	Date
	WB034/CVM 7404 DMM	+31 45 5787128	19 July 2001

Human experience: eye irritation in workers and volunteers

Eye irritation is the most sensitive toxicological endpoint related to formaldehyde exposure in volunteers.

DECOS discussed the study of Wilhemsson and Holmstrom (1992) in one paragraph with that of Andersen et al (1983) as a basis for discomfort. This is not well possible. Wilhelmsson and Holmström (1992) carried out monitoring during the time of the study but in their questionnaires they asked for symptoms over the last years. So the effects reported cannot be related to the measured exposure. In addition, the average exposure levels over the day hide the short term higher fluctuations of exposure levels over the day, which increase the irritation experience.

DECOS considers the study of Bender et al. (1983) as a key study for setting an upper limit for eye irritation over a short exposure period. In fact it is not well possible to draw a firm conclusion from this study. This study has been characterised by a strong selection of the volunteers. About half of the original volunteers reported eye irritation from clean air or were unresponsive to levels of 1.3 to 2.2 ppm formaldehyde in 6 minutes and therefore these volunteers were unacceptable according to the authors. Only volunteers were included, who responded to 1.3 to 2.2 ppm formaldehyde in 6 minutes with increased eye irritation. So the volunteers were a 50% selection of the staff members of the Battelle Memorial Institute, Columbus Ohio. Bender et al. (1983) conclude, that only at 1 ppm a significant difference in median response time for eye irritation was observed, but at all other levels this difference was not significant. In addition, the severity index of irritation when first noted, was not different from 0.35 to 0.9 ppm and was about 0.8 in a scale from 0 to 3 (0=none, 1=slight, 2=moderate and 3=severe). In addition, the severity index decreased during exposure indicating a decrease of response in time. The only clear result from this study is, that at 1 ppm formaldehyde and higher the eye irritation response is increasing from slight to moderate.

In the study of Andersen (1983) 16 volunteers were exposed to formaldehyde at levels of 0.3, 0.5, 1 0 and 2.0 mg/m3. After 2 and a half hour respectively 3, 2 , 7 and 9 persons of 16 volunteers experienced some discomfort. The average scale of experienced discomfort was respectively 2, 1, 7 and 18. The average discomfort values while not exposed to formaldehyde were between 1 and 3. The highest individual scale scores were 30, 20, 40 and 50 scale units respectively at 0 3, 0.5, 1.0 and 2 0 mg/m3 After 3 hours of exposure the discomfort decreased strongly and after 5 hours of exposure the average scale of discomfort was 8.5, 5, 9.5 and 10.5 respectively.

The explanation of the scale of discomfort is in the table below

Type of discomfort	Scale score
Intolerable discomfort	100
Strong discomfort	67-99
Discomfort	34-66
Slight discomfort	1-33
No discomfort	0

Benchmark dose analysis of the data after 2.5 hours of exposure showed that an increase of the background response or background score with a factor of 2 is to be expected at a dose level of about 0.5 ppm. After 5 hours of exposure this benchmark level changed into 1.2 ppm due to the decrease of sensitivity for the discomfort of formaldehyde
The DECOS-report states, that at a level of 0.3 mg/m3, 19% of the volunteers showed discomfort. This is half the truth. At an even higher level of 0.5 mg/m3, only 12.5% showed discomfort, fully comparable with exposure to clean air. This is consistent with the study of Bender et al. (1983), who could not observe a statistically significant increase in eye irritation in the range from 0.35 to 0.9 ppm formaldehyde.

Weber-Tschopp et al (1977) studied the eye irritation by steadily increasing the exposure level over a period of 37 minutes. Every 5 minutes the volunteers completed a questionnaire and in addition, the eye blinking rate of the volunteers was measured. The same procedure was carried out with exposure to clean air. An eye irritation index was developed on the basis of questions with a 5 grade scale The following grades were discerned: 1=none, 2=slight, 3=moderate, 4=strong and 5=very strong. In the table below the score of Weber-Tschopp et al. (1977) in volunteers exposed to formaldehyde is presented.

Formaldehyde exposure level ppm	eye irritation index
0 03	1.2
0.5	1.3
1.2	1.75
1.7	2.1
2.1	2.3
2 5	2.5
2.8	2.8
3 2	2.9

It is clear from this table, that the eye irritation index hardly increases going from 0.03 to 0.5 ppm. The authors state, that below 1.2 ppm the eye irritation index did not increase significantly. Also the eye-blinking rate (measure of eye irritation) did not increase at levels between 0.03 and 1.2 ppm formaldehyde, but significantly increased at levels above 1.2 ppm On the basis of the study of Weber-Tschopp (1977) the formaldehyde level should not exceed 1 2 ppm in the workroom in order to prevent eye irritation.

Kulle (1993) exposed 19 healthy non-smoking volunteers to formaldehyde in order to explore eye irritation Nineteen volunteers were exposed for 3 hours to 0, 1 and 2 ppm formaldehyde at rest and to 2 0 ppm formaldehyde with intermittent moderate exercise for 8 minutes each half hour. Ten subjects were also exposed to 0.5 ppm in the same way and 9 subjects to 3.0 ppm only at rest. Symptom questionnaires were completed directly before and immediately after each exposure. The following severity levels were assigned: 0=none, 1=mild (present but not annoying); 2=moderate (annoying), and 3=severe (debilitating).

The results are presented in the table below:

Formaldehyde level	Mild eye irritation	Moderate eye irritation
0.0	1 of 19	0 of 19
0.5	0 of 10	0 of 10
1.0	5 of 19	1 of 19
2.0	10 of 19	4 of 19
3.0	9 of 9	4 of 9

Benchmark analysis according to a Weibull model provided the following estimates of the exposure level of an increase of 5 % response:

- 0.7 ppm for a 5% increase of the response for mild eye irritation.
- 1.0 ppm for a response of 5% for moderate eye irritation.

The experiments of Kulle (1993) are qualitatively and quantitatively well described. Also Kulle observed, that it was not possible with a panel of 19 volunteers to make a distinction between air with 0.5 ppm formaldehyde and clean air It is not clear, why DECOS did not consider the study of Kulle (1993) for standard setting of eye irritation.

Conclusions

The studies in volunteers show clearly, that up to 0.5 ppm exposure to formaldehyde perceptions of eye irritation are comparable in exposed and non exposed volunteers. The best data for dose-response modelling are those from Kulle (1993). The Benchmark dose for a 5% increase of slight eye irritation was estimated to be 0.7 ppm in the volunteers, studied by Kulle (1993). An occupational standard of 0.3 ppm formaldehyde for 8 hours time weighted average and a short term exposure standard of 1 ppm for 15 minutes is more than sufficient to avoid a significant increase of eye irritation in workers.

Occupational Hygiene monitoring

DECOS proposes a very low occupational exposure limit. Not all methods of industrial hygiene monitoring of formhaldehyde are comparable concerning their detection limit. Therefore DECOS is urgently requested to indicate their preference for a personal sampling and monitoring method for formaldehyde at a level of 0.15 mg/m3.

References

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Zwart A, Woutersen RA, Wilmer JWGM, Spit BJ and Feron VJ, 1988 Cytotoxic and adaptive effects in rat nasal epithelium after 3 day and 13 week exposure to low concentrations of formaldehyde vapour. Toxicology 51, 87-99, 1988

Gezondheidsraad
Health Council of the Netherlands

mr dr W ten Berge
Corporate Safety, Health, Environment and Manufactoring
Milieu & Productveiligheid
Postbus 6500
6401 JH Heerlen

Subject	: Comments in public draft 'Formaldehyde'
Your reference	: WB034/CVM 7404 DMM
Our reference	: 01504/AvdB/459 P38
Enclosure(s)	: 1
Date	: January 27, 2003

Dear dr Ten Berge,

In 2001, the Dutch Expert Committee on Occupational Standards (DECOS) published a draft report on formaldehyde for public review. Your organisation used the opportunity to comment on the draft report. The committee thanks you for your comments, which were used in finalising the report. On behalf of the President of the Health Council of the Netherlands I herewith present you the DECOS' reaction to your comments.

You are of the opinion that several animal studies (Zwart et al 1988, Reuzel et al 1990 and Kamata et al 1997) show that a concentration of 1 ppm appears to be the No Observed Adverse Effect Level for formaldehyde. Taking the interspecies variation in nasal cell epithelium proliferation into account as well, you suggested a HBROEL of 0.3 ppm (0.36 mg/m^3) in stead of the HBROEL of 0.12 ppm (0.15 mg/m^3) that the committee recommended. You concluded that the study of Wilhelmsson and Holmstrom (1992) cannot be the basis of deriving a HBROEL because the exposure levels were not measured at the time the sympoms were studied and thus cannot be related. The committtee is however of the opinion that based on the review of Paustenbach et al (1997) and the studies of Anderson et al (1983) and Wilhelmsson (1993), it can be concluded that (minimal) effects are found in humans at an exposure level of 0.3 mg/m^3. The committee therefore considered this level as a LOAEL. The committee concluded that a factor of 2 (instead of 3) should be sufficient for the extrapolation from LOAEL to NAEL because the incidence of the effect is low, the effects are not systemic and 'accomodation' might occur at low exposure levels.

P.O Box 16052
NL-2500 BB Den Haag
Telephone +31 (70) 340 75 20
Telefax +31 (70) 340 75 23

Visiting Address
Parnassusplein 5
NL - 2511 VX Den Haag
email: GR@gr.nl

Gezondheidsraad
Health Council of the Netherlands

Moreover, you commented that the study of Bender et al has been characterised by a strong selection of the volunteers. Only volunteers were included in the study who responded to 1.3-2.2 ppm formaldehyde within 6 minutes. The committee agrees with your comment on this study and concluded that this study can not be used for deriving a STEL. Therefore, the committee is of the opinion that the total body of acute studies (Paustenbach et al, 1997, Bender et al, 1983) indicate that at an exposure level of 1.0 to 1.2 mg/m^3 sensory irritation will still be present. The committee considered an safety factor of 2 sufficient for the extrapolation from LOAEL to NAEL. Therefore, DECOS recommends a STEL of 0.5 mg/m^3.

The final report was published on January 27, 2003. Enclosed you will find a copy.

Yours sincerely,

Mw dr ASAM van der Burght
Scientific Secretary DECOS

P.O Box 16052
NL-2500 BB Den Haag
Telephone +31 (70) 340 75 20
Telefax +31 (70) 340 75 23

Visiting Address
Parnassusplein 5
NL - 2511 VX Den Haag
email. GR@gr.nl

B25

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

National Institute for Occupational
Safety and Health
Robert A. Taft Laboratories
4676 Columbia Parkway
Cincinnati OH 45226-1998

September 5, 2001

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Health Council of the Netherlands
c/o Dr. ASAM van der Burght
Scientific Secretary
DECOS/Committee on Compounds Toxic to Reproduction
P.O. Box 16052
2500 BB Den Haag
THE NETHERLANDS

Dear Dr. Van der Burght:

Thank you for the opportunity to review the draft DECOS document on formaldehyde and the draft documents on toluene, styrene, and xylene prepared by the Committee on Compounds Toxic to Reproduction. We apologize for not getting these comments to you at an earlier date.

If you have any questions regarding these reviews, please contact me at: 513/533-8320 (telephone) or email: RDZ1@CDC.gov.

Sincerely yours,

Ralph D. Zumwalde
Senior Scientist
Document Development Branch
Education and Information Division

Enclosures (4)

Formaldehyde—Health-based Recommended Occupational Exposure Limit
DECOS/NEG Draft Document
Comments of the National Institute for Occupational Safety and Health (NIOSH)

General Comment

The conclusion made in the document appears to have been significantly influenced by the meta-analysis by Collins et al. [JOEM, 39(7): 639-651]. This industry sponsored meta-analysis did find, as did the previous meta-analyses, a significantly elevated relative risk estimate for nasopharyngeal cancer (NPC). This excess risk was not apparent in the cohort studies once it was corrected for the missing information from studies that did not report findings for NPC. In this regard, the meta-analysis by Collins et al. study is superior to the earlier reported meta-analyses. However, an excess of NPC was still observed among the case-control studies, which was borderline significant (p=0.06). The analysis performed by Collins et al. dismisses the findings from the case-control studies on the basis that these studies had substantial potential for misclassification of exposures. Although this is undoubtably true, the fact is that this kind of non-differential exposure misclassification is well known to lead to bias towards the null (i.e., towards not seeing an effect). Thus, if anything, the results from the case-control studies would be expected to be stronger than observed if this bias could be eliminated. Furthermore, another NPC case-control study has been recently published, which was not included in the meta-analysis by Collins et al. or cited in the draft document. This study by Vaughan et al. [Occ. Environ. Med 2000; 57(6):376-384] found a significant association between formaldehyde exposure and NPC risk that increased with both duration of exposure and cumulative exposure. If this study were included in an updated meta-analysis it would most likely make the results for NPC statistically significant particularly for the case-control studies.

Given the results from the 3 meta-analyses and the study by Vaughan et al., there is evidence to suggest that occupational exposure to formaldehyde is causally related to NPC. In addition, there is an incomplete review of many existing epidemiologic and other human studies that could collectively provide more evidence of a potential adverse effect from formaldehyde exposure. If there was a reason for omitting these studies, it should be stated. Consideration may also want to be given to including a statement about the *in vivo* generation of formaldehyde from the metabolism of some chemicals that can be consumed or used for therapeutic purposes. For example, one of the metabolites of cyclophosphamide is formaldehyde.

Specific Comments

Page 5, Current limit values: the National Institute for Occupational Safety and Health (NIOSH) recommended exposure limit (REL) for formaldehyde is: 0.016 ppm TWA and 0.1 ppm ceiling limit (15-minutes); the U.S. Occupational Safety and Health Administration (OSHA) permissible exposure limit is: 0.75 ppm TWA and 2 ppm STEL.

Section 7

In section 7, exposure concentrations are expressed in mg/m^3 (ppm) whereas earlier in the document concentrations were expressed in ppm (mg/m^3). Some concentrations are expressed in mg/m^3 only. Readability would be enhanced by using the same units for concentration (e.g., ppm (mg/m^3)) throughout the document.

Page 27, first paragraph, last sentence

Unclear whether this refers to IgE, IgG, or both IgE and IgG antibody titers.

Page 27, 2nd paragraph

The summary of this study refers to "formaldehyde sensitivity", but the definition of formaldehyde sensitivity isn't indicated. In the 4th sentence, formaldehyde sensitivity appears to be based on self-reported information whereas elsewhere in the document the phrase may refer to the presence of formaldehyde-specific IgE. It's unclear if formaldehyde sensitivity in the 5th sentence of this paragraph is based on self-report information or the results of allergen-specific IgE results.

Section 7.1.4, Effects on pulmonary function in healthy and asthmatic subjects

The discussion of pulmonary effects is inconsistent. Of the studies discussed in section 7.1.4, only one found an association between pulmonary function and formaldehyde exposure (i.e., Her94). In contrast, Table 1 on page 30-31 includes several studies in which a difference in lung function was observed (i.e., Her94, Akb94, Kil89, and Kri93). It's not clear why only Her94 was discussed in section 7.1.4.

In the summary of cross-sectional studies of workers occupationally exposed to formaldehyde on page 29, the document states that "after exposure for a few hours decreases of the FEV1 and FVC have been observed". In contrast, in the summary of human studies of pulmonary function on page 52, the document states that "no changes in pulmonary function have been found in humans exposed to formaldehyde concentrations up to 3.6 mg/m^3 (3 ppm).

The discussion of pulmonary effects also appears to be incomplete. A literature search revealed a number of other studies evaluating pulmonary function among individuals exposed to formaldehyde. These studies included:

Abkar-Khanzadeh F, Mlynek JS. Changes in respiratory function after one and three hours of exposure to formaldehyde in non-smoking subjects. Occup Environ Med 1997; 54(5):296-300.

Malaka T. Kodama AM. Respiratory health of plywood workers occupationally exposed to formaldehyde. Arch Environ Health 1990;45(5);288-294.

Alexandersson R, Hedenstierna G. Pulmonary function in wood workers exposed to formaldehyde: a prospective study. Arch Environ Health 1989;44(1):5-11.

Holness DL, Nethercott JR. Health status of funeral service workers exposed to formaldehyde. Arch Environ Health 1989;44(4);222-228.

Horvath EP, Anderson H, Pierce WE, et al. Effects of formaldehyde on the mucous membranes and lungs: a study of an industrial population. J Amer Med Assoc 1988; 259(5):701-707.

Green DJ, Sauder LR, Kulle TJ, Bascom R. Acute response to 3.0 ppm formaldehyde in exercising healthy nonsmokers and asthmatics. Am Rev Respir Dis 1987;135(6):1261-1266.

More recent (i.e., after 1997) studies include Kriebel D, Myers, D, Cheng M, et al. Short-term effects of formaldehyde on peak expiratory flow and irritant symptoms. Arch Environ Health 2001; 56(1): 11-18.

Section 7.1.7

Page 32, 2nd paragraph–The percentage of exposed workers with dyspasia is reported to be 18%, but what was the percentage of dyspasia in the non-exposed? Were the differences in dyspasia significant? If so, then this study should not have been dismissed for its having too small numbers. Small sample size would be a concern if the findings were negative, but shouldn't be a concern if the findings are positive.

The text and table headings imply that the table in this section (and similar tables in other sections) is a comprehensive summary of the studies. But, the tables only contain selected studies. The basis for including (or omitting) a study is unclear.

In addition, some studies are discussed in the text of the document but not in the appropriate tables (e.g., Sal91) and others are mentioned in the tables but not in the text.

Retrospective cohort mortality/morbidity studies, page 33-37

Only 3 retrospective cohort mortality studies (and related follow-up/related studies) are included in Table 2 which summarizes the retrospective cohort mortality studies of workers occupationally exposed to formaldehyde. Only the cohort mortality study by Blair and colleagues and the re-analyses and follow-up studies of this study are discussed in the text. Yet, there have been many mortality studies of formaldehyde-exposed individuals. The document should either include a more comprehensive review of the studies or clearly state why only selected studies are discussed.

Case-control studies, page 37-39

Again, only selected studies are presented, but this is not clearly stated and the reason for focusing on these studies is not discussed. Then, on page 39, the committees appear to make a conclusion about the relationship between occupational exposure to formaldehyde and cancer based on only these selected studies.

Meta-analysis, page 39-40

If the committee is going to rely on the results of one or more of the meta-analysis papers, instead of providing a comprehensive review of the individual studies, the document should include a comprehensive critique of the meta-analysis papers. Currently, the committees point out that the meta-analysis by Collins and colleagues included more studies than the previous meta-analyses and an evaluation of the exposure potential for jobs in the general population case-control studies, but they do not provide a thorough critique of the three meta-analysis papers and adequately justify their reliance on the meta-analysis by Collins and colleagues.

The meta-analysis by Collins and colleagues included 47 epidemiologic studies. Yet, only a few of these studies are discussed in the document. No rationale for discussing only selected papers is given. Thus, it is unclear whether the document accurately reflects what is known about the carcinogenic effects of formaldehyde. In addition, the document does not clearly state that only a few of the many studies evaluating the carcinogenicity of formaldehyde are presented. Instead, the initial impression is that the document provides a comprehensive review of all studies.

Page 50, 5th line- The statement "Clearly, for tumour formation drastic conditions seem to be required" doesn't seem to be appropriate given the range of exposure concentrations used in animal studies. This section fails to point out that there was one study where a significant increase in tumors was observed at 2 ppm (Ker83), and another where it was observed at 0.3 ppm (Kam97). Thus the exposures producing effects in the animal studies are at least within a order of magnitude, and perhaps within a factor of 2 of those found in the workplace.

Page 54, carcinogenic effects in man

The summary appropriately focuses on respiratory and nasopharyngeal cancers. However, the summary of the carcinogenic effects in man should also include a brief statement about what is known about the relationship between formaldehyde exposure and other cancers.

Genotoxicity, page 55

The draft document states that there are no adequate data available on genetic effects of formaldehyde in humans. If the committee feels that the studies of genetic effects are inadequate, this needs to be discussed in the document. Three studies were mentioned that suggested effects of formaldehyde exposure (Bal92, Boy90, Sur93). The rationale for discounting the findings of

the study by Boysen and colleagues should be strengthened. The rationale for not discussing other studies and/or discounting the findings of other studies also needs to be discussed. The following articles should be considered for inclusion in the document:

Ying CJ, Ye XL, Xie H. et al. Lymphocyte subsets and sister-chromatid exchanges in the students exposed to formaldehyde vapor. Biomed Environ Sci 1999;12(2):88-94.

He J. Jin Lf, Jin HY. Detection of cytogenetic effects in peripheral lymphocytes of students exposed to formaldehyde with cytokinesis-blocked micronucleus assay. Biomed Environ Sci 1998;11(1):87-92.

Ying CJ, Yan WS, Zhao MY, et al. Micronuclei in nasal mucosa, oral mucosa and lymphocytes in students exposed to formaldehyde vapor in anatomy class. Biomed Environ Sci 1997;10(4):451-455.

Vasudeva N, Anand C. Cytogenetic evaluation of medical students exposed to formaldehyde vapor in the gross anatomy dissection laboratory. J Am Coll Health 1996;44(4):177-179.

Page 63, 2nd paragraph, 1st sentence-This statement isn't consistent with the fact that at least one study found a significant excess of tumors at 3 ppm, which is close to the exposure concentrations experienced by some workers.

Editorial Comments

Page 6 paragraph 5 line 4: Replace the word "auteurs" with the word "**authors**". The word "auteurs" appears in several places in the text. Please make similar corrections in other places as well.

Page 6 paragraph 6 line 7: rewrite "hyper/metaplasia" as **hyperplasia and metaplasia** as separate entities

Page 7 paragraph 2 line 1: Replace the word " inhalatory" with the word "**inhalation**."

Page 9 paragraph 3 line 5: Word "auteurs". See above.

Page 11 Item 1.1 line 9: "In the latter case on ...". Replace "on" with the word "**an**"

Page 12 Item 1.3 line 2: "... DECOS in, respectively, 1981 and 1987 (WGD, RA 4/81: RA 3/87). Rewrite this as " ... **DECOS in 1981 (WGD RA 4/81) and 1987 (RA 3/87), respectively.**

Page 13 Item 2 line 2: " ... protect occupational exposed ...". Rewrite as "... protect occ**upationally** exposed ..."

Continued-NIOSH comments on the draft Formaldehyde DECOS/NEG document

Page 14 Item 3.1: "Identity and properties". Replace with "**Identification and Chemical Properties".**

Page 16 Item 4.2.2 line 4: replace the word "fibreboard" with "**fiberboard**"

Page 16 Item 4.2.2 line 6: The words "auto applications" does **not** make sense. Probably it should be "automobile applications" or "automobile manufacturing".

Page 17 Item 5.1 last line: "... formaldehyde are potentiated by ... ." The exact toxicological definition of "potentiation" does not apply here. Perhaps the word " **increased"** should replace the word "potentiated".

Page 18 Item 5.2 paragraph 1 line last: Replace the word "Annex" with "**appendix**".
Page 18 Item 5.2 paragraph 2 line 1: "The following data ... date." Rewrite this sentence as " **The following represents more recent occupational exposure data"**

Page 22 Item 7.1.2 paragraph 2 line 4: "(during of exposure not described)". Rewrite as " (**duration** of exposure not described).

Page 26 paragraph 2 line 2: ".... The reference group existed ...". Replace the word existed with the word "**consisted.**"

Page 31 Table 1 continued reference Kri93 under effects line 3: Replace the word "rares" with "**rates.**"

Page 32 paragraph 2 line 4: "... 37 age-matched referents." Replace the word referents with the word "con**trols.**"

Page 36 paragraph 1 lines 2 and 7: Replace the word " significant" in both places with the word "**significantly".**

Page 37 paragraph 2 line 5: Replace the word " referents" with the word "**controls**"

Page 40 paragraph 1 line 17: replace the word "auteurs" with the word "**authors.**"

Page 43 paragraph 1 line 1: "... middle mates). Replace the word mates with the word "**meatus.**"

Page 47 paragraph 1 line 2: replace Annex with "**appendix**"

Page 47 paragraph 3 line 4: "... formaldehyde during 6 hours...." Replace the word "during" with the word "**for**"

Page 48 Item 7.2.8 paragraph 2 line 3: "... following exposure by inhalation ...". Rewrite as "... **following inhalation exposure ...**"

Continued-NIOSH comments on draft Formaldehyde DECOS/NEG document

Page 49 paragraph 2 lines 5 and 12: Replace the words "hyper- and metaplasia" with " **hyperplasia and metaplasia**" in each case

Page 49 paragraph 2 line 6: Replace the word "precize" with the word "**precise**"

Page 49 paragraph 2 line 16: **Delete the period** between the words "non-exposure" and "observation"

Page 50 Item 7.2.9: "Reproduction toxicity" should read as "**Reproductive toxicity**"

Page 50 Item 7.2.9 paragraph 1 line 1: "... concluded in her ..." Should read as "... **concluded in its ...**"

Page 50 Item 7.2.9 **paragraph** 1 line 8: "... of the embryo being ..." Should read as "... **of the embryo, it being ...**"

Page 50 Item 7.2.9 **paragraph** 2 line 1: "... the reproduction toxicity..." Should read as ".... the **reproductive toxicity**..."

Page 51 Item 7.2.10 paragraph 1 line 3: " ... during 28 days...." Should read "... **for 28 days**..."

Page 52 Item 7.3 paragraph 3 line 1: "Transient rhinitis have been ..." Should read as "**Transient rhinitis has been....**"

Page 53 paragraph 3 line 18: "... same collection of data ... Should read as "... **same data**..."

Page 53 paragraph 4 lines 4 and 5: " ...population and confounding by ..." Should read as "... **population confounded by** ..."

Page 54 paragraph 2 line 6: Replace "auteurs" with "**authors**"

Page 54 paragraph 4- short term exposure line 6: "hyper/metaplasia" Rewrite as **hyperplasia and metaplasia** or - hyperplasia or metaplasia. I think the former is the correct way.

Page 59 under Sweden line 2: "... was dated from ..." Delete the word "**from**"

Page 62 paragraph 1 last line: " Both ... conclusion". Put a **period** after the word "conclusion"

Page 62 paragraph 2 line 6: "maldehyde than humans...." **Delete the words "than humans**"

Page 63 paragraph 2 lines 6 and 7: " ... has meanwhile been.... and thus should be ...". Rewrite as " **and has meanwhile been .... Thus should be** ..."

Continued-NIOSH comments on the draft Formaldehyde DECOS/NEG document

Page 63 paragraph 3 lines 2 and 3: "... experimental animals reveals a NOAEL ... while in all..." Rewrite as "...**experimental animals reveal a NOAEL .... However in all** ..." (delete the word "while.")

Page 63 paragraph 3 lines 9 and 11: "... formaldehyde ... with respect to ... damaging or not damaging the nasal.." Rewrite as "**... formaldehyde {1.2 mg/m^3 (1ppm)}... with respect to its effects on the nasal...**"

Page 64 paragraph 1 lines 6 and 11: "... auteurs". Replace it with the word "**authors**" in each ease.

Page 65 paragraph 1 line 5: "committee consideres a factor ...". Rewrite as "committee **considers** a factor ..."

Gezondheidsraad
Health Council of the Netherlands

mr dr RD Zumwalde
National Institute for Occupational Safety and Health
Robert A Taft Laboratories
4676 Columbia Parkway
Cincinnati OH 45226-1998
United States of America

1,130328147189

Subject	: Comments in public draft 'Formaldehyde'
Your reference	: September 5, 2001
Our reference	: 1957/AvdB/459/R38
Enclosure(s)	: 1
Date	: January 27, 2003

Dear dr Zumwalde,

In 2001, the Dutch Expert Committee on Occupational Standards (DECOS) published a draft report on formaldehyde for public review. Your organisation used the opportunity to comment on the draft report. The committee thanks you for your comments, which were used in finalising the report. On behalf of the President of the Health Council of the Netherlands I herewith present you the DECOS' reaction to your comments.

You commented that the metaanalysis of Collins et al (JOEM, 39(7):639-651) would most likely have found a statistically significant association between exposure to formaldehyde and nasopharyncheal cancer (NPC) if the study of Vaughan et al was included. Therefore you concluded that there is evidence to suggest that occupational exposure to formaldehyde is causally related to nasopharyngeal cancer. Although. the committee is of the opinion that there is no concvincing evidence for a positive association between exposure and NPC, she decided to adjusted her conclusions to: 'The committees conclude that although a small number of studies produce limited evidence for the association between nasopharyngeal cancer and exposure to formaldehyde, the overall total body of epidemiological data does not support a causal relationship for a nasal cancer risk at the experienced exposure levels (see last alinea par 7.1.7). Moreover, the commitee is of the opinion that if sensory irritation is prevented, as a consequence workers will be protected against to potential risk of nasal cancer.

Your comments concerning the current limit values are incorporated in the final report. In addition, you suggested to include several studies discussing pulmonary effects. The committee did not include the human studies of Akbar-Khanzadeh, Mlynek,

P.O Box 16052
NL-2500 BB Den Haag
Telephone +31 (70) 340 75 20
Telefax +31 (70) 340 75 23

Visiting Address
Parnassusplein 5
NL - 2511 VX Den Haag
email GR@gr.nl

Gezondheidsraad
Health Council of the Netherlands

Malaka, Alexander et al, Holness et al and Green et al in the final report because the exposure levels in these studies were high and there were no new additional effects were found. Moreover, the human study of Kriebel et al is not added to the report either because the differences between the exposed groups and the controls is (although relevant and significant) limited. The study of Horvath et al is included in the report. The results of this study confirm the presence of irritation after exposure to formaldehyde but not the effects on the pulmonary function.

The genotoxic studies you mentioned in your commented are derscribed in the final report.

Finally, DECOS appreciated very much your general comments on the quality of the report. Based on these comments, several editorial corrections have been made. Because of your extended and detailed comments, DECOS is of the opinion that the quality and clearness of the report is improved, and hopes that the report is easier to follow.

The final report was published on January 27, 2003. Enclosed you will find a copy.

Yours sincerely,

Mw dr ASAM van der Burght
Scientific Secretary DECOS

P.O Box 16052
NL-2500 BB Den Haag
Telephone +31 (70) 340 75 20
Telefax +31 (70) 340 75 23

Visiting Address
Parnassusplein 5
NL - 2511 VX Den Haag
email: GR@gr.nl

VERENIGING ACADEMISCHE ZIEKENHUIZEN

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Gezondheidsraad
t.a.v. mevr. dr. A.S.A..M. van der Burght
Secretaris Commissie WGD
Postbus 16052
2500 BB Den Haag

2,13032532809 4

Datum 10 juli 2001
Uw kenmerk -
Ons kenmerk 012555/JL/sas
Onderwerp Openbaar concept-rapport over beroepsmatige blootstelling aan formaldehyde, 2001/19OSH, d.d. 18 mei 2001

Geachte mevrouw van der Burght,

Naar aanleiding van uw brief van 18 mei j.l. (kenmerk: U 972/AvdB/mj/459-N33), zend ik u hierbij het commentaar van de Vereniging Academische Ziekenhuizen (VAZ) op het openbaar concept.
De VAZ onderschrijft het belang van het nemen van maatregelen om de blootstelling aan formaldehyde zoveel mogelijk te beperken. Regelgeving is een goed middel om adequate maatregelen landelijk voor te schrijven. De VAZ wil zich inzetten om mee te denken over de inhoud van deze regelgeving, zodat deze doeltreffend zijn, effect sorteren en werkbaar zijn. Tegen dat licht is het openbaar concept door ons beoordeeld.
Navraag bij één van de academische ziekenhuizen leverde het volgende beeld op:
Een investering voor afzuigtafels voor de uitsnijkamers, kasten voor opslag van formaline en bouwkundige infrastructuur heeft circa *f* 500.000,-- gekost. De extra afzuiging is aangebracht in een bestaande situatie, waarbij aangesloten is op het bestaande ventilatiesysteem. De ruimteventilatie in het laboratorium is 10x en is ruim voldoende. Het laboratorium voldoet aan de normen.
De eerste metingen na oplevering in 1997 gaven een gemiddelde waarde van 0,1 ppm formaldehyde boven de uitsnijtafel (de werkplekken). De metingen in 2000 bij de uitsnijtafels gaven een gemiddelde waarde aan van 0,2 - 0,225 ppm. Met ander woorden: de nieuwe MAC-waarde van 0,12 ppm is in deze meest optimale situatie niet haalbaar tenzij er opnieuw een forse investering gedaan wordt. Daarnaast zal een verdere sub-optimalisatie voor andere arbo-technische problemen, zoals tocht zorgen. Voornoemde situatie betreft een zeer moderne uitgeruste werksituatie, hetgeen landelijk gezien geenszins overal het geval zal zijn.
Daarom zijn wij tot de conclusie gekomen dat de door u voorgestelde verlaging van de MAC-waarden tot gigantische bouwkundige en technische investeringen zullen gaan leiden en ernstige problemen zullen geven bij de naleving van de door u voorgestelde waarden.

Wij vertrouwen er dan ook op dat u onze opmerkingen bij het opstellen van de definitieve rapport mee zult wegen.

Namens de Vereniging Academische Ziekenhuizen
Hoogachtend,

OCR dankbrief verz. 16/07/2001

mr. J. Landman,
algemeen secretaris

Postbus 9696 3506 GR Utrecht Oudlaan 4 telefoon (030) 2739880 fax (030) 2739532 email vaz@vaz.nl

Gezondheidsraad
Health Council of the Netherlands

Aan mr J Landman
Algemeen Secretaris Vereniging Academische Ziekenhuizen (VAZ)
Postbus 9696
3506 GR Utrecht

1,13032814791

Onderwerp	: Reactie OCR Formaldehyde
Uw kenmerk	: 012555/JL/sas
Ons kenmerk	: 01468/AvdB/459-Q38
Bijlagen	: 1
Datum	: 27 januari 2003

Geachte heer Landman,

In 2001 maakte de Voorzitter van de Gezondheidsraad een concept-rapport van de Commissie WGD van de Raad openbaar over formaldehyde. Belangstellenden werden in de gelegenheid gesteld commentaar te leveren op het rapport. U maakte van die gelegenheid gebruik. Op verzoek van de Voorzitter van de Raad doe ik u hierbij de reactie van de commissie op uw commentaar toekomen.

Uw commentaar heeft voornamelijk betrekking op de haalbaarheid van de voorgestelde gezondheidskundige advieswaarde. De Commissie WGD betrekt echter alleen *inhoudelijk* commentaar bij het afronden van het advies. Voor commentaar met betrekking tot de haalbaarheid van de advieswaarde verwijst de commissie u naar de Subcommissie MAC-waarden van de Sociaal Economische Raad (SER). Deze commissie stelt, rekening houdend met de haalbaarheid van de gezondheidskundige advieswaarde, in een tweede fase aan het Ministerie van SZW een MAC-waarde voor. Ik zal uw brief daarom ook doorsturen aan deze commissie.

Het rapport is op 27 januari 2003 gepubliceerd; bijgaand vindt u een exemplaar.

Hoogachtend,

Mw dr ASAM van der Burght
secretaris Commissie WGD

cc de heer mr JJ Brokamp, Subcommissie MAC-waarden, SER

Bezoekadres
Parnassusplein 5
2511 VX Den Haag
Telefoon (070) 340 75 20
email: GR@gr.nl

Postadres
Postbus 16052
2500 BB Den Haag
Telefax (070) 340 75 23