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TNO Report

V5357 |

Expert report on the formaldehyde criteria document

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Sponsor	Association of the Dutch Chemical Industry (VNCI)
TNO project number	010.48127
TNO study code	
Sponsor's study code	
Status	
Previous versions	
Number of pages	44
Number of tables	28
Number of figures	4
Number of annexes	
Number of appendices	

Contents

1 Introduction

Upon a request by the Association of the Dutch Chemical Industry (VNCI), TNO has performed a critical evaluation of the assessment employed by the Dutch Expert Committee on Occupational Standards (DECOS) in their criteria document on formaldehyde (HCN03a)

The assessment employed by DECOS was the basis for their proposal for a Health-Based Recommended Occupational Exposure Limit for formaldehyde.

TNO was asked to focus on the following aspects:

1. An overview of the degree of irritation (eyes, nose, throat) as well as dyspnoea, cough and headache in volunteers as a function of exposure
2. The optimal use of human data (including the use of dose-response data);
3. The 'assessment-method' as it is used by the Health Council;
4. A quantitative analysis of eye irritation as the critical effect by means of the Benchmark Dose method using the EPA software.
5. The lowest concentration giving rise to cytotoxicity (best estimate, if possible with a confidence interval) in the airways based on human and animal data

In the following sections, these aspects are elaborated on, with a special emphasis on the interpretation of the human studies and the extrapolation of these data to the proposed exposure limit.

2 Overview of sensory irritation, dyspnoea, cough and headache in volunteers following inhalation exposure to formaldehyde

Controlled volunteer studies are – in fact - the best way to examine human toxicity. There are several volunteer studies in which the sensory irritation (eyes, nose, throat) of formaldehyde is addressed.

2.1 Eye irritation

In a study of Weber-Tschopp et al (Web77) two experiments have been performed: one in which 33 volunteers had been exposed continuously to increasing formaldehyde concentrations of between 0 and 3.2 ppm for 35 min. In this study health questionnaires were used and eye blinking frequency was measured. In the second study, 48 volunteers were exposed to 0, 1, 2, 3 and 4 ppm for 1.5 min at each concentration with a clean air interval of 8 min in between. In this study only questionnaires were used. Based on the results, the authors concluded that on average eye and nasal irritation were reported at 1.2 ppm, throat irritation was reported at 2.1 ppm, and annoyance (preference to leave the room) at 1.2 ppm. An increase in eye blinking frequency was observed at 1.7 ppm. The general conclusion was that the irritation threshold was placed between 1 and 2 ppm (1.2-2.4 mg/m3). The (normalized) severity rating is indicated in Table 2.12 (see page 11).

In the study of Bender et al. (Ben83), volunteers (5-28 per group), shown to be sensitive to formaldehyde irritation upon pre-tests using 1.3 and 2.2 ppm formaldehyde, were exposed for 6 min to formaldehyde concentrations between 0 and 1.0 ppm. The subjects were asked to give a subjective rating of eye irritation. The severity was rated when irritation was first noted and again at the end of the 6-min exposure period.
Results are summarized in the table below (Table 2.1):

Table 2.1 – Eye irritation response to formaldehyde vapour in volunteers upon a 6-min exposure period (Ben83)

Conc. (ppm)	Total number	Median response time (sec)	Response number	Response percentage	Severity index Si	Severity index Sf
1.0	27	78	20	74 *	1.56	1.40
0.9	5	119	3	60	0.80	NA
0.7	7	72	4	57	0.86	0.57
0.56	26	217	14	54	0.79	0.52
0.35	12	268	5	42	0.71	0.63
0	28	360	-	-	-	-

0 = none, 1 = slight, 2 = moderate, 3 = severe; Si = severity when first noticed, Sf = severity at the end of the 6-min exposure period; NA= not available; * significantly different from control, $p < 0.05$

These results indicate that only at 1.0 ppm there was a significant difference between formaldehyde and clean air exposure. Responses at 0.7 and 0.9 ppm were not significant but this might have been due to the small group sizes. Only the 1.0 ppm (1.2

mg/m3) exposure averaged a slightly to moderately irritating rating (between 1 and 2). All other levels averaged less than slightly irritating (see also Table 2.12). In addition, severity ratings at the end of the 6-min exposure period were lower than when irritation was first noticed.

The study of And83 (page 45 of the DECOS report) is in fact considered by DECOS to be the key study for sensory irritation. Healthy volunteers (16) were exposed to 0.24, 0.42, 0.83 and 1.67 ppm formaldehyde for 5 hours. In this study, general discomfort was measured rather than specific eye, nose/throat irritation or else. The complaints reported were mainly conjunctival irritation and dryness in the nose and throat. Three out of 16 volunteers (19%) reported these complaints at the lowest level of 0.24 ppm (0.29 mg/m3). However, the following has not been taken into account in the DECOS report:

1. In several studies (Kul87; Sau87) it has been shown that a response percentage of eye irritation of up to 22% can be expected in a 0 ppm condition, that is exposure to clean air. Also nasal and/or throat irritation was often reported in the absence of formaldehyde (Sch86; Sch87; Hol89). Therefore, the response percentage of 19%, if at all a response, should be interpreted with caution.
2. The highest mean response score for discomfort at this level was about 18 on a scale of 100, indicating that the response was very limited. In fact this response was stated to be 'irritating (present) but not annoying'.
3. At the next higher tested concentration of 0.42 ppm (0.5 mg/m3) the mean discomfort rating was lower than at 0.24 ppm (0.29 mg/m3; see Table 2.12) which renders the results at the latter level less valuable.

In a study by Day et al. (Day84; not mentioned in the DECOS report), 18 subjects (9 of whom had previously complained of various non-respiratory adverse effects from the urea formaldehyde foam insulation in their homes) were exposed to 1.0 ppm (1.2 mg/m3) formaldehyde for 90 min. The following symptoms were scored (in incidence; nothing was mentioned on severity; Table 2.2):

Table 2.2 – Frequency of symptoms in 18 volunteers exposed to formaldehyde for 90 min (Day84)

Symptom	Number of previously complaining subjects	Number of not previously complaining subjects	Total	Percentage
Eye irritation	7	8	15	83
Nasal congestion	3	4	7	39
Tearing	3	3	6	33
Throat irritation	2	3	5	28
Nasal discharge	2	1	3	17
Cough	0	2	2	11
Chest tightness	1	0	1	6

[In addition, none of the measures of pulmonary function used (forced vital capacity, forced expiratory volume in 1 second or maximal midexpiratory flow rate) showed any clinically or statistically significant response to the exposure either immediately after or 8 hours after its beginning, indicating that this level had no effect on the lower

respiratory tract nor did it change pulmonary function. There were no significant changes between the two groups.]

In a study by Green et al (Gre87; not mentioned in the DECOS report), 22 healthy and 16 asthmatic subjects were exposed to 3 ppm (3.6 mg/m3) formaldehyde for 1 hour. The healthy subjects underwent intermittent heavy exercise (minute ventilation = 65 L/min) whereas the asthmatics performed intermittent moderate exercise (minute ventilation = 37 L/min). Symptoms and pulmonary function were assessed during exposure; non-specific airway reactivity was assessed after exposure. [One healthy subject exhibited occult airway hyperreactivity and was left out from the statistical analysis of pulmonary function and airway reactivity, leaving 21 healthy individuals.] No normal or asthmatic subject reported nose, eye irritation or odour perception above a mild level with the clean air exposure. At 3 ppm 82% of the volunteers reported detecting an odour and experiencing general irritation. Also, 32% responded with nose and throat irritation, and 19-27% responded with eye irritation. The individual scores for odour, nose/throat irritation and eye irritation ranged from none to severe. There were no differences between the two groups. The (normalized) severity rating is indicated in Table 2.12.
[With respect to pulmonary function, there were small decreases (up to 3.8%) in pulmonary function in normal subjects engaging in heavy exercise but not in asthmatics engaging in moderate exercise. A greater than 10% drop in FEV1 was observed in 2 normal subjects (10%) and in 2 asthmatics (13%).]

In a study by Kulle et al (Kul87; Kul93; not mentioned in the DECOS report), 19 subjects (10 males, 9 females) were randomly exposed for 3-h intervals to formaldehyde at 0, 1.0 and 2.0 ppm at rest plus at 2.0 ppm formaldehyde with exercise. Ten of these volunteers were also exposed to 0.5 ppm whereas the other 9 were also exposed to 3.0 ppm formaldehyde. [Nasal flow resistance (measured immediately before and after exposure) was increased at 3.0 ppm, but not at 2.0 ppm. There were no significant decreases in pulmonary function (measured at least before, during, and at the end and 24 h after exposure) or increases in bronchial reactivity to methacholine (measured at the end and 24 h after exposure).]
Symptom questionnaires were completed before, shortly after and 24 h after exposure. Shortly after exposure, at 0 ppm one subject (5%) reported mild eye irritation. At 0.5 ppm none of the 10 subjects had eye irritation, while at 1.0 ppm 4 of 19 subjects (21%) reported mild eye irritation and 1 subject (5%) experienced moderate irritation (total of 26%). At 2.0 ppm 6 subjects (32%) reported mild eye irritation and 4 subjects (21%) reported moderate eye irritation (total of 53%). At 3.0 ppm all 9 subjects (100%) experienced eye irritation, 5 at a mild and 4 at a moderate rate. Mild nose/throat irritation was reported in 3 out of 19 subjects (16%) at 0 ppm formaldehyde, in 1 of 10 subjects (10%) exposed to 0.5 ppm, and in one out of 19 subjects (5%) at 1.0 ppm. A mild response was also reported by 7 of 19 subjects (37%) at 2.0 ppm and 2 of 9 subjects (22%) at 3.0 ppm formaldehyde.
All together, the following mean values were obtained (9 subject series; Table 2.3):

Table 2.3 - Mean symptom differences (shortly after exposure – before exposure) with formaldehyde exposure in a group of 9 volunteers exposed for 3-h intervals (Kul87; Kul93)

	0 ppm	1.0 ppm	2.0 ppm	3.0 ppm	p value
Odour sensation	0 ± 0	0.22 ± 0.15	0.44 ± 0.18	1.00 ± 0.29	P < 0.0001
Nose/throat irritation	0 ± 0	0.11 ± 0.11	0.33 ± 0.17	0.22 ± 0.15	P = 0.054
Eye irritation	0 ± 0	0.44 ± 0.24	0.89 ± 0.26	1.44 ± 0.18	P < 0.0001
Chest discomfort	0 ± 0	0 ± 0	0.11 ± 0.11	0 ± 0	P = 0.62
Cough	0 ± 0	0.11 ± 0.11	0 ± 0	0 ± 0	P = 0.11
Headache	0 ± 0	0 ± 0	0 ± 0	0.11 ± 0.11	P = 0.33

0 = none, 1 = mild (present but not annoying), 2 = moderate (annoying), 3 = severe (debilitating)

From these data it can be seen that all mean scores were (well) below 1 (present but not annoying) except for odour sensation (1.00) and eye irritation (1.44) at 3.0 ppm formaldehyde. A linear concentration-response relationship was observed for odour sensation and eye irritation; the relationship for nose/throat irritation was near significant (p=0.054).
It was also noted that although nasal resistance, eye irritation and odour sensation significantly increased at 3.0 ppm formaldehyde, no significant correlations were observed between changes in resistance and either symptoms within subjects.

Exercise did not enhance the irritant effects except for a significant increase in nose/throat irritation. No symptoms were reported 24 hours following exposure at rest or following the exercise exposures.
In a second paper, Kulle et al (Kul93) re-examined the symptomatic response data and using additional statistical methodology, estimated the threshold levels for odour and irritant responses. Estimated thresholds were less than 0.5 ppm for odour sensation, 0.5-1.0 ppm for eye irritation, and 1.0 ppm for nose/throat irritation. No substantial differences were seen between the male and female symptom responses.

In a study by Sauder et al. (Sau86; not mentioned in the DECOS report), 9 healthy subjects were exposed to 0 and 3 ppm formaldehyde for 3 hours during intermittent exercise (minute ventilation = 60-70 L/min). The protocol consisted of clean air on the first day, formaldehyde exposure on the second day, and a 24-h follow-up on the third day. Pulmonary function, non-specific airway reactivity, and symptoms were assessed daily. [Thirty min of formaldehyde exposure resulted in a 2% decrease in FEV1 and a 7% decrease in forced midexpiratory flow rate. According to the authors, these decrements are not expected to result in any discernible decrease in physical capacity. These effects were no longer present between 1 and 3 hours. No changes in pulmonary function or airway reactivity were observed 24 h after exposure.]
At 0 ppm formaldehyde, 0% responded with eye irritation, 22% reported detection of odour, and 22% responded with nose and throat irritation. At 3 ppm, 67% responded with eye irritation, 56% reported detection of odour, and 78% responded with nose and throat irritation. The degree of severity ranged from mild to moderate eye and upper respiratory tract irritation (see Table 2.4).

Table 2.4 - Mean symptom scores with formaldehyde exposure in a group of 9 volunteers exposed for 3-h (Sau86)

	Day 1 0 ppm	Day 2 3 ppm	Day 3 24-h follow-up
Odour	0.22	1.22 *	0.22
Nose/throat irritation	0.22	1.33 **	0
Eye irritation	0	0.78 **	0
Heart palpitations	0	0	0
Chest tightness	0	0.11	0
Cough	0.11	0	0.11
Headache	0.22	0.11	0.11
Double vision	0	0.11	0

0 = none, 1 = mild (present but not annoying), 2 = moderate (annoying), 3 = severe (debilitating); * $p<0.02$, ** $p<0.01$

In another study of Sauder et al. (Sau87) 9 asthmatics were exposed according to the same regimen as indicated in Sau86. [No significant changes in pulmonary function or airway reactivity were observed.] At 0 ppm, 22% responded with eye irritation and 33% with nose/throat irritation. At 3 ppm 78% responded with eye irritation and 78% responded with nose/throat irritation. The degree of severity ranged from mild to mild/moderate eye and upper respiratory tract irritation (see Table 2.5).

Table 2.5 - Mean symptom scores with formaldehyde exposure in a group of 9 asthmatic volunteers exposed for 3-h (Sau87)

	ppm	0 min	60 min	120 min	180 min
Chest tightness	0	0.22	0.22	0.44	0.44
	3	0.22	0.44	0.44	0.44
Tingling	0	0	0	0	0
feet/hands	3	0	0.22	0.22	0.11
Cough	0	0.11	0.11	0.22	0.33
	3	0.33	0.44	0.22	0.11
Nose/throat	0	0.33	0.33	0.55	0.55
irritation	3	0.33	1.11	1.00	1.00
Eye irritation	0	0	0.11	0.22	0
	3	0	1.33 *	1.44	1.33 **
Heart	0	0	0	0	0
Palpitations	3	0	0.11	0	0

0 = none, 1 = mild (present but not annoying), 2 = mild/moderate, 3 = moderate (annoying), 4 = moderate/severe, 5 = severe (debilitating); * $p<0.05$, ** $p<0.01$

In a study by Schachter et al. (Sch86; not mentioned in the DECOS report), 15 healthy individuals were exposed to 0 and 2.0 ppm formaldehyde for 40 min while at rest. On separate days, they were also exposed in the same way with a 10-min period of moderate exercise. Pulmonary function was measured before, during and after exposures, symptom diaries were given for up to 24 h after exposures. [No significant bronchoconstriction reactions were noted.] The following incidences for the symptoms were reported (see Table 2.6). Symptoms were mild to moderate in severity (see Table 2.7).

Table 2.6 – Frequency of symptoms (in percentages) in a group of 15 volunteers exposed to formaldehyde for 40 min (Sch86)

	0 ppm		2 ppm	
	Rest	Exercise	Rest	Exercise
Odour	47	13	80	86
Eye irritation	0	7	53	53
Sore throat	13	0	27	33
Nasal irritation	27	13	40	33

Table 2.7 – Mean symptom scores with formaldehyde exposure in a group of 15 volunteers exposed for 40 min (Sch86)

	0 ppm		2 ppm	
	Rest	Exercise	Rest	Exercise
Odour	0.47	0.13	1.20	1.47
Eye irritation	0	0.07	0.80	0.60
Sore throat	0.13	0	0.27	0.40
Nasal irritation	0.27	0.13	0.47	0.40

0 = none, 1 = minimal, 2 = moderate, 3 = severe, 4 = incapacitating

In another study of Schachter et al (Sch87; not mentioned in the DECOS report), 15 hospital laboratory workers routinely exposed to formaldehyde were exposed to 0 and 2.0 ppm for 40 min with and without mild exercise. Pulmonary function was measured before, during and after exposures, symptom diaries were given for up to 24 h after exposures. [No significant changes in pulmonary reactions were noted.] The following incidences for the symptoms were reported (see Table 2.8). Symptoms were mild to moderate in severity (see Table 2.9). As these results were comparable to the former study it was concluded by the authors that occupational exposed individuals had similar upper respiratory tract symptom frequency and severity, and tolerance was therefore not suggested in this worker group.

Table 2.8 – Frequency of symptoms (in percentages) in a group of 15 laboratory workers exposed to formaldehyde for 40 min (Sch87)

	0 ppm		2 ppm	
	Rest	Exercise	Rest	Exercise
Odour	47	33	80	87
Eye irritation	0	0	47	40
Sore throat	7	0	0	0
Nasal irritation	7	0	0	7

Table 2.9 - Mean symptom scores with formaldehyde exposure in a group of 15 laboratory workers exposed for 40 min (Sch87)

	0 ppm		2 ppm	
	Rest	Exercise	Rest	Exercise
Odour	0.67	0.53	1.47	1.80
Eye irritation	0	0	0.60	0.67
Sore throat	0.13	0	0	0
Nasal irritation	0.13	0	0	0.20

0 = none, 1 = minimal, 2 = moderate, 3 = severe, 4 = incapacitating

In a study of Witek et al (Wit87; not mentioned in the DECOS report), 15 volunteers with mild asthma were exposed to 0 or 2.0 ppm formaldehyde for 40 min, in the same way as reported by Sch86 and Sch87. No changes in pulmonary function were noted. Nonspecific airway hyperresponsiveness upon exposure to methacholine demonstrated a lower, although insignificant, threshold. The following incidences for the symptoms were reported (see Table 2.10). Symptoms were mild to moderate in severity (see Table 2.11). As these results were comparable to the former studies (Sch86; Sch87) it can be concluded that mild asthmatics had comparable upper respiratory tract symptom frequency and severity as healthy volunteers and laboratory workers occupationally exposed to formaldehyde.

Table 2.10 – Frequency of symptoms (in percentages) in a group of 15 asthmatics exposed to formaldehyde for 40 min (Wit87)

	0 ppm		2 ppm	
	Rest	Exercise	Rest	Exercise
Odour	33	57	100	100
Eye irritation	7	14	73	36
Sore throat	27	21	33	43
Nasal irritation	20	14	47	36

Table 2.11 - Mean symptom scores with formaldehyde exposure in a group of 15 asthmatics exposed for 40 min (Wit87)

	0 ppm		2 ppm	
	Rest	Exercise	Rest	Exercise
Odour	0.47	0.64	2.00	1.79
Eye irritation	0.13	0.14	1.07	0.57
Sore throat	0.27	0.21	0.40	0.79
Nasal irritation	0.27	0.21	0.67	0.64

0 = none, 1 = minimal, 2 = moderate, 3 = severe, 4 = incapacitating

With respect to eye irritation, it can be concluded that:
1. Eye irritation has been reported in healthy volunteers at levels below 1 ppm (Web77; And83; Ben83; Kul87; Kul93). However, at these levels (a) the incidence was low and usually comparable to incidences reported at 0 ppm ('placebo effect') and/or (b) the severity of the symptoms was – on a normalized scale (see Table 2.12) – below 1, that is between none and slight/mild, in some studies even characterized as a symptom present but not annoying.
2. In all these studies, using exposure levels up to 4.0 ppm, the mean normalized symptom score did not reach 2, indicating less than moderate eye irritation.
3. If, on this normalized scale (Table 2.12), a mean score of at least 1 (minimal/mild/slight but not annoying) is taken as a starting level (cut off level) for eye irritation, then eye irritation is found at formaldehyde levels of 1.0 ppm (Ben83), or even 3.0 ppm (Gre87; Kul87; Kul93) and 4.0 ppm (Web77).
4. Therefore, based on these studies, it can be concluded that minimal/mild/slight eye irritation starts at levels of 1.0 ppm formaldehyde and higher.

Table 2.12 – Summary of reported eye irritation in healthy (non-asthmatic) volunteers exposed to formaldehyde

No of volunteers	Exposure regimen	Concentration (ppm)	Response (%)	Severity index	Normalized severity index *	Reference
33	37 min to increasing concentrations	0 0-3.2	Ni	1-1.25 $ 1-2	0-0.25 0-1	Web77
48	1.5 min for each concentration	0 1.0 2.0 3.0 4.0	Ni	1 $ 1.18 1.41 1.88 2.24	0 0.18 0.41 0.88 1.24	Web77
16	5 h for each concentration	0.24 0.42 0.83 1.67	19 31 94 94	2-9 @ 2-5 2-11 2-18	0.27 0.15 0.33 0.55	And83
5-28 /group	6 min for each concentration	0 0.35 0.56 0.7 0.9 1.0	- 42 54 57 60 74	- 0.71 # 0.79 0.86 0.80 1.56	- 0.71 0.79 0.86 0.80 1.56	Ben83
18	90 min	1.0	83	Ni	-	Day84
21	1 h	3.0	27% (≥ 3)	1.6 &	1.0	Gre87
9-19 /group	3 h for each concentration	0 0.5 1.0 2.0 3.0	5 0 26 53 100	0 # ni 0.44 0.89 1.44	0 ni 0.44 0.89 1.44	Kul87; Kul93
9	3 h for each concentration	0 3.0	0 67	0 # 0.78	0 0.78	Sau86
15	40 min for each concentration	0 2.0	0 53	0 ~ 0.80	0 0.80	Sch86
15	40 min for each concentration	0 2.0	0 47	0 ~ 0.60	0 0.60	Sch87

* normalized severity index, i.e. all ranges normalized to 0-3 (0=none, 1=slight, 2=moderate, 3=severe); $ range 1-4 (1=none, 2=slight, 3=moderate, 4=severe); @ range 1-100 (this response was not specifically based on eye irritation but on discomfort. However, complaints were mainly conjunctival irritation and dryness in the nose and throat; range no discomfort (0), slight discomfort (1-33), discomfort (34-66), strong discomfort (67-99), intolerable discomfort (100); # range 0-3 (0=none, 1=slight, 2=moderate, 3=severe); & range 0-5 (0=none, 1=mild, 2=mild/moderate, 3=moderate, 4=moderate/severe, 5=severe; ~ range 0-4 (0=none, 1=minimal, 2=moderate, 3=severe, 4=incapacitating; ni = not indicated

2.2 Nasal irritation

With respect to nasal irritation, it can be concluded that:
1. Nasal irritation has been reported in healthy volunteers at levels below 1 ppm (Web77; And83; Kul87; Kul93). However, at these levels (a) the incidence was low and usually comparable to incidences reported at 0 ppm ('placebo effect') and/or (b) the severity of the symptoms was – on a normalized scale (see Table 2.13) – below 1, that is between none and slight/mild, in some studies even characterized as a symptom present but not annoying.
2. In all these studies, using exposure levels up to 4.0 ppm, the mean normalized symptom score did not reach 2, indicating less than moderate nasal irritation.
3. If, on this normalized scale (Table 2.13), a mean score of at least 1 (minimal/mild/slight but not annoying) is taken as a starting level (cut off level) for nasal irritation, then nasal irritation is found at formaldehyde levels of 2.0 ppm (Web77) or even 3.0 ppm (Sau86; Gre87).
4. Therefore, based on these studies, it can be concluded that minimal/mild/slight nasal irritation starts at levels of 2.0 ppm formaldehyde and higher.

Table 2.13 – Summary of reported nose irritation in healthy (non-asthmatic) volunteers exposed to formaldehyde

No of volunteers	Exposure regimen	Concentration (ppm)	Response (%)	Severity index	Normalized severity index *	Reference
33	37 min to increasing concentrations	0 0-3.2	Ni	1.11-1.41 $ 1.11-2.12	0.11-0.41 0.11-1.12	Web77
48	1.5 min for each concentration	0 1.0 2.0 3.0 4.0	Ni	1.11 $ 1.53 2.06 2.35 2.65	0.11 0.53 1.06 1.35 1.65	Web77
16	5 h for each concentration	0.24 0.42 0.83 1.67	19 31 94 94	2-9 @ 2-5 2-11 2-18	0.27 0.15 0.33 0.55	And83 ∞
18	90 min	1.0	39	Ni	-	Day84
21	1 h	3.0	32 (≥ 3)	1.8 &	1.1	Gre87
9-19 /group	3 h for each concentration	0 0.5 1.0 2.0 3.0	16 10 5 37 22	0 # ni 0.11 0.33 0.22	0 - 0.11 0.33 0.22	Kul87; Kul93
9	3 h for each concentration	0 3.0	22 78	0.22 # 1.33	0.22 1.33	Sau86
15	40 min for each concentration	0 2.0	27 40	0.27 ~ 0.47	0.27 0.47	Sch86
15	40 min for each concentration	0 2.0	7 0	0.13 ~ 0	0.13 0	Sch87

∞ In the study of And83 nose irritation was reported as dryness in the nose.
* normalized severity index, i.e. all ranges normalized to 0-3 (0=none, 1=slight, 2=moderate, 3=severe); $ range 1-4 (1=none, 2=slight, 3=moderate, 4=severe); @ range 1-100 (this response was not specifically based on nasal irritation but on discomfort. However, complaints were mainly conjunctival irritation and dryness in the nose and throat; range no comfort (0), slight discomfort (1-33), discomfort (34-66), strong discomfort (67-99), intolerable discomfort (100); # range 0-3 (0=none, 1=slight, 2=moderate, 3=severe); & range 0-5 (0=none, 1=mild, 2=mild/moderate, 3=moderate, 4=moderate/severe, 5=severe; ~ range 0-4 (0=none, 1=minimal, 2=moderate, 3=severe, 4=incapacitating; ni = not indicated

2.3 Throat irritation

With respect to throat irritation, it can be concluded that:
1. Throat irritation has been reported in healthy volunteers at levels below 1 ppm (Web77; And83; Kul87; Kul93). However, at these levels (a) the incidence was low and usually comparable to incidences reported at 0 ppm ('placebo effect') and/or (b) the severity of the symptoms was – on a normalized scale (see Table 2.14) – below 1, that is between none and slight/mild, in some studies even characterized as a symptom present but not annoying.
2. In all these studies, using exposure levels up to 4.0 ppm, the mean normalized symptom score did not reach 2, indicating less than moderate throat irritation.
3. If, on this normalized scale (Table 2.14), a mean score of at least 1 (minimal/mild/slight but not annoying) is taken as a starting level (cut off level) for throat irritation, then throat irritation is found at levels of 3.0 ppm (Sau86; Gre87).
4. Therefore, based on these studies, it can be concluded that minimal/mild/slight throat irritation starts at levels of 3.0 ppm and higher.

Table 2.14 – Summary of reported throat irritation in healthy (non-asthmatic) volunteers exposed to formaldehyde

No of volunteers	Exposure regimen	Concentration (ppm)	Response (%)	Severity index	Normalized severity index *	Reference
33	37 min to increasing concentrations	0 0-3.2	Ni	1.11-1.24 $ 1.11-1.18	0.11-0.24 0.11-0.18	Web77
48	1.5 min for each concentration	0 1.0 2.0 3.0 4.0	Ni	1.11 $ 1.11 1.41 1.41 1.68	0.11 0.11 0.41 0.41 0.68	Web77
16	5 h for each concentration	0.24 0.42 0.83 1.67	19 31 94 94	2-9 @ 2-5 2-11 2-18	0.27 0.15 0.33 0.55	And83 ∞
18	90 min	1.0	28	Ni	-	Day84
21	1 h	3.0	32 (≥ 3)	1.8 &	1.1	Gre87
9-19 /group	3 h for each concentration	0 0.5 1.0 2.0 3.0	16 10 5 37 22	0 # ni 0.11 0.33 0.22	0 - 0.11 0.33 0.22	Kul87; Kul93
9	3 h for each concentration	0 3.0	22 78	0.22 # 1.33	0.22 1.33	Sau86
15	40 min for each concentration	0 2.0	13 27	0.13 ~ 0.27	0.13 0.27	Sch86
15	40 min for each concentration	0 2.0	7 0	0.13 ~ 0	0.13 0	Sch87

∞ In the study of And83 throat irritation was reported as dryness in the throat.

* normalized severity index, i.e. all ranges normalized to 0-3 (0=none, 1=slight, 2=moderate, 3=severe); $ range 1-4 (1=none, 2=slight, 3=moderate, 4=severe); @ range 1-100 (this response was not specifically based on throat irritation but on discomfort. However, complaints were mainly conjunctival irritation and dryness in the nose and throat; range no comfort (0), slight discomfort (1-33), discomfort (34-66), strong discomfort (67-99), intolerable discomfort (100); # range 0-3 (0=none, 1=slight, 2=moderate, 3=severe); & range 0-5 (0=none, 1=mild, 2=mild/moderate, 3=moderate, 4=moderate/severe, 5=severe; ~ range 0-4 (0=none, 1=minimal, 2=moderate, 3=severe, 4=incapacitating; ni = not indicated

2.4 Dyspnoea

With respect to dyspnoea (chest tightness/discomfort), it can be concluded that:
1. Dyspnoea has been reported in healthy volunteers at levels of 1 ppm and higher (Day84; Kul87; Kul93; Sau86). However, at these levels (a) the incidence was very low and (b) when reported, the severity of the symptom was slight/mild (Table 2.15).

2. Therefore, based on these studies, it can be concluded that exposure to formaldehyde up to levels of 3 ppm did not result in dyspnoea (chest tightness/discomfort).

Table 2.15 – Summary of reported dyspnoea (chest tightness/discomfort) in healthy (non-asthmatic) volunteers exposed to formaldehyde

No of volunteers	Exposure regimen	Concentration (ppm)	Response (%)	Severity index	Normalized severity index *	Reference
18	90 min	1.0	6	Ni	-	Day84
9-19 /group	3 h for each concentration	0 0.5 1.0 2.0 3.0	0 ni 0 11 0	0 # ni 0 0.11 0	0 - 0 0.11 0	Kul87; Kul93
9	3 h for each concentration	0 3.0	0 11	0 # 0.11	0 0.11	Sau86

* normalized severity index, i.e. all ranges normalized to 0-3 (0=none, 1=slight, 2=moderate, 3=severe); # range 0-3 (0=none, 1=slight, 2=moderate, 3=severe); ni = not indicated

2.5 Cough

With respect to cough, it can be concluded that:
1. Cough has been reported in healthy volunteers at a level of 1 ppm (Day84; Kul87; Kul93) but also at 0 ppm (Sau86). However, at 1 ppm (a) the incidence was very low and (b) when reported, the severity of the symptom was slight/mild (Table 2.16).
2. Therefore, based on these studies, it can be concluded that exposure to formaldehyde up to levels of 3 ppm did not result in cough.

Table 2.16 – Summary of reported cough in healthy (non-asthmatic) volunteers exposed to formaldehyde

No of volunteers	Exposure regimen	Concentration (ppm)	Response (%)	Severity index	Normalized severity index *	Reference
18	90 min	1.0	11	Ni	-	Day84
9-19 /group	3 h for each concentration	0 0.5 1.0 2.0 3.0	0 ni 11 0 0	0 # ni 0.11 0 0	0 - 0.11 0 0	Kul87; Kul93
9	3 h for each concentration	0 3.0	11 0	0.11 # 0	0.11 0	Sau86

* normalized severity index, i.e. all ranges normalized to 0-3 (0=none, 1=slight, 2=moderate, 3=severe); # range 0-3 (0=none, 1=slight, 2=moderate, 3=severe); ni = not indicated

2.6 Headache

With respect to headache, it can be concluded that:
1. Headache has been reported in healthy volunteers at a level of 3 ppm (Kul87; Kul93; Sau86) but also at 0 ppm (Sau86). However, at 3 ppm (a) the incidence was very low and (b) when reported, the severity of the symptom was slight/mild (Table 2.16).
2. Therefore, based on these studies, it can be concluded that exposure to formaldehyde up to levels of 3 ppm did not result in headache.

Table 2.17 – Summary of reported headache in healthy (non-asthmatic) volunteers exposed to formaldehyde

No of volunteers	Exposure regimen	Concentration (ppm)	Response (%)	Severity index	Normalized severity index *	Reference
9-19 /group	3 h for each concentration	0 0.5 1.0 2.0 3.0	0 ni 0 0 11	0 # ni 0 0 0.11	0 - 0 0 0.11	Kul87; Kul93
9	3 h for each concentration	0 3.0	22 11	0.22 # 0.11	0.22 0.11	Sau86

* normalized severity index, i.e. all ranges normalized to 0-3 (0=none, 1=slight, 2=moderate, 3=severe); # range 0-3 (0=none, 1=slight, 2=moderate, 3=severe); ni = not indicated

Overall conclusion:

Based on the available human volunteer studies, it can be concluded that slight eye irritation starts at levels of 1.0 ppm formaldehyde and higher. Slight nasal and throat irritation start at levels of 2.0 ppm respectively 3.0 ppm formaldehyde and higher. Exposure up to levels of 3 ppm formaldehyde did not result in dyspnoea (chest tightness/discomfort), in cough, nor in headache.

3 Optimal use of human data

A large number of adequate human volunteer studies are available for formaldehyde. In line with the recommendations by the Health Council, the greatest significance was given to these data (HCN96).

Several relevant studies on formaldehyde in humans were found in addition to those already summarized and evaluated by DECOS. The observations made in these additional studies were in line with those of the critical studies identified by DECOS.

It is noted that in the DECOS evaluation generally only the data on the incidence of a predescribed effect are used, but not the severity of the effect. Taking the severity of the effect into account would have made the comparison of the available studies more accurate (see chapter 2 of this report)

4 Assessment

In view of the extensive database on formaldehyde with a great number of adequate human studies, as well as the 'local' nature of the critical effect, the use of a minimal assessment factor, if any, is warranted. Neither argument is mentioned in the DECOS evaluation as a health-based occupational exposure limit of 0.12 ppm (0.15 mg/m^3) is proposed based on an assumed effect level of 0.3 mg/m^3 in humans and the application of a safety factor of 2 for the extrapolation of a Lowest Observed Adverse Effect Level (LOAEL) to a No Adverse Effect Level (NAEL). The application of an assessment factor of 2 should be discussed in view of severity and thus adversivity of the effects at the level of 0.3 mg/m3 (see section 2 and 5 of this report).

5 Benchmark dose method

5.1 Introduction

In a recent methodological advisory report, the Health Council has discussed the use of the 'benchmark dose' or BMD method in deriving health-based occupational exposure limits as an alternative to the generally employed 'NOAEL-approach' (HCN03b). The responsible Committee identified some aspects that need further attention in the continuing development of the method. Nothwithstanding this need for further development, the Committee considered the BMD method to be a useful technique for the derivation of recommended exposure limits. It even concluded that where toxicological data makes its application possible, the BMD method is preferred above the NOAEL approach. The BMD method is acknowledged to yield improved foundations for health-based recommended exposure limits.

The general principle of the BMD method is illustrated in figure 1. The BMD method takes all individual data into account by means of a curve based on all the data points. The BMD is subsequently defined by the intercept between the curve and the predefined Benchmark Response (BMR) or Critical Effect Size (CES), representing the cut-off between an adverse and a non-adverse effect. Finally, the lower limit of the confidence interval of the BMD (BMDL) is used as a starting point for the derivation of limit values. The BMDL is therefore the counterpart of the NOAEL in the traditional method.

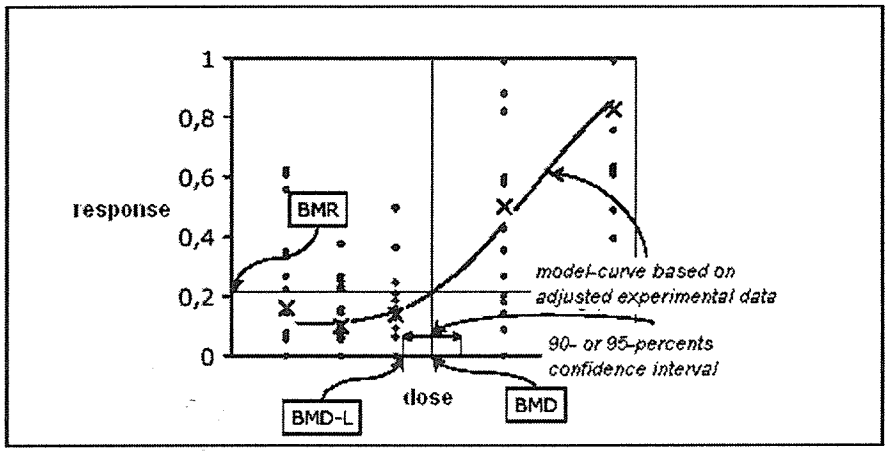

Figure 1 Schematic presentation of the derivation of the BMD and the BMD-L. The dots represent the individual data (responding subjects) for the different dose levels, whereas the crosses indicate the mean values per dose group. The BMR indicates the benchmark-respons and represents e.g. the increase in the fraction of responding subjects above the unexposed reference group (based on HCN03b).

5.2 BMD for eye irritation induced by formaldehyde

Based on these recommendations by the Health Council, the studies of Andersen and Molhave (And83; identified as the critical study in the DECOS report) and Kulle et al (Kul87; not mentioned in the DECOS report), both were analyzed quantitatively using EPA Benchmark Dose Software (Version 1.3.2).

In the study of Andersen and Molhave (And83) the incidence of 'discomfort' following 1 up to 5 hours of exposure to 0, 0.3, 0.5, 1, and 2 mg/m^3 formaldehyde (equal to 0, 0.24, 0.42, 0.83, and 1.67 ppm) was scored. The endpoint discomfort was divided into 4 different scales. None of the mean group scores were higher than 18 which is within the first level of discomfort ('slight', range 1-33). The incidences of slight discomfort at 2.5 hours and 4-5 hours of exposure at different concentrations is given in table 5.1 and 5.2, respectively. Besides incidences, average scores per concentration were given, however standard deviations are missing and therefore dose response analyses can not be performed. The incidences were analyzed using the BMD software and the results are given in tables 5.1 and 5.2 as well. The incidence data are dichotomous. Using different BMD models for dichotomous data small differences in final output (Benchmark Doses (BMDs)) were observed. The Gamma model resulted in the lowest BMDs. Therefore data generated by the Gamma model are presented in the tables. The confidence interval to calculate the lower limit of the BMD (BMDL) is set at 90% and 95%.

For each accepted level of Extra Risk, expressed as percentage (%) of the population at risk for slight discomfort a BMD and BMDL can be calculated. For example if 10% Extra Risk for slight discomfort is accepted as Benchmark response (BMR) after 4-5 hours of exposure to formaldehyde a concentration of 0.11 ppm (based on a confidence interval of 90%) would be acceptable (see Table 5.2). See also figure 2.

Table 5.1 Incidence of slight discomfort after 2.5 hours of exposure (data from And83)

Dose (ppm)	Exposed (n)	Responders (n)	Extra risk (%)	BMD (ppm)	BMDL $^{0.90}$ (ppm)	BMDL $^{0.95}$ (ppm)
0	16	0	1	0.02	0.01	0.01
0.24	16	3	5	0.09	0.07	0.06
0.42	16	2	10	0.18	0.14	0.13
0.83	16	7	15	0.28	0.21	0.20
1.67	16	10	**17**	0.32	**0.24**	0.22
			18.2	0.34	0.26	**0.24**
			20	0.38	0.29	0.27
			50	1.16	0.89	0.83
			54.5	1.32	1.00	0.94
			57.0	1.42	1.07	1.00

Table 5.2 Incidence of slight discomfort after 4-5 hours of exposure (data from And83)

Dose (ppm)	Exposed (n)	Responders (n)	Extra risk (%)	BMD (ppm)	$BMDL^{0.90}$ (ppm)	$BMDL^{0.95}$ (ppm)
0	16	0	1	0.02	0.01	0.01
0.24	16	9	5	0.09	0.06	0.05
0.42	16	3	10	0.17	0.11	0.10
0.83	16	6	15	0.27	0.18	0.16
1.67	16	10	**20**	0.37	**0.24**	0.22
			21.5	0.40	0.26	**0.24**
			50	1.14	0.75	0.69
			60.6	1.54	1.00	0.92
			63.5	1.66	1.08	1.00

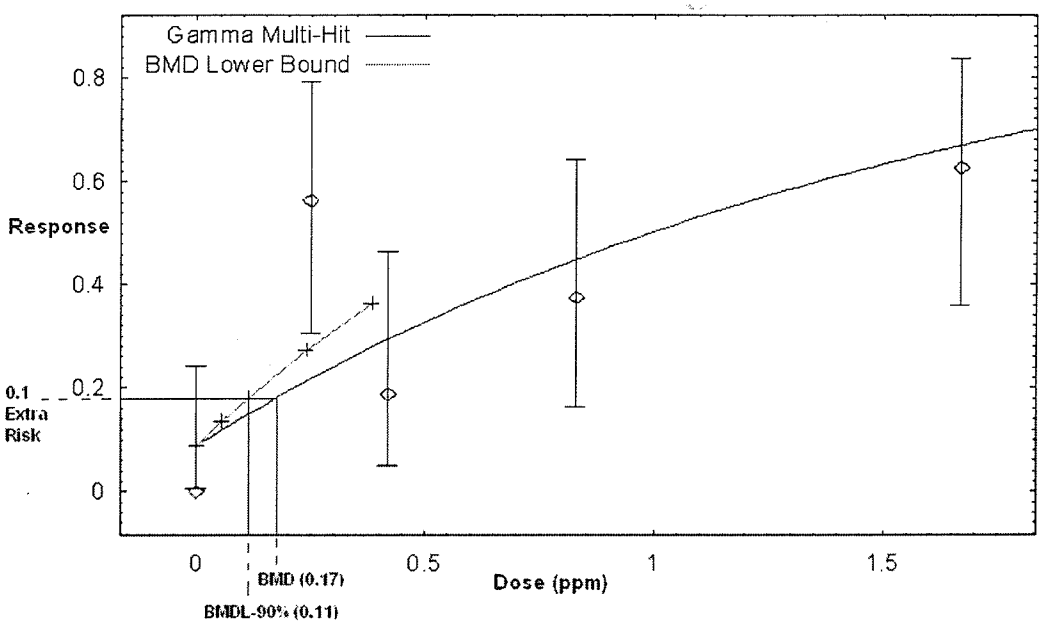

Figure 2 Incidence of slight discomfort after 4-5 h (data from And83)

In the study of Kulle et al. (1987) the incidence and severity of developed eye and nose/throat irritation was scored after 3 hours of formaldehyde exposure at concentrations of 0, 0.5, 1, 2, and 3 ppm. Eye irritation and nose/throat irritation were scored as 0 = none; 1= mild (present but not annoying), 2=moderate (annoying), and 3=severe (debilitating). Incidences are given in tables 6.3 (eye) and 6.4 (nose/throat). No severe eye irritation and no moderate or severe nose/throat irritation were noted at any formaldehyde concentration. The data were both analyzed for dose-response (severity) and incidence.

The dose response information was analyzed on a continuous scale (0, 1, 2, 3) using a linear model for continuous data. Depending on the severity of eye irritation accepted a BMD can be calculated. The corresponding BMDL is calculated using a confidence interval of 90% and 95%. The results are also presented in tables 5.3 and 5.4. For example if mild eye irritation is accepted as BMR a concentration of formaldehyde in the air of 2.11 ppm (using a confidence interval of 90%) would be acceptable. See also figure 3.

Table 5.3 Dose response information on eye irritation (data from Kul87)

Dose (ppm)	Exposed (n)	Incidence 'none' (score 0)	Incidence 'mild' (score 1)	Incidence 'moderate' (score 2)	BMR (score)	BMD (ppm)	$BMDL^{0.90}$ (ppm)	$BMDL^{0.95}$ (ppm)
0	19	18	1	0	0	0	0	0
0.5	10	10	0	0	1	2.45	2.11	2.06
1	19	14	4	1	2	4.89	4.01	3.90
2	19	9	6	4				
3	9	0	5	4				

Table 5.4 Dose response information on nose/throat irritation (data from Kul87)

Dose (ppm)	Exposed (n)	Incidence 'none' (score 0)	Incidence 'mild' (score 1)	BMR (score)	BMD (ppm)	$BMDL^{0.90}$ (ppm)	$BMDL^{0.95}$ (ppm)
0	19	16	3	0	0	0	0
0.5	10	9	1	1	13.04	7.62	6.86
1	19	18	1				
2	19	12	7				
3	9	7	2				

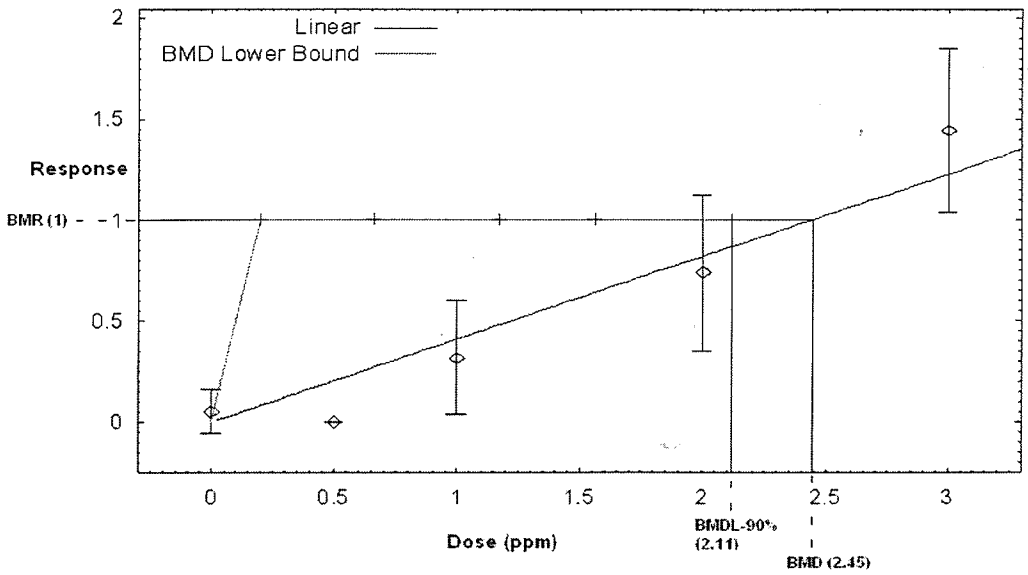

Figure 3 Dose response curve of eye irritation (data from Kul87)

The incidences of irritation were analyzed for mild and moderate eye irritation, for both scored levels of eye irritation together and for mild nose/throat irritation. The analyses were performed similar to the Andersen data, thus on a dichotomous scale using the Gamma model and confidence intervals for the BMD of 90% and 95%. The results are presented in tables 5.5, 5.6, 5.7, and 5.8.

For each accepted level of Extra Risk of eye or nose/throat irritation a BMD and BMDL can be calculated. For example if 10% Extra Risk for mild eye irritation due to formaldehyde exposure is accepted a concentration of 0.45 ppm (based on a confidence interval of 90%) would be acceptable (see table 5.5). At this level about 5% extra risk for moderate eye irritation (see table 5.6) and 5-10% extra risk for mild nose/throat irritation (see table 5.8) is expected as well. See also figure 4.

Table 5.5 Incidence of mild eye irritation[1] (data from Kul87)

Dose (ppm)	Exposed (n)	Responders (n)	Extra risk in %	BMD (ppm)	$BMDL^{0.90}$ (ppm)	$BMDL^{0.95}$ (ppm)
0	19	1	1	0.26	0.043	0.037
0.5	10	0	5	0.62	0.22	0.19
1	19	4	**5.5**	0.65	**0.24**	0.21
2	19	6	**6.2**	0.70	0.27	**0.24**
3	9	5	10	0.92	0.45	0.39
			15	1.18	0.69	0.61
			20	1.43	0.95	0.83
			21.0	1.47	1.00	0.88
			23.5	1.59	1.13	1.00
			50	2.90	2.26	2.13

[1] present but not annoying

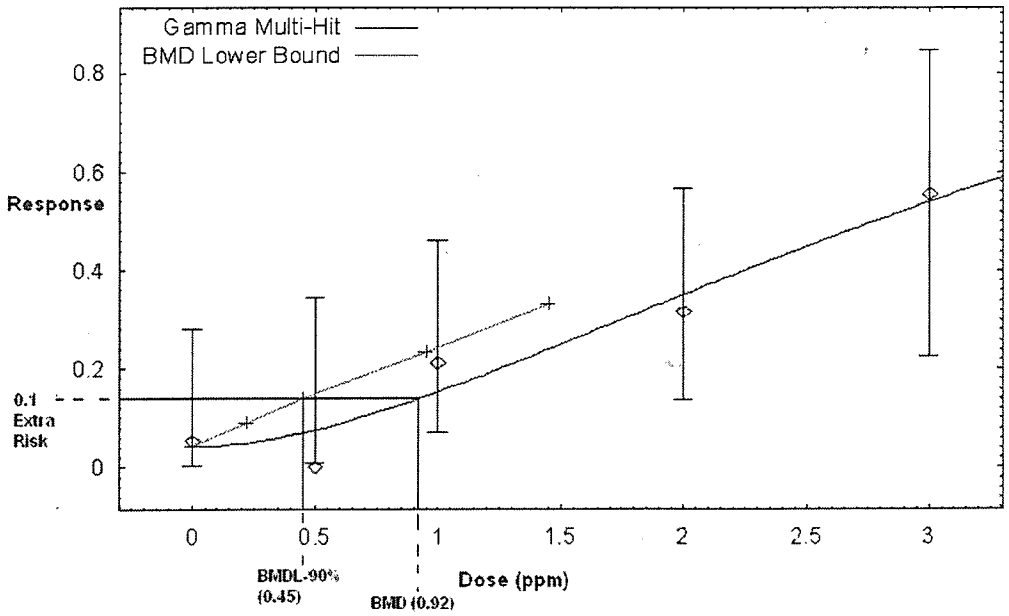

Figure 4 *Incidence of mild eye irritation (data from Kulle et al., 1987)*

Table 5.6 Incidence of moderate eye irritation[1] (data from Kul87)

Dose (ppm)	Exposed (n)	Responders (n)	Extra risk (%)	BMD (ppm)	$BMDL^{0.90}$ (ppm)	$BMDL^{0.95}$ (ppm)
0	19	0	1	0.58	0.17	0.08
0.5	10	0	**1.6**	0.68	**0.24**	0.13
1	19	1	**2.9**	0.86	0.38	**0.24**
2	19	4	5	1.05	0.57	0.41
3	9	4	10	1.40	1.00	0.79
			13	1.57	1.15	1.00
			15	1.67	1.28	1.14
			20	1.92	1.54	1.43
			50	3.27	2.62	2.51

[1] annoying

Table 5.7 . Incidence of eye irritation (mild + moderate) (data from Kul87)

Dose (ppm)	Exposed (n)	Responders (n)	Extra risk (%)	BMD (ppm)	$BMDL^{0.90}$ (ppm)	$BMDL^{0.95}$ (ppm)
0	19	1	1	0.42	0.19	0.13
0.5	10	0	**1.7**	0.49	**0.24**	0.18
1	19	5	**2.9**	0.57	0.31	**0.24**
2	19	10	5	0.68	0.41	0.33
3	9	9	10	0.85	0.56	0.50
			15	0.99	0.72	0.64
			20	1.10	0.85	0.77
			26.5	1.24	1.00	0.92
			30.0	1.31	1.08	1.00
			50	1.72	1.49	1.43

Table 5.8 Incidence of nose/throat irritation (data from Kul87)

Dose (ppm)	Exposed (n)	Responders (n)	Extra risk (%)	BMD (ppm)	$BMDL^{0.90}$ (ppm)	$BMDL^{0.95}$ (ppm)
0	19	3	1	0.54	0.08	0.06
0.5	10	1	**3.1**	0.92	**0.24**	0.20
1	19	1	**3.7**	1.00	0.29	**0.24**
2	19	7	5	1.16	0.39	0.33
3	9	2	10	1.66	0.80	0.67
			12.4	1.86	1.00	0.84
			14.6	2.04	1.19	1.00
			15	2.07	1.23	1.03
			20	2.45	1.64	1.42
			50	4.67	3.03	2.83

In the tables on incidence analyses (5.1, 5.2, 5.5, 5.6, 5.7, and 5.8) the level of extra risk expected at 0.24 ppm (the lowest effect level used by DECOS as the basis for their proposal for an health-based occupational exposure limit) is presented in bold. In case the level of 0.24 ppm is accepted as the lowest effect level, this means that the following extra risks are implicitly accepted at a confidence interval of 90%:

- 20% of exposed subjects experience 'slight discomfort' after 4-5 hours of exposure (based on And83),
- 0% of exposed subjects experience 'discomfort' after 4-5 hours of exposure (based on And83),
- 5.5% experience 'mild' (i.e. present but not annoying) eye irritation after 3 hours of exposure (based on Kul87),
- 1.6% experience 'moderate' (i.e. annoying) eye irritation (based on Kul87), and
- 3.1% experience 'mild' (i.e. present but not annoying) nose/throat irritation (based on Kul87).

Based on the BMD analysis, it may be concluded that the proposed health-based occupational exposure limit is a rather conservative value.

The level of 1 ppm at which slight irritation of the eyes is first observed (see chapter 2) is associated with the following extra risks (90% confidence interval):

- 60.6% of exposed subjects experience 'slight discomfort' after 4-5 hours of exposure (based on And83),
- 0% of exposed subjects experience 'discomfort' after 4-5 hours of exposure (based on And83),
- 21% experience 'mild' (i.e. present but not annoying) eye irritation (based on Kul87),
- 10% experience 'moderate' (i.e. annoying) eye irritation (based on Kul87), and
- 12.4% experience 'mild' (i.e. present but not annoying) nose/throat irritation (based on Kul87).

Overall conclusion:

Based on the BMD analysis, it may be concluded that the level of 0.24 ppm that is taken as the lowest effect level is a rather conservative estimate of the LOAEL as at this exposure level it is expected that only a small part of the exposed subjects (5-20%) experience irritation characterised as 'slight' and/or 'present but not annoying' (lower limit 90% confidence interval).

6 Respiratory tract toxicity of formaldehyde based on animal and volunteer studies

This section on respiratory tract toxicity of formaldehyde is used to determine the lowest concentration giving rise to cytotoxicity (best estimate, if possible with a confidence interval) in the airways based on human and animal data.

6.1 Animal studies

Several of the animal inhalation toxicity studies point to a high susceptibility of the nasal mucosa to formaldehyde. In the long-term studies (see Table 6.2) slight nasal epithelial toxicity, consisting of respiratory epithelial hyperplasia and squamous metaplasia, was generally seen at levels of about 2 ppm, whereas overt toxicity, consisting of rhinitis, cell necrosis, and extensive restorative hyper/metaplasia, was seen at levels of about 6 ppm and higher. An increased incidence of nasal squamous cell carcinomas was observed at even higher levels, i.e. from 9.9 ppm (Mon96) and higher, although it was noted that in this study and the study of Ker83, nasal squamous cell carcinomas were observed at about 6 ppm at a very low incidence. In the study of Ker83, 2/235 animals exposed to 5.6 ppm exhibited nasal squamous cell carcinomas whereas in the study of Mon96, 1/90 animals exposed to 6.0 ppm showed this type of tumour. In the study of Ker83, nasal tumours were already observed at levels of 2 ppm. However, most of the tumours they found at this level and at 5.6 ppm were polypoid adenomas, benign tumours, for which F344 rats apparently are more sensitive than Wistar rats.

These findings indicate that formaldehyde induces nasal cell carcinomas at exposure levels causing severe damage to the nasal epithelium. Severe damage is caused at cytotoxic concentrations causing cell necrosis, which generally leads to restorative hyperproliferation. With respect to formaldehyde, this occurs at levels of about 6 ppm and higher. Respiratory epithelial hyperplasia was, however, also seen at lower formaldehyde concentrations (2-3 ppm). Apparently, proliferation as such is not a risk factor for nasal carcinomas as substantiated in longterm (lifetime) studies in which respiratory epithelial metaplasia/hyperplasia occurred without tumour formation at low concentrations, i.e. from about 2-6 ppm.
Thus severe damage to the nasal mucosa may be an important factor, if not a prerequisite for the induction of nasal tumours by formaldehyde. This was substantiated by the study of Woutersen et al (Wou89) in which at 9.8 ppm a high incidence of nasal cell carcinomas was found only in animals with a mechanically damaged nose.

In contrast to all other long-term studies, in the study by Kamata et al. (Kam97) nasal histopathological changes, that is respiratory epithelial hyper/metaplasia, were observed at a level well below 1 ppm, namely 0.3 ppm. There are, however, a few items that need to be considered:

1. The lesions observed in animals of the low concentration group (0.3 ppm), i.e. respiratory epithelial squamous metaplasia and basal cell hyperplasia, were seen at a very low incidence (4/32). The severity of the changes was not reported. The toxicological significance of the findings (hyper/metaplasia of the nasal respiratory epithelium) at 0.3 ppm, however, might be doubtful because of the relatively high incidence of inflammatory cell infiltration,

erosion, and oedema observed in all exposure groups (including the 0 ppm group and room controls; see Table 6.3) without any concentration-response relationship, and in view of the relatively small number of rats used per group (5, 5, 5, 17 per sacrifice point per group; 32 per group in total).
2. Also, the incidence of hyper/metaplasia at a 7-times higher concentration (2.1 ppm) was only slightly higer (7/32), and might also have been the result of the relatively high incidence of inflammatory cell infiltration, erosion and oedema (see Table 6.3). A clear incidence of hyper/metaplasia was observed at 14.8 ppm (29/32).
3. The type of these lesions is similar to the lesions observed in the other long-term studies. However, in all other studies these lesions are scheduled under non-neoplastic lesions, whereas in the present study, these lesions are scheduled under proliferative lesions (together with the neoplastic lesions).
4. Although it might not be of importance it should be noted that the present study (published in 1997) has already been made public in 1985 (Tobe M, Kaneko T, Uchida Y, Kamata E, Ogawa Y, Ikeda Y, and Saito M. Studies of the Inhalation Toxicity of Formaldehyde. National Sanitary and Medical Laboratory Service, Toxicity Department of Organism Safety Research Center. Report no. TR-85-0236, Tokyo, Japan).

From the results of this study it is concluded that 14.8 ppm is a clear cytotoxic level; the study does seem to be inconclusive with respect to 0.3 and 2.1 ppm formaldehyde being a no-effect-level for the nasal epithelium.

In short-term exposure studies (see Table 6.1), the presence of respiratory epithelial metaplasia/hyperplasia was confirmed at about similar levels, i.e. starting from about 3 ppm. The only exception was an increased cell turnover (increased labeling index) of respiratory epithelium at 1 ppm following exposure for 3 days (Zwa88). However, in this study, histopathological changes were only observed at the next higher level tested of 3 ppm, which results were in fact confirmed by the studies of Swe83 and Swe86 in which both histopathological changes and increased cell turnover were also seen at 3 ppm. In these studies increased cell proliferation was also seen at levels of 0.5 ppm and 2 ppm; however as these increases were transient (only after 1 day), slight (without a concentration-response relationship) in contrast to the next higher level tested of 6 ppm, the toxicological relevance of these findings is not clear.
Overt toxicity (rhinitis, necrosis, extensive hyper/metaplasia) was observed at levels from about 6 ppm and higher, except for one study by Cassee et al (Cas94b) in which frank necrosis was observed at 3.6 ppm for 3 days. However the exposure regimen used clearly differed from all others in that each 8-h exposure was followed by a 4-h non-exposure period. Perhaps the 4-h non-exposure periods were too short for the nasal defense mechanism to repair the damage, thus rendering the inflamed and hyper/metaplastic nasal respiratory epithelium more susceptible to formaldehyde.

Overall, in agreement with the DECOS report (page 78), exposure levels of 2-3 ppm induced slight respiratory epithelial hyper/metaplasia, whereas levels of about 6 ppm and higher induced extensive hyper/metaplasia, necrosis, and severe rhinitis. An increased incidence of nasal cell carcinomas was seen from about 10 ppm, concomitant with clear cytotoxic effects.
Therefore, cytotoxicity (cell necrosis) was seen at formaldehyde levels of about 6 ppm and higher, which is considered a main risk factor for nasal cell carcinomas, as this did not occur at levels lower than 6 ppm.

Table 6.1 – Histopathological changes in animals following short-term exposure (up to 13 weeks) to formaldehyde

Species	Exposure design	Effect(s) in the nose	NOAEL (ppm)	LOAEL (ppm)	Reference
F344 rats	0, 0.5, 2, 6, 15 ppm; 6h/d, 3d	Increased nasal epithelial cell proliferation	2#	6	Swe83; Swe86
B6C3F1 mice	0, 0.5, 2, 6, 15 ppm; 6h/d, 3d	Increased nasal epithelial cell proliferation	6	15	Swe83; Swe86
F344 rats	0, 3ppm/12h, 6ppm/6h, 12 ppm/3h, 3d/10d	Increased nasal epithelial cell proliferation; labelling index decreased after 10 days exposure Resp epith hyperplasia (10d)	-	3	Swe83; Swe86
F344 Rats	0, 2, 15 ppm; 10, 20, 45, 90min or 6h	Inhibition of mucociliary clearance	2	15	Mor86A
Wistar rats	0, 1, 9.7. 19.8 ppm; 6h/d, 5d/wk, 13wks	Resp epith squamous metaplasia Resp epith hyperplasia Resp epith keratinization Olfactory epith keratinization	1 $	9.7	Wou87
Wistar rats	0, 1, 9.7, 19.8 ppm; 6h/d, 3d	Increased labeling index of resp epith lining the nasoturbinates	1	9.7	Wou87
Wistar rats	0, 5, 10 ppm; 8h/d (continuous), 3d	Increased labeling index of resp epith lining the nasal and maxillary turbinates, septum and lateral wall	-	5	Wil87
Wistar rats	0, 5, 10 ppm; 8h/d (continuous), 5d/wk, 4wks	Increased labeling index of resp epith lining the nasal and maxillary turbinates, septum and lateral wall (at 10 ppm) Resp epith sqamous metaplasia, basal cell hyperplasia (at 5 ppm)	-	5	Wil87
Wistar rats	0, 10, 20 ppm; 8x60 min (30min exp + 30 min non-exposure; intermittent), 3d	Increased labeling index of resp epith lining the nasal and maxillary turbinates, septum and lateral wall	-	10	Wil87
Wistar rats	0, 10, 20 ppm; 8x60 min (30min exp + 30 min non-exposure; intermittent), 5d/wk, 4wks	Increased labeling index of resp epith lining the nasal and maxillary turbinates, septum and lateral wall Thinning and disarrangement of resp epith, resp epith sqamous metaplasia, basal cell hyperplasia Intermittent exposure induced more severe nasal lesions than continuous exposure (at the same total dose)	-	10	Wil87
Wistar rats	0, 0.3, 1.0, 3.0 ppm; 6h/d, 3d	Increased cell turnover (at 1 ppm) Basal cell hyperplasia with loss of cilia (at 3 ppm)	0.3	1	Zwa88
Wistar rats	0, 0.3, 1.0, 3.0 ppm; 6h/d, 5d/wk, 13wks	Increased cell turnover Squamous metaplasia with/without keratinization	1	3	Zwa88
Wistar rats	0, 0.1, 1, 9.4 ppm; 6h/d, 5d/wk, 13wks	Resp epith squamous metaplasia Resp epith cell hyperplasia Rhinitis	1	9.4	App88

Species	Exposure design	Effect(s) in the nose	NOAEL (ppm)	LOAEL (ppm)	Reference
Rhesus monkeys	0, 6 ppm; 6h/d, 5d/wk, 1wk	Increased cell proliferation Mild degneration trans + resp epith Resp epith squamous metaplasia Trans epith squamous metaplasia @	-	6	Mon89
Rhesus monkeys	0, 6 ppm; 6h/d, 5d/wk, 6wks	Increased cell proliferation Mild degneration trans + resp epith Resp epith squamous metaplasia Trans epith squamous metaplasia @ (Minimal progression compared to 1 week; however percent area affected was sign increased)	-	6	Mon89
Wistar rats	0, 1, 2 ppm; 8h/d (continuous), 3d	-	2	-	Wil89
Wistar rats	0, 1, 2 ppm; 8h/d (continuous), 5d/wk, 13wks	-	2	-	Wil89
Wistar rats	0, 2, 4 ppm; 8x60 min (30min exp + 30 min non-exposure; intermittent), 3d	-	4	-	Wil89
Wistar rats	0, 2, 4 ppm; 8x60 min (30min exp + 30 min non-exposure; intermittent), 5d/wk, 13wks	Increased cell turnover Resp epith disarrangement Resp epith sqamous metaplasia Resp epith hyperplasia Resp epith keratinization	2	4	Wil89
Wistar rats	0, 0.3, 1.1, 3.1 ppm; 22h/d, 3d	Increased cell turnover Disarrangement of resp epith Loss of cilia Resp epith squamous metaplasia Resp epith hyperplasia Resp epith keratinization Rhinitis	1.1	3.1	Reu90
F344 rats	0, 0.7, 2.0, 6.2, 9.9, 14.8 ppm; 6h/d, 5d/wk, 4d	Increased cell proliferation Mild multifocal cell necrosis Mild neutrophilic infiltrate Resp epith hyperplasia	2	6.2	Mon91
F344 rats	0, 0.7, 2.0, 6.2, 9.9, 14.8 ppm; 6h/d, 5d/wk, 9d	Increased cell proliferation Mild multifocal cell necrosis Mild neutrophilic infiltrate Resp epith hyperplasia Resp epith squamous metaplasia	2	6.2	Mon91
F344 rats	0, 0.7, 2.0, 6.2, 9.9, 14.8 ppm; 6h/d, 5d/wk, 6wks	Increased cell proliferation Resp epith hyperplasia Resp epith squamous metaplasia	2	6.2	Mon91
F344 rats	0, 0.7, 2.0, 5.9, 10.0, 14.5 ppm; 6h/d, 5d/wk, 11wks	Increased cell proliferation Resp epith hypertrophy/hyperplasia Resp epith squamous metaplasia	2	5.9	Cas94a

Species	Exposure design	Effect(s) in the nose	NOAEL (ppm)	LOAEL (ppm)	Reference
Wistar rats	0, 3.6 ppm, 6x12h (8h exp + 4h non-exposure)	Increased cell proliferation Necrosis Resp epith squamous metaplasia Resp epith hyperplasia Rhinitis	-	3.6	Cas94b
Wistar rats	0, 3.2, 6.4 ppm; 6h/d, 1d	-	6.4	-	Cas96
Wistar rats	0, 1, 3.2, 6.4 ppm; 6h/d, 3d	Increased cell proliferation Resp epith disarrangement Resp epith basal cell hyperplasia	1	3.2	Cas96

A transient, slight increase in cell proliferation (about 3-times at 0.5 ppm and about 2-times at 2 ppm; a concentration-response relationship was absent and no statistical analysis was performed) was seen in rats exposed to 0.5 or 2 ppm for just 1 day. This increase was not present 3 or 9 days of exposure. In contrast, rats exposed to 6 ppm showed a massive increase after one day (about 30-times), still a high increase (about 20-times) after 3 days, and a small increase (about 4-times) after 9 days.

$ According to the DECOS report, the level of 1 ppm being a no-effect level was doubtful according to the authors. This might imply that a no-effect-level was not found. However it was concluded by the authors 'that in view of (a) the low incidence and scantiness seen at the 1 ppm level, (b) the uncertainty as to the exact localization of the most sensitive area of the nasal respiratory mucosa, and (c) the problem of standardizing the cross section to be examined, it is quite possible that the changes found at 1 ppm actually are not treatment-related.' They therefore concluded that 'the present study was inconclusive with respect to 1 ppm formaldehyde being a cytotoxic or a no-cytotoxic level in rats'.

@ also mild degeneration and squamous metaplasia of the respiratory epithelium of trachea and main bronchi

Table 6.2 – Histopathological changes in animals following long-term exposure to formaldehyde (or short-term exposure followed by long-term observation periods)

Species	Exposure design	Effect(s) in the nose	NOAEL (ppm)	LOAEL (ppm)	'Tumour' Level (ppm)	Ref.
F344 rats	0, 2.0, 5.6, 14.3 ppm; 6h/d, 5d/wk, 24mo + 6mo recovery	Rhinitis Resp epith hyperplasia Resp epith squamous metaplasia Squamous cell carcinomas (2/235 at 5.6 ppm; 103/232 at 14.3 ppm) Polypoid adenomas (1/232, 8/236, 6/235, 5/232 at 0, 2.0, 5.6, and 14.3 ppm, respectively)	-	2	5.6	Ker83
C57BL/6 x C3HF1 Mice	0, 2.0, 5.6, 14.3 ppm; 6h/d, 5d/wk, 24mo + 6mo recovery	Rhinitis Necrosis Resp epith dysplasia Resp epith squamous metaplasia Squamous cell carcinomas (2 males $) at 14.3 ppm	2	5.6	14.3	Ker83
SD rats	0, 14.8 ppm; 6h/d, 5d/wk, lifetime	Rhinitis Resp epith hyperplasia Resp epith squamous metaplasia @ Nasal squamous cell carcinomas (38/100) at 14.8 ppm	-	14.8	14.8	Sel85
Wistar rats	0, 0.1, 1, 9.4 ppm; 6h/d, 5d/wk, 52wks damaged/ undamaged nose	Resp epith squamous metaplasia Resp epith cell hyperplasia Rhinitis No nasal tumours	1	9.4	-	App88
Wistar rats	0, 9.2, 19.7 ppm; 6h/d, 5d/wk, 4wks + 126wks recovery	Resp epith hyperplasia Resp epith squamous metaplasia Polypoid adenoma (1/45) at 19.7 ppm	-	9.2	-	Fer88
Wistar rats	0, 9.4, 19.7 ppm; 6h/d, 5d/wk, 8wks + 122wks recovery	Resp epith hyperplasia Resp epith squamous metaplasia Polypoid adenoma (1/43) at 19.7 ppm	-	9.4	-	Fer88
Wistar rats	0, 9.7, 19.8 ppm; 6h/d, 5d/wk, 13wks + 117wks recovery	Resp epith hyperplasia Resp epith squamous metaplasia Squamous cell carcinomas (3) and carcinoma in situ (1; total 4/44) at 19.8 ppm	-	9.7	19.8	Fer88

Species	Exposure design	Effect(s) in the nose	NOAEL (ppm)	LOAEL (ppm)	'Tumour' Level (ppm)	Ref.
Wistar rats	0, 0.1, 1, 9.8 ppm; 6h/d, 5d/wk, 28mo damaged/ undamaged nose	Resp epith squamous metaplasia Resp epith basal cell hyperplasia Olfactory epith thinning/ disarrangement Rhinitis No sign increase in nasal tumours (In animals with damaged nose: Squamous cell carcinomas (15), Adenosquamous carcinoma (1), Adenocarcinoma (1; total 17/58) at 9.8 ppm	1	9.8	9.8 (damaged nose)	Wou89
Wistar rats	0, 0.1, 1, 9.2 ppm; 6h/d, 5d/wk, 3mo + 25mo recovery damaged/ undamaged nose	Resp epith squamous metaplasia Resp epith basal cell hyperplasia Rhinitis No sign increase in nasal tumours (In animals with damaged nose: also no sign increase in tumours)	1	9.2	-	Wou89
F344 rats	0, 0.7, 2.0, 6.0, 9.9, 15.0 ppm; 6h/d, 5d/wk, 24mo	Resp epith squamous metaplasia Resp epith hypertrophy/ hyperplasia Mixed inflammatory cell infiltrate Increased cell proliferation (at 9.9 and 15.0 ppm) Squamous cell carcinomas (1/90 at 6.0 ppm, 20/90 at 9.9 ppm, 69/147 at 15.0 ppm) Polypoid adenomas (0/90, 0/90, 0/96, 0/90, 5/90, 14/147 at 0, 0.7, 2.0, 6.0, 9.9, 15.0 ppm, respectively)	2	6	6	Mon96
F344 rats	0, 0.3, 2.1, 14.8 ppm; 6h/d, 5d/wk, 28mo	Resp epith squamous metaplasia Resp epith cell hyperplasia Epithelial cell hyperkeratosis Squamous cell carcinomas (13/32) at 14.8 ppm	2.1 #	14.8	14.8	Kam97

$ Total number of evaluated nasal cavities was not given; total number of animals exposed was stated to be 119-121 animals/sex/group.

Changes found at this level and the next lower level of 0.3 ppm might have been the result of the relatively high incidence of inflammatory cell infiltration, erosion and oedema which was also found in the 0 ppm group and room controls (see text and Table 6.3)

@ Also hyperplasia and squamous metaplasia in larynx and trachea

Table 6.3 – Incidences of non-proliferative nasal lesions in F344 rats exposed to formaldehyde for 28 months (Kam97)

	RC	0 ppm	0.3 ppm	2.1 ppm	14.8 ppm
Cell infiltration	3/32	5/32	6/32	5/32	Ni
Erosion	2/32	2/32	2/32	0/32	Ni
Oedema	0/32	2/32	2/32	0/32	Ni

RC = room control; Ni = not indicated

6.2 Human studies

There were not many human studies found in which nasal histopathological changes have been examined. Chronic inflammation of the nasal mucosa with a higher incidence of squamous metaplasia was observed in a group of 15 workers working in a plywood factory. The reported exposure level of these workers was 0.08-0.32 ppm formaldehyde (Bal92).
In a group of 37 workers exposed to formaldehyde levels of 0.5 to more than 2 ppm in a chemical company, more pronounced metaplastic nasal changes, and epithelial dysplasia were observed (Boy90). Although in both studies a matched control group was used, it is difficult to judge the relevance of these results as (a) there was co-exposure to wood dust in the study of Bal92, and (b) the actual exposure levels are not known.

With respect to carcinogenicity of formaldehyde, three meta-analysis studies (Bla90a, Par93, Col97) were available. The first study of Blair et al (Bla90a) showed that the Relative Risk (RR) for nasopharyngeal cancer rose to 2.1 in the high exposure category (> 5.5 ppm.year cumulative exposure). The authors concluded amongst others that a causal role for formaldehyde is most probable for cancers of the nasopharynx, and an association with nasal cancer is also plausible. In the study by Partanen et al (Par93) using the same sources as Bla90a with some updating, increases in RR for sinonasal cancer and nasopharyngeal cancer were reported within the 'substantial' exposure category. In the third (and most extended) study of Collins et al (Col97; taking positive and negative studies into account) it was, however, concluded by the authors that the available studies do not support a causal relation between formaldehyde exposure and nasopharyngeal cancer. In a more recent study of Vaughan et al (Vau00), it was concluded that their study supported the hypothesis that occupational exposure to formaldehyde increased the risk of nasopharyngeal cancer (specific for squamous cell carcinomas). However, in this study no actual exposure levels were measured. Instead self reported occupational histories were used.

It is therefore concluded that if there is an association between formaldehyde exposure and nasopharyngeal cancer in humans, that this association is only found at high exposure levels (perhaps in analogy to animal studies in which nasal tumours were clearly observed at levels of 10 ppm and higher).

Overall conclusion:

In animals, exposure levels of 2-3 ppm induced slight respiratory epithelial hyper/metaplasia, whereas levels of about 6 ppm and higher induced extensive hyper/metaplasia, necrosis, and severe rhinitis. An increased incidence of nasal cell carcinomas was seen from about 10 ppm, concomitant with clear cytotoxic effects.
In humans, there is an association between formaldehyde exposure and nasopharyngeal cancer This association is only found at high exposure levels (perhaps in analogy to animal studies in which nasal tumours were clearly observed at levels of 10 ppm and higher).
It can be concluded, primarily based on animal data, that cytotoxicity (cell necrosis) was seen at formaldehyde levels of about 6 ppm and higher. Cytotoxicity (cell necrosis) is considered a main risk factor for nasal cell carcinomas, as this did not occur at levels lower than 6 ppm.

7 General conclusion

The reviewers acknowledge the extensive and thorough description of the studies on formaldehyde. The critical effects have been adequately described although the reviewers have a different opinion compared to DECOS as to the concentrations at which these effects become relevant. This can be read below from the responses to the specific questions on which the evaluation has focussed:

1. An overview of the degree of irritation (eyes, nose, throat) as well as dyspnoea, cough and headache in volunteers as a function of exposure

Based on the available human volunteer studies, it can be concluded that slight eye irritation starts at levels of 1.0 ppm formaldehyde and higher. Slight nasal and throat irritation start at levels of 2.0 ppm respectively 3.0 ppm formaldehyde and higher. Exposure up to levels of 3 ppm formaldehyde did not result in dyspnoea (chest tightness/discomfort), in cough, nor in headache.

2. The optimal use of human data (including the use of dose-response data);

In line with the recommendations by the Health Council, the greatest significance was given to these data. In the DECOS evaluation generally only the data on the incidence of a predescribed effect are used, but not the severity of the effect. Taking the severity of the effect into account would have made the comparison of the available studies more accurate.

3. The 'assessment-method' as it is used by the Health Council;

In view of the extensive database on formaldehyde with a great number of adequate human studies, as well as the 'local' nature of the critical effect, the use of a minimal assessment factor, if any, is warranted. The application of an assessment factor also should be discussed in view of severity of the effects at the lower exposure levels.

4. A quantitative analysis of eye irritation as the critical effect by means of the Benchmark Dose method using the EPA software.

Based on the BMD analysis, it may be concluded that the level of 0.24 ppm that is taken as the lowest effect level is a rather conservative estimate of the LOAEL as at this exposure level it is expected that only a small part of the exposed subjects (5-20%) experience irritation characterised as 'slight' and/or 'present but not annoying' (lower limit 90% confidence interval).

5. The lowest concentration giving rise to cytotoxicity (best estimate, if possible with a confidence interval) in the airways based on human and animal data

In animals, exposure levels of 2-3 ppm induced slight respiratory epithelial hyper/metaplasia, whereas levels of about 6 ppm and higher induced extensive hyper/metaplasia, necrosis, and severe rhinitis. An increased incidence of nasal cell carcinomas was seen from about 10 ppm, concomitant with clear cytotoxic effects.

In humans, there is an association between formaldehyde exposure and nasopharyngeal cancer This association is only found at high exposure levels (perhaps in analogy to animal studies in which nasal tumours were clearly observed at levels of 10 ppm and higher).

It can be concluded, primarily based on animal data, that cytotoxicity (cell necrosis) was seen at formaldehyde levels of about 6 ppm and higher. Cytotoxicity (cell necrosis) is considered a main risk factor for nasal cell carcinomas, as this did not occur at levels lower than 6 ppm.

8 References

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App88 see DECOS list of references

Bal92 see DECOS list of references

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9 Signature

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