Formaldehyde

Health-based recommended occupational exposure limit

Gezondheidsraad **Voorzitter**
Health Council of the Netherlands

Aan de Staatssecretaris Sociale Zaken en Werkgelegenheid

Onderwerp : Aanbieding advies 'Formaldehyde'
Uw kenmerk : DGV/MBO/U-932542
Ons kenmerk : U 110/AvdB/mj/459-S38
Bijlagen : 1
Datum : 27 januari 2003

Mijnheer de staatssecretaris,

Bij brief van 3 december, nr DGV/BMO-U-932542, verzocht de Staatssecretaris van Welzijn, Volksgezondheid en Cultuur namens de Minister van Sociale Zaken en Werkgelegenheid de Gezondheidsraad om gezondheidskundige advieswaarden af te leiden ten behoeve van de bescherming van beroepsmatig aan stoffen blootgestelde personen.

In dat kader bied ik u hierbij een advies aan over formaldehyde. Dit advies is opgesteld door de Commissie WGD van de Gezondheidsraad en beoordeeld door de Beraadsgroep Gezondheid en Omgeving. Het advies is een *update* van een advies dat is verschenen in 1987.

Formaldehyde is verbinding waaraan mensen ook in de woonomgeving kunnen worden blootgesteld. Daarom is de Gezondheidsraad voornemens na te gaan of de vigerende aanbevelingen ter beperking van die blootstelling voor de algemene bevolking aanpassing behoeven op grond van deze nieuwe wetenschappelijke gegevens.

Ik heb dit advies vandaag ter kennisname toegezonden aan de Minister van Volksgezondheid, Welzijn en Sport en de Minister van Volkshuisvesting, Ruimtelijke Ordening en Milieu.

Hoogachtend,

prof. dr JA Knottnerus

Bezoekadres
Parnassusplein 5
2511 VX Den Haag
Telefoon (070) 3407520
E-mail: A.vd.burght@gr.nl

Postadres
Postbus 16052
2500 BB Den Haag
Telefax (070) 340 75 23
www.gr.nl

Formaldehyde

Health-based recommended occupational exposure limit

Dutch Expert Committee on Occupational Standards,
a Committee of the Health Council of the Netherlands,
in co-operation with the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals

to

the Minister and State Secretary of Social Affairs and Employment

No. 2003/02OSH, The Hague, 27 January 2003

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is "to advise the government and Parliament on the current level of knowledge with respect to public health issues..." (Section 21, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Housing, Spatial Planning & the Environment, Social Affairs & Employment, and Agriculture, Nature Preservation & Fisheries. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

Most Health Council reports are prepared by multidisciplinary committees of Dutch or, sometimes, foreign experts, appointed in a personal capacity. The reports are available to the public.

This report can be downloaded from www.gr.nl

Preferred citation:
Health Council of the Netherlands: Dutch Expert Committee on Occupational Standards. Formaldehyde; Health-based recommended occupational exposure limit. The Hague: Health Council of the Netherlands, 2003; publication no. 2003/02OSH.

ISBN: 90-5549-469-0

Contents

Samenvatting en advieswaarde

1 Vraagstelling

Op verzoek van de minister van Sociale Zaken en Werkgelegenheid beveelt de Gezondheidsraad gezondheidskundige advieswaarden aan voor beroepsmatige blootstelling aan toxische stoffen in de lucht op de werkplek. Deze aanbevelingen worden opgesteld door de Commissie WGD van de Raad, de opvolgster van de Werkgroep van Deskundigen. Zij vormen de eerste stap in een drietrapsprocedure die moet leiden tot wettelijke grenswaarden (MAC-waarden).

Dit rapport is opgesteld in samenwerking met de 'Nordic Expert Group'. In het voorliggende rapport bespreekt de commissie de gevolgen van blootstelling aan formaldehyde in de lucht op de werkplek, en beveelt zij een gezondheidskundige advieswaarde aan. De conclusies van de commissie zijn gebaseerd op wetenschappelijke publicaties die vóór oktober 2002 zijn verschenen.

2 Fysische en chemische eigenschappen

Formaldehyde is bij kamertemperatuur een kleurloos gas. Het is brandbaar, reactief en polymeriseert gemakkelijk bij deze temperatuur. Onder normale druk, kan formaldehyde met zuurstof en lucht een explosief mengsel vormen. Formaldehyde is oplosbaar in water.

Het molecuulgewicht van formaldehyde is 30.03, en het smelt- en kookpunt is respectievelijk -92^{0}C en -20^{0}C.

Formaldehyde wordt ondermeer gebruikt als uitgangsstof bij chemische reacties en is een intermediair voor de synthese van vele uiteenlopende producten. Daarnaast vindt het medische toepassing als desinfectant.

3 Monitoring

De meest gebruikte monitoringsmethoden zijn gebaseerd op fotometrische bepalingen. De keuze voor de methode hangt voornamelijk af van het medium waarin formaldehyde moet worden bepaald. Formaldehyde in de lucht kan worden bepaald door middel van passieve diffusie. Biologische monitorings methoden zijn niet goed ontwikkeld maar beide commissies zien hier ook geen noodzaak voor.

4 Huidige grenswaarden

De huidige bestuurlijke MAC-waarde voor formaldehyde in Nederland is 1.5 mg/m^3 (8 uurs gemiddelde) en een STEL van 3.0 mg/m^3 (15 minuten).

De Amerikaanse ACGIH heeft een ceilingwaarde vastgesteld van 0.37 mg/m^3 (0.3 ppm) en formaldehyde geclassificeerd als een ‘ verdacht kankerverwekkende stof voor de mens’. De Duitse DFG heeft een MAK-waarde van 0.37 mg/m^3 (8 uurs gemiddelde) voorgesteld en formaldehyde geclassificeerd in carcinogeniteits groep 4, wat betekent dat de genotoxiciteit geen of alleen een ondergeschikte rol speelt. Groot Brittanie heeft een grenswaarde (MEL) van 2.5 mg/m^3 (8-uurs gemiddelde).

Tenslotte heeft de Europese Unie formaldehyde geclassificeerd in categorie 3, verdacht kankerverwekkend voor de mens.

5 Toxicokinetiek

Onder normale omstandigheden wordt ingeademde formaldehyde geabsorbeerd in de bovenste luchtwegen. Na absorptie van ^{14}C-formaldehyde is te zien dat de radioactiviteit zich verspreid over verschillende organen en weefsels in het lichaam. De hoogste radioactiviteit wordt gevonden in de slokdarm, gevolgd door de nieren, lever, darmen en longen.

Naar schatting wordt 319 mg/cm^2 per uur opgenomen door de huid na blootstelling aan geconcentreerde oplossing formaline.

Formaldehyde is een fysiologisch (normaal) stofwisselingsproduct dat in mens en dier kan voorkomen en snel wordt omgezet in formate, welke wordt afgebroken via de normale metabole wegen. Via uitademing en via de nieren wordt formaldehyde uiteindelijk door het lichaam uitgescheiden.

6 Effecten

De doelorganen van formaldehyde dampen zijn de ogen, neus en keel.

Een veel voorkomend effect na kortdurende blootstelling aan formaldehyde in mensen is irritatie van de zintuigen, bij lage concentratie waargenomen in de ogen (waarna ook de geur waar te nemen is) en bij iets hogere concentraties ook irritatie van de neus en keel veroorzaakt. Dit uit zich in onwelzijn, tranen, niezen, hoesten, misselijkheid en kortademigheid. Door de meeste mensen wordt bij een kortdurende blootstelling aan 1-1.2 mg/m^3 formaldehyde alleen lichte irritatie van de zintuigen waargenomen.

Ook wanneer mensen gedurende langere tijd aan lagere concentraties formaldehyde (0.26-0.29 mg/m^3) worden blootgesteld, treedt irritatie van de zintuigen op in een aanzienlijk deel van deze personen. In een (niet goed beschreven) studie, gaf 19% van de mensen die waren blootgesteld aan 0.29 mg/m^3 formaldehyde nog irritatie van de ogen aan. In een andere studie werden echter geen effecten gevonden op de longfunctie van mensen die waren blootgesteld aan 3.6 mg/m^3.

In dieren is irritatie van de ogen, neus, keel en longen waargenomen bij blootstellingen hoger dan 2.4 mg/m^3. In muizen is de 10-min RD_{50} (die concentratie die correspondeert met 50% afname van de ademhalingsfrequentie) voor formaldehyde 3.6 +/- 0.34 mg/m^3.

Er zijn geen duidelijke aanwijzingen dat formaldehyde in staat is de luchtwegen te sensibiliseren. Huidsensibilisatie wordt veroorzaakt door direct contact van de huid met formaldehydeoplossingen van meer dan 2% ($^v/_v$). Er wordt geschat dat het percentage formaldehyde geïnduceerde contact dermatitis dat voorkomt in de algemene bevolking 3 tot 6% is.

Het is overduidelijk dat hoge concentraties formaldehyde (12 mg/m^3) in ratten neus kanker kan veroorzaken, maar in de mens zijn veel minder duidelijke aanwijzingen dat formaldehyde kanker aan de ademhalingswegen veroorzaakt. Er zijn drie verschillende meta-analyses naar de relatie tussen formaldehyde blootstelling en kanker aan de luchtwegen uitgevoerd. Twee daarvan laten een duidelijke relatie zien tussen blootstelling aan formaldehyde en nasopharyngeal (neuskeelholte) kanker (maar niet met kanker in de neus). In beide meta-analyses hebben de auteurs echter niet gecorrigeerd voor het feit dat er een onderrapportage te verwachten is voor studies met negatieve resultaten. In de derde, meest recente, meta-analyse is deze correctie wel uitgevoerd. De onderzoekers concludeerden dat de humane gegevens een relatie tussen blootstelling aan formaldehyde en nasopharyngeal kanker niet onderbouwen. De commissie is het met deze conclusie eens en vindt tevens dat op basis van de

beschikbare humane gegevens niet geconcludeerd mag worden dat er een risico op kanker (neus en long) bestaat bij blootstellingen lager dan 0.3 mg/m^3 (een concentratie waarbij nog net irritatie wordt waargenomen).

Na kortdurende blootstelling aan formaldehyde kan bij dieren schade (van cytotoxiciteit tot proliferatie) aan het neus- en ademhalingsepitheel optreden. De histopathologische schade varieert van onder meer lichte hyperplasie bij lage blootstellingen van 2.4-3.6 mg/m^3 tot ernstige rhinitis, necrose en metaplasie bij hogere blootstellingen (vanaf 7.2 mg/m^3). De NOAEL's (de concentraties waarbij geen effecten zijn waargenomen in een studie) na kortdurende blootstelling variëren van 1.2 tot 2.4 mg/m^3.

Ook na langdurigere blootstellingen aan formaldehyde wordt in dieren schade aan het neusepitheel gevonden (ontsteking, celdood etc.). Bij lage blootstellingen (2.4 mg/m^3) wordt onder meer minimale hyperplasie en metaplasie van het neus- en ademhalingsepitheel gevonden en bij hogere blootstellingen (7.2 mg/m^3) kan ondermeer rhinitis en celdood optreden. Bij concentraties hoger dan 12 mg/m^3 worden hoge incidenties squamous-cel carcinomen in ratten gevonden. In de meeste langetermijnstudies zijn NOAELs van 1.2-2.4 mg/m^3 waargenomen. In één studie met ratten is echter een LOAEL van 2.4 mg/m^3, terwijl in een andere studie de LOAEL 0.36 mg/m^3 was.

Er zijn alleen zeer summiere gegevens bekend over de genotoxiciteit van formaldehyde in mensen. De genotoxiciteit van formaldehyde is echter uitgebreid aangetoond in dierexperimenten, zowel *in vivo* als *in vitro*. Chromosoom aberraties zijn gevonden in longen van ratten en micronuclei in maagdarm cellen na inhalatoire en orale blootstelling. Inademing van formaldehyde kan leiden tot de formatie van DNA-eiwit cross-links in het neus-epitheel van ratten en apen. In V79-hamster cellen induceert formaldehyde DNA-eiwit crosslinks, sister-chromids exchange (SCE) en micronuclei, maar geen genmutaties, bij concentraties die ook cytotoxiciteit veroorzaken. Dit suggereert dat de geinduceerde DNA-eiwit crosslinks gerelateerd zijn aan cytotoxiciteit en clastogeniteit. Ook wordt gesuggereerd dat ontsteking en proliferatie van de neus bijdragen aan het genetische veranderingen via verschillende mechanismen (o.a. via reactieve zuurstof species, veranderingen in nucleotide pool, vorming van vrije radicalen etc.).

De commissie is van mening dat vele gegevens met betrekking tot de carcinogeniteit (van de neus) van formaldehyde een associatie suggereren tussen de cytotoxiciteit, genotoxiciteit en carcinogeniteit. De steile (niet lineaire) dosis-effect relatie voor neustumoren is waarschijnlijk het gevolg van bij lage concentraties effectief werkende afweer en herstel mechanismen in de neus. Als gevolg hiervan treedt alleen bij hoge concentraties cel en weefsel schade op met tumoren als resultaat.

Dit betekent ook dat formaldehyde bij blootstellingen die niet leiden tot weefselschade niet als een volledig carcinogeen werkt.

Tot slot zijn in dierexperimenten geen aanwijzingen gevonden voor reproductietoxische effecten.

7 Evaluatie*

Het is duidelijk dat de belangrijkste effecten in dieren na langdurige blootstelling aan formaldehyde irritatie van de zintuigen, en door cytotoxiciteit geïnduceerde hyper- en metaplasie van het neus en ademhalingsepitheel gevold door neustumoren zijn.

Studies met vrijwilligers laten een grote variatie zien in individuele gevoeligheid voor irritatie van de luchtwegen. Bij de meeste mensen wordt geen irritatie van de zintuigen gevonden bij concentraties lager dan 1.2 mg/m^3 (1 ppm). Bij lagere concentraties kan echter bij een aanzienlijke groep mensen nog irritatie optreden. In een niet goed beschreven studie is in 19% van de onderzochte mensen na een blootstelling aan 0.29 mg/m^3 (0.24 ppm) nog oog irritatie waargenomen. In dieren wordt irritatie van ogen, neus, keel en longen waargenomen bij concentraties hoger dan 2.4 mg/m^3 (2 ppm).

De Commissie WGD concludeert op basis van alle studies met betrekking tot de irritatie, dat 0.3 mg/m^3 als een LOAEL (laagst waargenomen nadelig effect nivo) beschouwd moet worden, waarbij nog irritatie van de zintuigen kan optreden bij een deel van de blootgestelde werknemers. Als alleen naar de gegevens over irritatie gekeken zou worden, resulteert dit volgens de commissie in een advieswaarde van 0.15 mg/m^3 (0.12 ppm), waarbij de extrapolatiefactor van 2 rekening houdt met het feit dat (1) het kritische effect een lokaal effect is, (2) het percentage mensen dat bij 0.3 mg/m^3 last heeft van irritatie laag is (19%) en wellicht niet veel afwijkt van de achtergrond incidentie en (3) bij lichte irritatie gewenning kan optreden.

Vervolgens heeft de Commissie WGD beoordeeld of een advieswaarde van 0.15 mg/m^3 laag genoeg is om werknemers te beschermen tegen schade aan het neus- en ademhalingsepitheel, en dus tegen een potentieel risico op neus tumoren.

In ratten worden neus carcinomen alleen gevonden na een blootstelling aan hoge, cytotoxische formaldehyde concentraties. Onderzoek heeft duidelijk aangetoond dat voor ontstaan van neustumoren het optreden van celbeschadiging, gevolgd door hyper- en metaplasie van het neus-ademhalingsepitheel van cruciaal belang is. Dit gegeven is een belangrijk uitgangspunt voor de humane risicoschatting geweest. Beide commissie vonden aannemelijk dat mensen hetzelfde op formaldehyde blootstelling reageren als dieren. Als blootstelling aan formaldehyde in mensen weefselschade veroorzaakt, zal

* Voor de aanbeveling van de advieswaarde is alleen de Commissie WGD (en dus niet de Nordic Expert Group) verantwoordelijk.

bij de carcinogeniteit waarschijnlijk ook de cytotoxiciteit een belangrijke rol in het mechanisme spelen. Als er in mensen geen schade aan het ademhalingsorgaan optreedt bij lage blootstellingsconcentraties, gaat de commissie ervan uit dat het risico op kanker verwaarloosbaar klein is.

Beide commissies (Commissie WGD en NEG) concluderen dat in een groot deel van de inhalatie studies met dieren, na zowel kortdurende als langdurige blootstelling, de NOAEL varieert van 1.2 tot 2.4 mg/m^3. In een klein aantal studies worden nog histopathologische veranderingen van het neus- en ademhalingsepitheel gevonden bij concentraties van 0.36-2.4 mg/m^3 formaldehyde.

Drie meta-analyses laten verschillende resultaten zien. Twee bevestigen een significante relatie tussen blootstelling aan formaldehyde en neus- keelholte kanker (maar niet de relatie tussen blootstelling aan formaldehyde en neustumoren). Beide meta-analyses hebben echter niet gecorrigeerd voor de onderrapportage van studies met negatieve resultaten. Beide commissie zijn van mening dat dit een overschatting van het risico op neus- keelholte kanker tot gevolg heeft. In de derde, meest recente meta-analyse heeft deze correctie wel plaatsgevonden; De auteurs concludeerden dat er geen aanwijzingen waren die de relatie tussen neus- keelholtekanker en blootstelling aan formaldehyde onderbouwen. Beide commissies zijn het met deze conclusie eens en concluderen dan ook op basis van de huidige epidemiologische gegevens dat blootstelling aan formaldehyde bij de lage concentraties (0.3 mg/m^3) geen verhoogd risico op kanker met zich mee brengt.

Samenvattend is de Commissie WGD van mening dat de voorgestelde advieswaarde (0.15 mg/m^3, bij een achturige werkdag) op basis van het voorkomen van irritatie, laag genoeg is om werknemers ook te beschermen tegen schade aan het neus en ademhalingsepitheel en daarmee samenhangend tegen het risico op neustumoren.

Tevens is de Commissie WGD van mening dat de humane studies naar de gevolgen van kortdurende blootstelling aan formaldehyde bevestigen dat bij concentraties van 1-1.2 mg/m^3 nog (lichte) irritatie van de ogen kan optreden. Daarom adviseert de Commissie WGD een advieswaarde van 0.5 mg/m^3, gedurende 15 minuten (STEL).

8 Gezondheidskundige advieswaarde

De Commissie WGD van de Gezondheidsraad adviseert een gezondheidskundige advieswaarde van 0.15 mg/m^3 (0.12 ppm) in de lucht, gemiddeld over een achturige werkdag en een advieswaarde (STEL) van 0.5 mg/m^3 (0.42 ppm) in de lucht, gemiddeld over 15 minuten.

Executive summary

1 Scope

At the request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands recommends health-based occupational exposure limits for the concentration of toxic substances in air at the workplace. These recommendations are made by the Council's Dutch Expert Committee on Occupational Standards (DECOS). They constitute the first step in a three-step procedure that leads to legally binding limit values.

The present report is a co-production of DECOS and the Nordic Expert Group. In the report the committees discuss the consequences of occupational exposure to formaldehyde. In conformity with its mission, DECOS had evaluated the data in order to derive a health-based occupational exposure limit. This assessment is an update of previous documents published by DECOS in 1981 (RA 4/81) and 1987 (RA 3/87).

The committees' conclusions are based on scientific publications prior to October 2002.

2 Physical and chemical properties

Formaldehyde is a colourless gas at normal temperature and pressure. It is flammable, reactive and readily polymerizes at room temperature. It forms explosive mixtures with air and oxygen at atmospheric pressure. Formaldehyde is present in aqueous solutions

as a hydrate and tends to polymerize. Under atmospheric conditions, formaldehyde is readily photo-oxidized in sunlight to carbon dioxide.

The relative molecular mass of formaldehyde is 30.03, the boiling point is -20^{0}C and the melting point -92^{0}C. The compound is miscible in water.

Formaldehyde is used as a raw material in chemical reactions, is an intermediate in the manufacture of numerous products and has a wide medical application as a disinfectant or as a preservative.

3 Monitoring

The most widely used methods for the determination of formaldehyde concentrations are based on photometric measurements. The type of sampling depends on the medium in which formaldehyde is to be determined. Formaldehyde in air may be collected in an absorbing medium by diffusion (passive sampling). For active sampling, aqueous solutions and solutions containing sulfite, 3-methyl-2-benzothiazolene hydrazine (MBTH), chromotropic acid or 2,4-dinitrophenylhydrazine (DNPH) are generally used for absorption.

Biological monitoring methods for exposure to formaldehyde have not been assessed in any detail. Given the knowledge of its critical effects and the target organs, the committees see no need for biological monitoring.

4 Current limit values

The current occupational exposure limit for formaldehyde in the Netherlands is 1.5 mg/m^3 (1 ppm), TWA-8 h and 3.0 mg/m^3 (1,5 ppm), TWA-15 min. This limit is still not legally binding.

The American Conference of Governmental Industrial Hygienists (ACGIH) has set a Threshold Limit Value of 0.37 mg/m^3 (0.3 ppm), as a ceiling and classified formaldehyde as a ‘suspected human carcinogen’, Group A_2. The Deutsche Forschungsgemeinschaft endorsed a MAK value of 0.37 mg/m^3 (0.3 ppm) as an 8 hour time-weighted-average (TWA-8 h), with a notation as a sensitizing agent, and classified formaldehyde into carcinogen category 4 (genotoxicity playing no or at most a minor part).

The United Kingdom adheres to an MEL of 2.5 mg/m^3 (2 ppm), TWA-8 h.

The European Union has classified the carcinogenic effects of formaldehyde in category 3.

5 Toxicokinetics

Under normal conditions, inhaled formaldehyde is absorbed in the upper respiratory tract. After absorption of ^{14}C-formaldehyde, radio-activity is distributed to various organs and tissues with the highest concentrations found in the oesophagus, followed by the kidneys, liver, intestine and lungs. Retention in the nasal passages of the rat was estimated at 93% of the inhaled amount, regardless of airborne concentrations. It was estimated that absorption of concentrated solutions of formalin through the skin amounted to 319 mg/cm^2 per hour.

Formaldehyde is a normal metabolite in mammalian systems and it is rapidly metabolized to formate, which is partially incorporated via normal metabolic pathways into the one-carbon pool of the body or further oxidized to carbon dioxide. There are two pathways of final elimination: via exhalation and via the kidneys.

6 Effects

The target organs of formaldehyde vapour are the eyes, nose and throat.

The predominant effect of short-term formaldehyde exposure in humans is sensory irritation, first experienced in the eyes, followed by perception of the odour and then irritation of the nose and throat accompanied by discomfort, lachrymation, sneezing, coughing, nausea and dyspnoea. For most individuals sensory irritation does only slightly occur until an (short-term) exposure concentration of 1.2 mg/m^3 (1 ppm).

However, at lower exposure levels (0.26-0.29 mg/m^3 (0.22-0.24 ppm) for a longer time period sensory irritation may still occur in a substantial percentage of exposed persons. In one, not well documented, study, 19% of the exposed subjects still reported eye irritation at an exposure concentration of 0.29 mg/m^3 (0.24 ppm). No changes in pulmonary function have been found in humans exposed to formaldehyde concentrations up to 3.6 mg/m^3 (3 ppm).

In experimental animals, irritation of eyes, nose, throat and lungs was observed at exposure concentrations higher than 2.4 mg/m^3 (2.0 ppm). In mice a 10-min RD_{50} (the concentration associated with a 50% decrease in respiratory rate) for formaldehyde of 3.6 ± 0.34 mg/m^3 (3.0 ppm ± 0.28 ppm) has been reported.

There is no convincing evidence of formaldehyde being able to sensitize the respiratory tract. Skin sensitization is induced by direct skin contact with formaldehyde solutions in concentrations higher than 2%. Formaldehyde-induced allergic contact dermatitis has been estimated to occur in 3 to 6% of the population.

There is overwhelming evidence that high concentrations of formaldehyde vapour (12 mg/m^3 (10 ppm) or higher) can induce nasal cancer in rats but there is no convincing evidence for respiratory tract cancer risk in humans.

Three different meta-analyses of epidemiological studies have shown inconsistent results. In two of them, a relationship between exposure to formaldehyde and the occurrence of nasopharyngeal cancer was observed, while an association with nasal cancer was ambiguous. In these two meta-analyses, the authors did not correct for the unreported studies in which no cases of nasal cancers were found. This must have led to an overestimation of the overall relative risk for nasopharyngeal cancer. In a third, more recently published meta-analysis, this correction for the underreporting was made. In addition, the exposure potential for the jobs included in the analysis was evaluated. The authors concluded that the epidemiological studies do not support a causal relationship between formaldehyde exposure and nasopharyngeal cancer. The committees endorse this conclusion and further conclude that the currently available epidemiological database does not provide support for a nasal cancer risk at exposure levels lower than 0.3 mg/m^3 (LOAEL for sensory irritation). Also from the epidemiological studies it seems unlikely that exposure to formaldehyde affects lung cancer risk.

The effects of short-term exposure to airborne formaldehyde in experimental animals are cytotoxic damage to and regenerative proliferation of the nasal respiratory epithelium. The histopathological changes range from slight hyperplasia and squamous-cell metaplasia of the ciliated and non-ciliated respiratory epithelium in specific areas (found at low effective exposure concentrations, ie. 2.4 to 3.6 mg/m^3 (2 to 3 ppm)) to severe rhinitis, necrosis and extensive hyperplasia and metaplasia of major portions of the nasal respiratory epithelium (found at exposure concentrations of about 7.2 mg/m^3 (6 ppm) and higher. Substantial increases in nasal epithelial cell turnover rates occur in rats after exposure to concentrations of 7.2 mg/m^3 (6 ppm). Most NOAELs in these short-term studies were found between 1.2 and 2.4 mg/m^3 (1 or 2 ppm). In all studies with a NOAEL of 1.2 mg/m^3 (1 ppm) the LOAEL was higher than 2.4 mg/m^3 (2 ppm). This might indicate that also in these studies 2.4 mg/m^3 might have been a NOAEL if indeed this exposure level would have been included in these experiments. However, (slightly and transiently) increased cell turnover rates have occasionally been found at levels between 0.6 to 2.4 mg/m^3 (0.5 to 2 ppm).

Effects after long-term inhalation exposure to formaldehyde in experimental animals include inflammatory, degenerative and regenerative changes of the nasal mucosa and squamous-cell carcinomas of the nasal respiratory epithelium. The non-neoplastic nasal changes range from a minimal degree of hyperplasia and squamous-cell metaplasia of the nasal respiratory epithelium (occasionally seen at concentrations of approximately 2.4 mg/m^3 (2 ppm) or lower) to rhinitis, necrosis and

extensive restorative hyperplasia and metaplasia of the nasal respiratory epithelium invariably seen at concentrations of about 7.2 mg/m^3 (6 ppm) and higher. High incidences of squamous-cell carcinomas have been found in rats at exposure levels of 12 mg/m^3 (10 ppm) or higher. In most long-term studies, a NOAEL of 1.2 or 2.4 mg/m^3 has been reported. However, in one long-term study in rats 2.4 mg/m^3 (2 ppm) appeared to be a LOAEL and in another long-term rat study a LOAEL as low as 0.36 mg/m^3 (0.3 ppm) was reported.

No adequate data were available on genetic effects of formaldehyde in humans. Formaldehyde is comprehensively genotoxic in a variety of experimental systems, ranging from bacteria to rodents *in vivo*. Formaldehyde given by inhalation or gavage to rats induced chromosomal aberrations in lung cells, micronuclei in gastro-intestinal tract cells and sperm-head anomalies. Inhalation of formaldehyde leads to formation of DNA-protein cross-links in the nasal respiratory epithelium of rats and monkeys. The formation of DNA-protein cross-links is a sublinear function of the formaldehyde concentration in inhaled air from 0.86 to 18.4 mg/m^3 (0.7-15 ppm). There is no detectable accumulation of DNA-protein cross-links during repeated exposures. In V79 Chinese hamster cells, formaldehyde induced DNA-protein crosslinks, sister-chromatid exchanges and micronuclei, but no gene mutations, in concentrations similar to those inducing cytotoxicity, suggesting that formaldehyde-induced DNA-protein crosslinks are related to cytotoxicity and clastogenicity. It has been suggested that the nasal inflammation and proliferation induced by formaldehyde exposure may contribute to the induction of genetic alterations through a variety of mechanisms including generation of reactive oxygen species, alterations in nucleotide pools, free radical formation, and clonal expansion with further mutation of genetically altered cells.

With respect to the mechanism underlying the nasal carcinogenicity of formaldehyde in rats, there is a large body of data suggesting an association between the cytotoxic, genotoxic and carcinogenic effects of formaldehyde. The steep non-linear dose-response curve for nasal tumours — indicating a more than proportionate decrease in carcinoma incidence at low concentrations — is most probably due to the fact that defence mechanisms of the nose (mucociliary clearance, detoxification by dehydrogenase, DNA repair) are very effective at low concentrations, but can be overwhelmed and inactivated at high concentrations; consequently, cell and tissue damage and finally tumours occur at high concentrations only. This also means that formaldehyde in concentrations not leading to tissue damage most probably cannot act as a complete carcinogen (causing initiation, promotion and progression).

In several animal studies, inhalation of formaldehyde was not found to affect reproduction.

7 Hazard assessment*

From the toxicological data base, it was evident that the effects of concern of formaldehyde are sensory irritation and cytotoxicity-induced regenerative hyperplasia and metaplasia of the nasal respiratory epithelium accompanied by nasal carcinomas in rats after long-term exposure to high cytotoxic concentrations.

Controlled studies in volunteers revealed a wide variation in individual susceptibility to sensory irritation from formaldehyde. For most persons sensory irritation (eye, nose and/or throat) did not occur until an exposure concentration of at least 1.2 mg/m^3 (1.0 ppm). However, at lower exposure levels sensory irritation may still occur in a substantial percentage of exposed individuals, and in one, not well documented study 19% of the exposed subjects reported eye irritation at an exposure concentration of 0.29 mg/m^3 (0.24 ppm). In experimental animals, irritation of eyes, nose, throat and lungs was observed at exposure concentrations greater than 2.4 mg/m^3 (2.0 ppm).

Overall, weighing the total body of data, both committees estimated that 0.3 mg/m^3 (0.25 ppm) formaldehyde is the lowest obeserved adverse effect level (LOAEL) at which sensory irritation may occur in a low but significant percentage of exposed workers. Therefore, based on sensory irritation only, DECOS would recommend a HBR-OEL for formaldehyde of 0.15 mg/m^3 (0.12 ppm), providing a margin of safety (of 2) which DECOS considers large enough to prevent significant sensory irritation in workers, taking into account that (I) the critical effect (sensory irritation) is a local effect, (II) the incidence of the effect at 0.3 mg/m^3 is low (19%) and may not be different from the background incidence in controls and (III) minimal sensory irritation may rapidly subside due to accommodation.

Then, the DECOS discussed whether an exposure limit of 0.15 mg/m^3 (0.12 ppm), is low enough to protect workers against cytotoxic-induced hyperproliferation of the nasal respiratory epithelium, and consequently also against the potential risk of nasal cancer.

Nasal carcinomas in rats have only been found after exposure to high, cytotoxic concentrations causing rhinitis, necrosis and regenerative hyperplasia and squamous metaplasia of the nasal respiratory epithelium. The crucial role of tissue damage followed by hyperplasia and metaplasia of the nasal respiratory epithelium in formaldehyde carcinogenesis has been demonstrated in a convincing way, has meanwhile been widely recognized, and has been included in human cancer risk

* For the recommendation of a health-based occupational exposure limit only DECOS takes responsibility.

assessment of formaldehyde. The committees found it reasonable to conclude that the response of the respiratory tract to formaldehyde will be qualitatively similar in rats and humans. If in humans exposure of formaldehyde is accompanied by recurrent tissue damage at the site of contact, formaldehyde may be assumed to have carcinogenic potential in man via mechanisms of cytotoxicity. Correspondingly, if the respiratory tract tissue is not recurrently injured, exposure of humans to relatively low, non-cytotoxic levels of formaldehyde can be assumed to be associated with a negligible cancer risk.

Both committees (DECOS and NEG) observed that the majority of short- and long-term inhalation studies with formaldehyde in experimental animals reveals a NOAEL of 1.2 or 2.4 mg/m^3 (1 or 2 ppm). However, in a few studies slight histopathological changes of the nasal respiratory epithelium were observed at levels ranging from 0.36 to 2.4 mg/m^3 (0.3 to 2 ppm) formaldehyde.

Three meta-analyses of human epidemiological studies have shown inconsistent results. In two of them a significant relation between exposure to formaldehyde and nasopharyngeal cancer risk was observed. The association between formaldehyde exposure and nasal cancer was ambiguous. However, according to the committees, in these meta-analyses the authors did not correct for the unreported studies in which no cases of nasal cancers were found. This must have led to an overestimation of the overall relative risk of nasopharyngeal cancer. In the third, more recent, published meta-analysis, a correction was made for underreporting, and the authors concluded that there was no support for a causal relation between formaldehyde exposure and nasopharyngeal cancer. The committees endorsed this conclusion and concluded that the currently available epidemiological database on formaldehyde does not provide evidence for a respiratory tract cancer risk at exposure levels lower than 0.3 mg/m^3 (LOAEL for sensory irritation).

In conclusion, DECOS is of the opinion that an health based occupational exposure limit (HBR-OEL) of 0.15 mg/m^3 (0.12 ppm) formaldehyde is low enough to protect workers against nasal tissue damage, and as a consequence, also against the potential risk of nasal cancer.

To avoid peak exposures possibly entailing cytotoxicity-induced hyperproliferation and metaplasia of the nasal respiratory epithelium, the DECOS recommends a Short Term Exposure Limit (STEL). Data from human studies indicate that short term exposure to formaldehyde at concentrations up to approximately 1.0-1.2 mg/m^3 leads to slight irritation of the eyes only. Therefore, the DECOS recommends a STEL of 0.5 mg/m^3 (twa 15 minutes) which is considered low enough to avoid any significant sensory irritation, and thus nasal toxicity as well.

8 Recommended occupational exposure limit

DECOS recommends a health-based occupational exposure limit of 0.15 mg/m^3 (0.12 ppm) formaldehyde in air, TWA-8 h, and a short term exposure limit, 15 min TWA, of 0.5 mg/m^3 (0.42 ppm).

Chapter 1

Scope

1.1 Background

In the Netherlands occupational exposure limits for chemical substances are set using a three-step procedure. In the first step a scientific evaluation of the data on the toxicity of the substance is made by the Dutch Expert Committee on Occupational Standards (DECOS), a committee of the Health Council of the Netherlands, on request of the minister of Social Affairs and Employment (Annex A). This evaluation should lead to a health-based recommended exposure limit for the concentration in air of the substance. Such an exposure limit cannot be derived if sufficient data are not available or if the toxic action cannot be evaluated using a threshold model. In the latter case an exposure-response relationship is recommended for use in regulatory standard setting.

In the next phase of the three-step procedure the Social and Economic Council advises the minister on the feasibility of using the health-based value as a regulatory Maximal Accepted Concentration (MAC) or recommends a different MAC-value. In the final step of the procedure the State Secretary of the Ministry of Social Affairs and Employment sets the official exposure limit.

1.2 Committee and method of work

This document is a co-production of DECOS and the Nordic Expert Group (NEG). It is a result of an agreement between both groups to prepare jointly criteria documents

which can be used by the regulatory authorities in the Netherlands and in the Nordic countries. The members of DECOS and the NEG are listed in annex B.

The draft document has been prepared by dr AAE Wibowo, from the Coronel Institute, Academic Medical Centre, University of Amsterdam, by contract with the Ministry of Social Affairs and Employment, and was first reviewed by DECOS and thereafter by NEG.

In 1997 and in 2001, the president of the Health Council of the Netherlands released a draft of the report for public review. The individuals and organisations that commented on the second draft are listed in Annex C. The committees have taken these comments into account in deciding on the final version of the report.

1.3 Data

This document is an update of two previous documents published by DECOS in, respectively, 1981 (WGD RA 4/81) and 1987 (WGD RA 3/87).

Starting point in searching literature on the health effects to formaldehyde were the following reviews:

- IPCS International Programme on Chemical Safety, World Health Organisation. Environmental health criteria 89, Formaldehyde. Geneva, 1989
- European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC). Technical Report no 65, Formaldehyde and human cancer risk. May 1995, Brussels
- International Agency for Research on Cancer (IARC). Monographs on the evaluation of carcinogenic risks to humans. Wood dust and formaldehyde, Volume 62, 1995, Lyon
- Conaway, Whysner, Verna and Williams. Formaldehyde mechanistic data and risk assessment: endogenous protection from DNA adduct formation. Pharmacol Ther, 1996 (Con96)
- Paustenbach D., Alarie Y, Kulle T *et al*. A recommended occupational exposure limit for formaldehyde based on irritation. J Toxicol Environ Health 1997; 50: 217 - 263.

Unless otherwise indicated, data were derived from these documents. Data considered to be critical were evaluated by reviewing the original publications. In addition, literature was retrieved from the on-line data bases Medline (starting at 1966) and Mbase (from 1988 onwards) prior to January 1997, and from NIOSH-TIC and HSE-line from 1996 backwards.

In addition, Toxline and Medline were searched for studies published between January 1997 and October 1999. Those studies that were considered relevant to the

conclusion of the committee were included in the document. A final search was performed in October 2002. Studies published between October 1999 and October 2002 were no reason for the committee to adjust her recommendations and therefore not included in this document.

Chapter 2

Previous DECOS reports

In 1981, DECOS concluded that a health-based occupational exposure limit for formaldehyde of 0.2 ppm (0.24 mg/m^3), 8 h TWA, would protect occupationally exposed persons against cytotoxic effects on the nasal mucosa. The committee judged formaldehyde to be a proven genotoxic carcinogen in experimental animals and was of the opinion that the induction of cancer in humans by formaldehyde exposure could not be excluded. Based on the then available data, DECOS estimated, using linear extrapolation, that exposure to 0.1 mg/m^3 formaldehyde for 8 hours per day, 5 days per week for 40 years and a lifespan of 75 years, was associated with a cancer risk of maximally 1 in 40,000. Exposure to 0.5 mg/m^3 formaldehyde during the same timespan was calculated to be associated with a cancer risk of maximally 1 in 10,000.

In its 1987 review of formaldehyde, DECOS concluded that at concentrations not exceeding 1.2 mg/m^3 (1 ppm), 15 min TWA, formaldehyde exposure was not associated with an increased nasal cancer risk. The role of cytotoxicity for the induction of nasal cancers in rats was taken into account. At subcytotoxic levels the risk of induction of nasal cancer appears to be negligibly small. Therefore, the conclusions in the 1981 report with respect to the exposure-response relationship for cancer induction were withdrawn. The committee recommended an occupational exposure limit of 1.2 mg/m^3 (1 ppm), 15 min TWA.

Chapter 3

Identity, properties and monitoring

3.1 Identity and chemical properties

Chemical formula:	CH_2O (HCHO)
Identification numbers:	
CAS registry number:	50-00-0
RTECS registry number:	LP 8925000
UN number:	1198, 2209, 2213
EC numbers:	605-001- 01 (sol 5% to < 25%) 605-001- 02 (sol 1% to < 5%) 605-001-005 (sol ³ 25%)
IUPAC name:	methanal
Common synonyms:	formaldehyde, methanal, methylene oxide, oxymethylene, methylaldehyde, oxomethane
Common names for solutions of formaldehyde:	formalin, formol

3.2 Physical characteristics

(IPCS/WHO, 1989, 1991; CKB97)

Relative molecular mass:	30.03
Boiling point:	-20°C
Melting point:	-92°C
Relative density (water=1):	0.8
Solubility in water:	miscible
Relative vapour density (air = 1):	1.08
Flash point:	flammable gas, 60 °C
Auto-ignition temperature:	300°C
Explosive limits:	7-73 vol% in air
Vapour pressure:	0.2 kPa at 20 °C, 101.3 kPa at -19°C, 52.6 kPa at -33°C
Conversion factors: (25°C, 1066 m bar)	1 ppm = 1.2 mg/m^3 1 mg/m^3 = 0.83 ppm

Formaldehyde is a colourless gas at room temperature and pressure. It is flammable, reactive and readily polymerizes at room temperature. It forms explosive mixtures with air and oxygen at atmospheric pressure.

Formaldehyde is present in aqueous solutions as a hydrate and tends to polymerize. At room temperature and a formaldehyde content of 30% and more, the polymers precipitate and render the solution turbid. Under atmospheric conditions, formaldehyde is readily photo-oxidized in sunlight to carbon dioxide.

3.3 Validated analytical methods

3.3.1 Environmental exposure monitoring

The most widely used methods for the determination of formaldehyde are based on photometric measurements. The sampling method depends on the medium in which formaldehyde is to be determined.

The IPCS/WHO (IPC89) reported a number of different methods for determination of formaldehyde, using spectrophotometric, colorimetric, fluorometric, high performance liquid chromatography (HPLC), polarographic, gas chromatographic, infrared, and visual analytical methods. On each method the analytical sensitivity was reported.

Formaldehyde in air may be collected in an absorbing medium by diffusion (passive sampling). Aqueous or 50% 1-propanol solutions are also used for formaldehyde sampling. For active sampling, aqueous solutions and solutions containing sulfite, 3-methyl-2-benzothiazolene hydrazine (MBTH), chromotropic acid or 2,4-dinitrophenylhydrazine (DNPH) are generally used as the absorbing solution. For passive sampling sodium bisulphite, triethanolamine and DNPH are used and sorbents such as silica gel, aluminium oxide and activated carbon, sometimes specially treated, may be useful for taking samples at the workplace.

3.3.2 Biological exposure monitoring

Until present, biological monitoring methods for exposure to formaldehyde have not been fully examined. Considering the critical effects and the target organs biological monitoring seems to be irrelevant.

Chapter 4

Sources

4.1 Natural sources

Formaldehyde is naturally formed in the troposphere during the oxidation of hydrocarbons.

Formaldehyde is one of the volatile compounds formed in the early stages of decomposition of plant residues in the soil.

4.2 Man-made sources

The most important man-made source of formaldehyde is automotive exhaust from engines not fitted with catalytic converters.

4.2.1 Production

Formaldehyde is produced by oxidizing methanol using two different procedures: (a) oxidation with silver crystals or silver nets at 600-720°C, and (b) oxidation with iron molybdenum oxides at 270-380 °C. Formaldehyde can be produced as a by-product of hydrocarbon oxidation processes.

In 1992 world-wide formaldehyde production was estimated to be 12 million tonnes. Major formaldehyde producing countries in 1990 were the United States and Japan with 3 million and 1.5 million tonnes, respectively. Other production numbers

were: Germany 680,000; China 467,000; Sweden 244,000; Finland 48,000 and Denmark 3000 tonnes (IARC95).

4.2.2 Uses

Formaldehyde is an inexpensive starting material for a number of chemical reactions, and a large number of products are made using formaldehyde as a base.

As an intermediate product, formaldehyde is used in the manufacture of particleboard, fibreboard, plywood, paper treatment, textile treatment, moulding compounds, surface coatings, foam, plywood adhesive, insulation, foundry binders, phenolic thermosetting, resin curing agents, explosives, lubricants, automobile applications, plumbing components, alkyd resins, synthetic lubricants, tall oil esters, foundry resins and controlled release fertilizers.

Furthermore, formaldehyde has medical applications as a preservative and disinfectant and it is used as a preservative in various consumer products.

Chapter 5

Exposure

5.1 General population

The possible sources of exposure to formaldehyde of the general population are tobacco smoke, automobile emissions, building and insulating materials, food products, cosmetics, household cleaning agents, medicinal products and in nature (IPC89). Routes of exposure are inhalation, ingestion and dermal absorption.

The IPCS/WHO (IPC89) made the following estimation on the contribution of various atmospheric environments to the total formaldehyde intake by inhalation of an individual.

Guicherit and Schulting (Gui85) reported an average concentration of 7.4 $\mu g/m^3$ (0.006 ppm) of formaldehyde in the ambient air of Terschelling Island, Delft and Rotterdam, in the 1980's.

The IPCS/WHO (IPC89) estimated that smoking 20 cigarettes per day would lead to an average daily intake of 1 mg formaldehyde per day. Formaldehyde produced by cigarettes may also mean considerable exposure for non-smokers through passive smoking. The more so since it has been reported that the effects of gaseous formaldehyde are potentiated by smoke particles and aerosols.

source	average intake (mg/day)
ambient air (10% of the time)	0.02
indoor air	
home (65% of the time)	
prefabricated (particle board)	1-10
conventional home	0.5-2
workplace air (25% of the time)	
without occupational exposure[a]	0.2-0.8
occupational exposure to 1 mg/m^3	5
environmental tobacco smoke	0.1-1.0
smoking (20 cigarettes/day)	1.0

[a] Assuming the normal formaldehyde concentration in conventional buildings.

5.2 Working population

Exposure to formaldehyde in the workplace can be caused by either the production or handling of this compound or products containing it. Concentrations of formaldehyde in an occupational setting in the US were reported by the ICPS/WHO (IPC89), these are presented in Annex D.

The following represents more recent occupational exposure data.

Akbar-Khanzadeh *et al*. (Akb94) reported concentrations ranging from 0.07 to 0.08-3.53 mg/m^3 (2.94 ppm) formaldehyde in a gross-anatomy laboratory of the Medical College in Ohio, USA. The eight-hour TWA exposure of 31.7% of the subjects working in the laboratory exceeded the action level of 0.6 mg/m^3 (0.5 ppm) set by the Occupational Safety and Health Association (OSHA).

The mean concentration of formaldehyde in area samples of an anatomy laboratory in Singapore was 0.6 mg/m^3 (0.5 ppm) with a range of 0.5-0.7 mg/m^3 (0.4-0.6 ppm). The mean of personal samples was 0.9 mg/m^3 (0.74 ppm) with a range of 0.5-1.4 mg/m^3 (0.41-1.20 ppm) during a session of 2.5 hours (Chi92).

Kilburn *et al*. (Kil92) reported 0.24-6.0 mg/m^3 (0.2-5 ppm) formaldehyde levels in the workplace air by area sampling in 10 representative histology laboratories in Los Angeles in 1983. The sampling duration was not reported. The levels were highest during selection of tissue samples for processing.

Kriebel *et al*. (Kri93) reported formaldehyde exposures in the breathing zone ranging from 0.59-1.12 mg/m^3 (0.49 to 0.93 ppm) with a geometric mean of 0.88 mg/m^3 (0.73 ppm) during a clinical anatomy laboratory course in the University of Massachusetts in the US.

Suruda *et al*. (Sur93) studied 29 mortician students who were taking a course in embalming. During a 85-day study period, the subjects performed an average of 62.9 embalmings and had average cumulative formaldehyde exposures of 14.8 ppm.hour, with an average air concentration of 1.68 mg/m^3 (1.4 ppm) during embalming. Since the average time spent embalming was 125 min, formaldehyde exposures calculated as an 8-hour time-weighted average were 0.40 mg/m^3 (0.33 ppm).

Mean levels of 8 hour TWA exposure to formaldehyde ranged from about 0.09 mg/m^3 (0.08 ppm) in the sawmill and shearing-press departments to 0.39 mg/m^3 (0.32 ppm) in the warehouse area of a plywood factory in Italy (Bal92).

Herbert *et al*. (Her94) examined the concentrations of formaldehyde from particles and vapour at five sampling sites in an oriented strand board plant in Canada. In the manufacture they used wood fiber derived from Aspen trees bonded by phenol formaldehyde. The highest total concentration of formaldehyde was 0.32 mg/m^3 (0.27 ppm) recorded at the preheat conveyor. The lowest was 0.08 mg/m^3 (0.07 ppm) recorded at the saw line. The samples were collected for 21 hours continuously at the sites.

Chapter 6

Kinetics

6.1 Absorption

There are limited human data regarding absorption of formaldehyde through inhalation. Under normal conditions, absorption is expected to occur in the upper respiratory tract (nasal passages in obligate nose-breathers; trachea and bronchi in oral breathers).

From animal data absorption of formaldehyde through the upper respiratory tract is estimated to be 100% as concluded from the removal of formaldehyde from the air (IPC89). Detailed studies on the distribution of ^{14}C-formaldehyde in the rat nasal cavities have confirmed that it is absorbed primarily in the upper respiratory system.

Loden (Lod86) performed an *in vitro* experiment to study the permeability of human skin to formaldehyde using excised skin in a flow-through diffusion cell. The rate of resorption was determined by measuring the amount of substance found in the receptor fluid beneath the skin at steady state. The resorption rates of formaldehyde were: from a concentrated solution of formalin, 319 mg/cm^2 per h, from a solution of 10% formalin* in phosphate buffer, 16.7 mg/cm^2 per hour. The fact that formaldehyde induces denaturation of the skin proteins may have influenced the absorption of the compound.

* Formalin is defined as 37% formaldehyde in water containing 10-15% methanol.

6.2 Distribution and biotransformation

The IPCS/WHO (IPC89) cited a study on rats which were exposed by inhalation for 6 hours to 18 mg/m^3 (15 ppm) ^{14}C-formaldehyde. The distribution of radioactivity in the tissues was determined. The highest concentrations occurred in the oesophagus, followed by the kidneys, liver, intestine and lungs.

Another study investigated the retention of formaldehyde gas in the nasal passages of anaesthetized male rats exposed in a nose-only system to ^{14}C-formaldehyde at 2.4-60 mg/m^3 (2-50 ppm) for 30 min. More than 93% of the substance was retained, regardless of airborne concentrations.

There are no data available on the distribution of formaldehyde in the human body. The mean formaldehyde concentration in human blood after inhalatory exposure to 2.3 mg/m^3 (1.9 ppm) formaldehyde vapour during 40 minutes was approximately 2.61 ± 0.14 mg/100 ml. However, no statistical difference was found with pre-exposure levels (IPC89). No increases in blood concentrations of formaldehyde were detected in rats or human beings exposed to formaldehyde through inhalation due to rapid metabolism.

The overall metabolism of formaldehyde is summarized in figure 1.

Of importance are the oxidation of formaldehyde into formic acid and carbon dioxide, the reaction with glutathione and the covalent linkage with proteins and nucleic acids.

Formaldehyde is an endogenous metabolite in mammalian systems and it is rapidly metabolised to formate, which is partially incorporated via normal metabolic pathways into the one-carbon pool of the body or further oxidized to carbon dioxide.

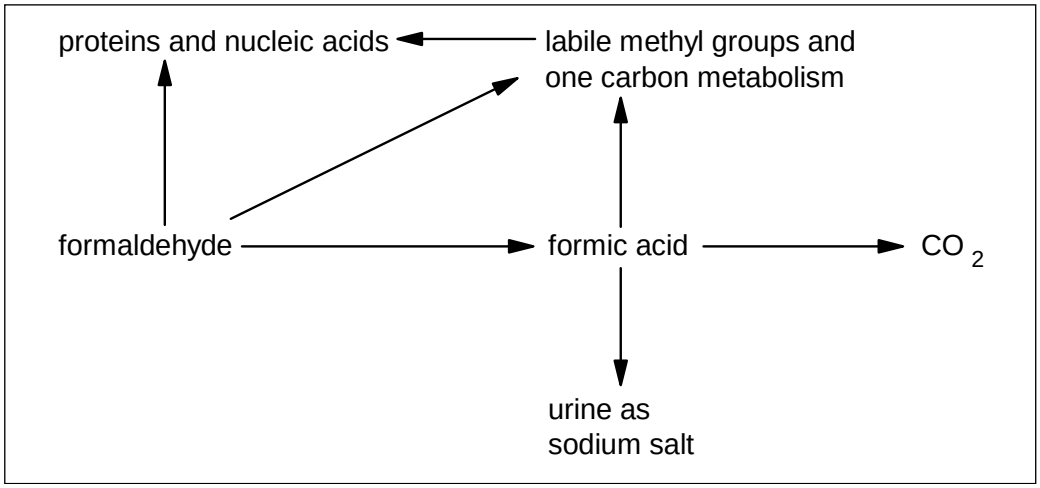

Figure 1 Overall metabolism of formaldehyde (Kit76).

6.3 Elimination

After absorption formaldehyde is rapidly metabolized to formate or enters the one-carbon pool to be incorporated into other molecules. Besides this, there are two pathways of final elimination, via exhalation or renal elimination. There are no human data available on the elimination of formaldehyde, but the IPCS/WHO (IPC89) reported that 81% of subcutaneously administered ^{14}C-formaldehyde to rats was found again as carbon dioxide and a small amount in choline.

6.4 Possibilities for biological monitoring

At present there are no biological monitoring methods available to determine the magnitude of past exposure to formaldehyde.

There have been a number of cytologic and cytogenetic studies of formaldehyde exposure in man. These studies examined nasal and buccal cells and blood lymphocytes of occupationally exposed workers and unexposed control volunteers. These studies will be evaluated in the respective chapters.

6.5 Summary

Under normal conditions it is expected that formaldehyde in ambient air is absorbed through inhalation in the upper respiratory tract. In animals absorption has been found to be 100%. From *in vitro* experiments using human skin, it is estimated that the absorption of a concentrated solution of formalin through the skin amounted to 319 mg/cm^2 per hour.

After inhalation of radioactive formaldehyde by the rat the radioactivity is distributed in the tissues, with the highest concentration in the oesophagus, followed by the kidney, liver, intestine and lung. Retention in the nasal passage of the rat is estimated at 93% of the dose, regardless of airborne concentrations.

Formaldehyde is an endogenous metabolite in mammalian systems and it is rapidly metabolized to formate, which is partially incorporated via normal metabolic pathways into the one-carbon pool of the body or further oxidized to carbon dioxide. There were two pathways for elimination: via exhalation and via the kidneys.

There are no biological monitoring methods at present to determine the magnitude of past exposure to formaldehyde.

Chapter 7

Effects

7.1 Observation in man

Only a selection of the most adequate human studies from the review of Paustenbach is discussed in this chapter (Pau97).

7.1.1 Odour

At high concentrations, eg 6-12 mg/m^3 (5-10 ppm), formaldehyde has a distinct and pungent odour. The odour of formaldehyde is detectable and/or recognizable by most individuals at concentrations around 1.2 mg/m^3 (1 ppm) (IPC89). The odour threshold (ie. the concentration at which a group of observers can detect the odour in 50% of the presentations) of formaldehyde ranges from 0.06 to 0.22 mg/m^3 (0.05-0.18 ppm)

7.1.2 Sensory irritation

For most odorous irritants, the trigeminal nerve has a higher threshold than the olfactory nerve. However, when the formaldehyde concentration is increased, sensory irritation is first experienced in the eyes, then the odour is perceived, and finally nasal irritation occurs (IPC89).

Surveys

Akbar-Khanzadeh *et al.* (Akb94) studied 34 workers employed in a gross anatomy laboratory in Toledo, USA. They were exposed to formaldehyde at (time-weighted average) concentrations ranging from 0.08 to 3.53 mg/m^3 (0.07-2.94 ppm) (duration of exposure not described). More than 94% of the subjects were exposed to formaldehyde concentrations exceeding 0.36 mg/m^3 (0.3 ppm). By more than 70% of the exposed subjects, irritation of the eyes (88%) and nose (74%) were reported.

Kriebel *et al.* (Kri93) investigated students exposed to formaldehyde during a clinical anatomy laboratory course when dissecting cadavers for 3 hours per week over a 10-week period. Formaldehyde exposures in the breathing zone ranged from 0.59-1.12 mg/m^3 (0.49-0.93 ppm), with a geometric mean of 0.88 mg/m^3 (0.73 ppm). Symptoms of irritation increased strongly during the day, and the effects were stronger at the beginning than at the end of the semester. The prevalence of symptoms at the start of the laboratory session ranged from 15% for cough to 46% for nose irritation. At the end of the session the prevalences were 20 and 67, respectively. The average increase in symptoms prevalence from beginning to end of laboratory session was greatest for eye irritation, with an increase of 43%. No statistical analyses were reported.

Wilhelmsson and Holmström (Wil92) performed a cross-sectional study on 66 employees of a formaldehyde producing plant in Sweden to determine whether chronic exposure to formaldehyde often causes symptoms by direct irritation. The workers were exposed almost exclusively to formaldehyde. Mean duration of exposure was 10 years (range 1-36 years). Thirty-six community clerks served as a reference group. The exposure level of the exposed group as measured by personal sampling was between 0.05 to 0.60 mg/m^3 (0.04 and 0.50 ppm) formaldehyde, with a mean of 0.26 mg/m^3 (0.22 ppm). The reference group was exposed to an average concentration of 0.09 mg/m^3 (0.07 ppm) formaldehyde over the year. From a (not specified) questionnaire, it appeared that 67% of the exposed group experienced general nasal discomfort compared to 25% of the reference group ($P<0.001$). Nasal discomfort strictly connected to the workplace occurred in 53% of the exposed group and in 3% of the reference group ($P<0.001$). However, the questionaire was not published. Therefore, the committees are of the opinion that this study might only suggest that after long-term occupational exposure (0.26 mg/m^3 formaldehyde), more than 50% of the exposed workers complained of nasal discomfort which was attributed to their occupation.

Liu *et al*. (Liu91) studied the irritant effects associated with formaldehyde exposure in mobile homes in California. Week-long integrated formaldehyde concentrations were measured in summer (663 mobile homes with 1394 residents) and winter (523 mobile homes with 1096 residents), using passive monitors while the mobile home

residents continued their normal activities. The concentrations varied from below the detection limit (0.0012 mg/m^3) to 0.55 mg/m^3. Irritant effects were found to be significantly associated with formaldehyde exposure after controlling for age, sex, smoking status and chronic illnesses. Effects included complaints of burning/tearing eyes, stinging/burning skin, fatigue, and sleeping problems in summer and burning/tearing eyes, chest pain, dizziness, sleeping problems and sore throat in winter. For the three weekly ranges of formaldehyde exposure that were distinguished (less than 8.4 mg/m^3-hour, between 8.4-14.4 mg/m^3)-hour, more than 14.4 mg/m^3 -hour), the percentages of people with burning/tearing eyes in the summer increased from 13.3% to 17.1% and then to 21.4%. In winter, percentages increased from 10.8% to 14.7% and then to 20.6%.

Controlled human studies

Weber-Tschopp *et al.* (Web77) exposed healthy volunteers to increasing concentrations of formaldehyde from 0.036 to 4.8 mg/m^3 (0.03 to 4 ppm). Thirty three subjects were continuously exposed for 35 minutes and 48 subjects were exposed for 1.5 minutes. The irritating effects were determined by the eye blinking rate of the individuals. The authors found that the irritating effects increased as a function of the formaldehyde concentration. The irritation threshold of formaldehyde was placed in the range between 1.2 and 2.4 mg/m^3 (1 and 2 ppm). The authors suggested that adaptation to the irritation occurred after a few minutes in subjects after prolonged exposure to formaldehyde.

Bender *et al.* (Ben83) studied eye irritation in groups of volunteers (n= 5-28 per group) exposed to 0, 0.42, 0.67, 0.84, 1.08 and 1.2 mg/m^3 (0, 0.35, 0.56, 0.7, 0.9 and 1.0 ppm) formaldehyde for 6 minutes. The authors reported that the subjective measurements of eye irritation may be affected by a variety of psychological and physiological factors, such as air flow over the eyes, dust particles, length of sleep the previous night, etc. In spite of the large variation in response time, there was still a significant relationship between formaldehyde concentration and time to detection of response. The authors concluded that eye irritation occurred at exposure concentrations of 0.42 - 1.1 mg/m^3 (0.35-0.9 ppm) formaldehyde. The response was slight until a concentration of 1.2 mg/m^3 (1 ppm) was reached.

Andersen and Molhave (And83) conducted a study in which 16 healthy subjects (5 smokers) were exposed to 0.29, 0.48, 0.97 or 1.92 mg/m^3 (0.24, 0.4, 0.81 or 1.6 ppm) formaldehyde for 5 hours. The purpose of the study was to determine the concentration at which eye irritation occurred. Nineteen percent of the respondents reported eye irritation at 0.29 mg/m^3 (0.24 ppm). Discomfort increased during the first 2 hours of exposure up to 0.97 mg/m^3 (0.81 ppm); then irritation stabilized for the remaining 3

hours. A decrease in discomfort was observed at 1.92 mg/m^3 (1.6 ppm), indicating acclimatization. After 5 hours of exposure, 38% of the subjects had no complaints at 1.92 mg/m^3 (1.6 ppm), and 63% had no discomfort at 0.97 mg/m^3 (0.81 ppm). This study illustrates the relatively wide variation in individual susceptibility to irritation from formaldehyde.

7.1.3 *Rhinitis*

Pazdrak *et al.* (Paz93) tried to characterize the nature of formaldehyde-induced nasal response consisting of symptoms of rhinitis and changes in nasal lavage fluid. Eleven healthy subjects and nine patients with specific skin sensitisation were provoked in an experimental chamber with formaldehyde at a concentration of 0.48 mg/m^3 (0.4 ppm) for 2 hours. Nasal lavage was performed prior to and immediately after provocation, and 4 and 8 hours later. It was found that the provocation caused transient symptoms of rhinitis and prolonged changes in nasal washing. There were increases in the relative number of eosinophils, and in albumin and total protein levels in the nasal fluid, 4 and 8 hours after provocation. No difference was found between the healthy subjects and patients. These data confirm the irritant effects of inhaled formaldehyde and might suggest that inhaled formaldehyde is capable of inducing non-specific inflammatory changes at a concentration of 0.48 mg/m^3 (0.4 ppm).

7.1.4 *Effects on pulmonary function in healthy and astmatic subjects*

Witek Jr *et al.* (Wit87) evaluated the respiratory effects in asthmatics after exposure to formaldehyde. Fifteen ashmatic volunteers were exposed in a double-blind manner to room air or 2.4 mg/m^3 (2 ppm) formaldehyde for 40 minutes. These exposures were repeated on a separate day during moderate exercise (450 kpm/min) for 10 min. Pulmonary function was assessed by using partial and maximal flow-volume curves. The following parameters were determined*: VC, RV, TLC, $FEV_{1.0}$, FVC, PEFR and MEF50%. No significant airway obstruction or airway resistance was noted in this group during and immediately after exposure. However, bad odour, sore throat and eye irritation were common during exposure, but the symptoms were infrequent afterward. No delayed bronchoconstriction was detected with measurements of peak expiratory flow.

The results of this study were substantiated by Sauder *et al*. (Sau87). In their study on nine non-smoking asthmatic volunteers, they also found no significant changes in the pulmonary function (FVC, FEV1, FEF 25-27%, SG_{aw} or FRC) or airway reactivity

* For abbreviations see Annex G.

when the volunteers were exposed to 3.6 mg/m^3 (3 ppm) formaldehyde vapour for 3 hours. However, there was a significant increase in nose and throat irritation at the 30th min and eye irritation at the 60th and 180th min of exposure.

Harving *et al.* (Har90) studied the possible effects of acute formaldehyde exposure on the lung function of asthmatic subjects. They exposed 15 non-smoking asthmatic subjects, with documented bronchial hyperresponsiveness, to 0.08, 0.12 or 0.85 mg/m^3 formaldehyde for 90 minutes. All except one subject required bronchodilator therapy and none were using methylxanthines or corticosteroids. Exposure occurred in a climate chamber and the protocol was double-blind. No control group was used in this experiment. Lung function tests were carried out before the exposure period and repeated near the end. The results showed no significant changes in the FEV_1, FRC, R_{aw}, SR_{aw}, and flow-volume curves during formaldehyde exposure. Furthermore, histamine challenge performed immediately after formaldehyde exposure showed no evidence of changes in bronchial hyperreactivity. No late reactions were registered during the first 14-16 hr after exposure. There was no association of subjective ratings of symptoms, if any, with increasing exposure. The rating of symptoms did not differ significantly when the three exposure levels were compared. The results of this study suggest that the exposure levels of formaldehyde used were of minor, if any, importance in the emergence of pulmonary symptoms in asthmatic subjects.

Chia *et al.* (Chi92) examined 150 first-year medical students exposed to formaldehyde during dissection of cadavers in a gross anatomy laboratory. As a reference group they used 189 third- and fourth-year medical students matched for sex, ethnic group and age. The mean concentration of formaldehyde in the area was 0.60 mg/m^3 (0.50 ppm) and the mean concentration of personal samples was 0.89 mg/m^3 (0.74 ppm). The latter had a range of 0.49 to1.44 mg/m^3 (0.41 to 1.20 ppm). No differences were found in forced expiratory volume (FEV_1) and forced vital capacity (FVC) among 22 randomly selected male and female subjects, when the measurements were compared between the first day after two weeks vacation and after the dissection period. Significant differences, however, were observed in the exposed group for symptoms of decreased ability to smell, eye irritation, and dry mouth in comparison with the reference group.

Herbert *et al.* (Her94) performed a cross-sectional study on 99 workers employed in the manufacture of oriented strand board. The reference group consisted of 165 unexposed workers from a petroleum industry. Both groups were investigated using questionnaires, spirometry and skin prick tests to common environmental antigens. Environmental monitoring showed dust levels with a mean of 0.27 mg/m^3. The mass mean aerodynamic diameter (MMAD) of the particles was 2.5 mm. The concentration of formaldehyde was between 0.08-0.32 mg/m^3 (0.07 and 0.27 ppm) in the strand board factory. Lung function tests showed significant differences between strand board

workers and workers from the petroleum industry in the FEV_1/FVC ratio and reductions of FEV_1 (P = 0.044) and FVC (P = 0.022) during the shift work. Also the strand board workers complained of self-reported asthma and of lower respiratory tract symptoms significantly more frequent than the oil workers. The prevalence of atopy did not differ between both groups. Lung function was significantly better in the strand board workers who had no symptoms, compared with symptomatic workers. Since the complaints of self-reported asthma and of lower respiratory tract symptoms by the exposed group occurred at rather low concentrations of formaldehyde and dusts, the authors concluded that the effects may have been related to small particles containing formaldehyde that penetrated deep into the airways.

Horvath *et al*. (Hor88) surveyed 109 workers (exposed to formaldhyde from 1 to 20 years) for symptoms of respiratory tract irritation. Estimates of the exposure ranged from 0.2 to 3.5 mg/m^3 (0.17-2.93 ppm) (mean 0.83 mg/m^3 (0.69 ppm)). The percentage of the exposed workers reporting respiratory irritation was significantly higher than in the non-exposed group (n=264).

7.1.5 Sensitization

Respiratory tract sensitization

Grammer *et al*. (Gra90) evaluated the immunological response to formaldehyde exposure in a group of 37 workers in a cross-sectional study. The durations of employment were not reported. Concentrations of formaldehyde in air sampling in several work areas at various times ranged from 0.004-0.087 mg/m^3 (0.003 to 0.073 ppm) as time-weighted averages. The workers were also exposed to phenol and organic solvents. A clinical assessment included review of a summary of medical history, physical examination, chest X-ray films and pulmonary function studies. Serologic assessment was made with an enzyme linked immunosorbent assay (ELISA) for IgE and IgG to formaldehyde-human serum albumin. It was found that none of the workers had IgE or IgG antibodies to formaldehyde-human serum albumin or an immunologically mediated respiratory or ocular disease caused by formaldehyde.

Thrasher *et al*. (Tra90) studied four groups of patients with long-term inhalation exposure to formaldehyde consisting of (1) mobile home residents, (2) office workers who had worked in a new office building, (3) subjects who had moved from mobile homes for at least one year, and (4) subjects who had worked in jobs with possible exposure to formaldehyde. All patients in this study had sought continuous medical attention because of multiple complaints involving the central nervous system (CNS). They were compared with a group of students who had been exposed to formaldehyde for 13 hours per week for 28 weeks while studying anatomy. No measurements of

formaldehyde in air were performed. When compared to the controls it was found that the patients had significantly higher autoantibodies and antibody titers and B-cell titers to formaldehyde-human serum albumin.

Sixty-three practicing pathologists in Alberta, Canada, were studied regarding atopy and sensitivity to formaldehyde (Sal91). Serum samples were assayed for total IgE levels and the presence of IgE with specificity toward formaldehyde. Twenty-nine of the subjects (46%) had a history of atopy that was confirmed in twelve by either IgE levels or a positive radio-allergosorbent test. Twenty-nine (46%) complained of formaldehyde sensitivity. In this study, none of the pathologists had allergen-specific IgEs directed against formaldehyde, and there was no evidence of a tendency for atopic subjects to be more prone to sensitivity to formaldehyde. However, the authors confirmed that this might have been related to the deliberate reduction in exposure by individuals experiencing adverse effects.

A case-report was described by Grammer *et al*. (Gra93b). The subject was a worker with clinical symptoms compatible with bronchospasm caused by formaldehyde exposure. An enzyme-linked immunosorbent assay showed that the worker had positive IgE and IgG titers to formaldehyde-human serum albumin. The worker had a positive intracutaneous test for formaldehyde-human serum albumin. The cutaneous reactivity could be transferred to a rhesus monkey through the worker's serum. The worker had a negative metacholine challenge at 25 mg/ml and negative formaldehyde inhalation challenges at 0.36, 1.2 and 6 mg/m^3 (0.3, 1, 3 and 5 ppm) for 20 minutes. The authors concluded that the worker's symptoms were probably not caused by immunologically mediated asthma. Based on their experience, they stated that immunologically mediated asthma caused by formaldehyde is extremely rare, if it exists at all.

In 1991, Bardana Jr and Montanaro (Bar91) made an extensive review and analysis of the immunological effects of formaldehyde. They concluded that formaldehyde is capable of acting as a respiratory irritant. But according to the authors of the review, there is no consistent evidence indicating that formaldehyde is a respiratory sensitiser. Formaldehyde does not induce transient or permanent bronchial hyperactivity, which has been associated with e.g. exposure to ozone or nitrogen dioxide. Almost the same conclusions were drawn by IPCS/WHO (IPC89). They commented that there are a few case-reports of asthma-like symptoms caused by formaldehyde, but none of these demonstrated a sensitisation effect (neither Type I nor Type IV) and the symptoms were considered to be due to irritation.

Garrett *et al.* (Gar98) studied a group of 148 children (age 7-14), 53 of whom were asthmatic, in houses in Australia between March 1994 and February 1995. The mean indoor formaldehyde exposure level was 15.8 mg/m^3 and an association between

formaldehyde exposure and athopy (OR 1.4 (0.98-2.00, 95%) was observed. The committees noted however the potential selection bias in this study.

Skin sensitization

According to the IPCS/WHO (IPC89) skin sensitisation by formaldehyde is induced only by direct skin contact with formaldehyde solutions in concentrations of 20 g/l (2%) and higher. The lowest patch test challenge concentration in an aqueous solution reported to produce a reaction in sensitized persons was 0.05% formaldehyde.

Flyvholm and Menne (Fly92) interviewed eleven patients with eczema and a positive patch test to formaldehyde. All patients used one or more products containing formaldehyde or formaldehyde releasers. Sources of exposure were cosmetics and personal care products, dishwashing liquids, waterbases paints, photographic products etc.

Liden *et al*. (Lid93) reported absence of specific IgE antibodies in allergic contact sensitivity to formaldehyde. They studied 23 patients with positive epicutaneous test reactions to formaldehyde, recruited from dermatologic departments in Sweden. The patients were between 21-74 years old and nineteen were women. The tests had been performed 6 months to 10 years before inclusion in the study. On re-testing, fifteen showed a positive reaction. Eight patients showed atopic diathesis, and eight had a history of ongoing atopic dermatitis. In the radio-allergosorbent test only two non-atopic patients had specific IgE antibodies to formaldehyde. In cellular infiltrates from biopsies of epicutaneous test sites cells reactive with monoclonal antibodies against IgE were found in positive and in negative formalin tests, both in atopics and non-atopics, as well as in control biopsies from nonlesional skin. Double immunofluorescence staining experiments showed that IgE occurred on Langerhans cells. The proportion of IgE-positive cells correlated to the level of serum IgE, but not to atopy. These cells were also found in the epidermis and in the dermis of non-atopic patients. The authors concluded that this study did not support the hypothesis that specific IgE antibodies are active in the pathogenesis of contact sensitivity to formaldehyde, neither in atopic nor in non-atopic patients.

Cronin (Cro91) performed an investigation in the St John Dermatology Center in London to determine the prevalence of formaldehyde sensitivity and to establish whether there is a significant correlation between formaldehyde sensitivity and hand eczema. The study spanned six years, from 1984 to 1989. In this period a total of 4553 men were patch tested with a 1% aqueous solution of formaldehyde. The prevalence of sensitisation was approximately 2-3% each year. During these 6 years, 98 men (2.2%) were sensitised. During the same period 6479 women were patch tested with a 1% aqueous solution of formaldehyde. The prevalence of sensitisation was remarkably

constant at approximately 4% each year. During these 6 years 235 women (3.6%) showed a positive reaction and 117 women were primarily sensitised by formaldehyde, of whom 61 (52%) had hand eczema. Of this group 2% was occupationally exposed and 88% domestic.

In their review Bardane and Montanaro (Bar91) pointed out that the threshold for induction of delayed hypersensitivity contact dermatitis has not been determined precisely. The frequency of allergic contact dermatitis to formaldehyde was estimated by the authors to range between 3% and 6% in the general population. Cross reactivity with other aldehydes has not yet been demonstrated; glutaraldehyde does not cross react. Formaldehyde has also been reported to cause contact urticaria, but the mechanism of action has never been clearly demonstrated.

7.1.6 *Toxicity due to acute and short-term exposures*

No cases of death from formaldehyde inhalation have been published (IPC89).

The IPCS/WHO (IPC89) summarized the clinical features of formaldehyde intoxication including weakness, headache, abdominal pain, vertigo, anaesthesia, anxiety, burning sensation in the nose and throat, thirst, clammy skin, central nervous system depression, coma, convulsions, cyanosis, diarrhoea, dizziness, dysphagia, irritation and necrosis of mucous membranes and gastrointestinal tract, vomiting, hoarseness, nausea, pallor, shock and stupor.

Effects on the respiratory system caused by high formaldehyde concentrations are pneumonia, dyspnoea, wheezing, laryngeal and pulmonary oedema, bronchospasm, coughing of frothy fluid, respiratory depression, obstructive tracheobronchitis, laryngeal spasm and sensation of substernal pressure.

Acute ingestion may cause renal injury dysuria, anuria, pyuria and haematuria, and leads to an increase in formate levels in the urine.

7.1.7 *Epidemiological studies*

Cross-sectional morbidity studies

A summary of cross-sectional morbidity studies of workers occupationally exposed to formaldehyde is presented in Table 1.

From these studies it may be concluded that symptoms of irritation of the upper respiratory tract already occurred after acute exposure to levels below 1.2 mg/m^3 (1 ppm) formaldehyde. After exposure for a few hours decreases of the FEV1 and FVC have been observed.

Of interest are the cross-sectional morbidity studies performed by Wilhelmsson and Holmström (Wil92), Herbert *et al.* (Her94) and Boysen *et al.* (Boy90).

Table 1 Cross-sectional morbidity studies of workers occupationally exposed to formaldehyde.

factory or professions (country)	number of subjects (C=controls)	levels of exposure in ppm (mg/m^3)	confounding factors	effects	ref.
airplane production (US)	37 (no control group)	0.003-0.073 (0.004-0.088)	co-exposure to phenol and organic solvents	14 workers with irritant syndrome. None of them had resporatory or ocular disease that was immunologically mediated.	Gra90
plywood factory (Italy)	15 (C=15, matched in age and sex)	0.08-0.32 (0.09-0.39)	co-exposure to wood dusts (0.23-0.73 mg/m^3)	Higher frequency of micronucleated cells in nasal respiratory cells. Chronic inflammation of the nasal mucosa. Higher frequency of squamous metaplasia cells.	Bal92
formaldehyde producing plant (Sweden)	66 (36% smokers) (C=36, 28% smokers)	0.04-0.50 (0.05-0.60 mean 0.22 (0.26)		53% of exposed group had nasal discomfort (3% in control group). 33% of exposed group had general lower respiratory tract discomfort (C=1%). 20% of exposed group had eye problems (C=0%).	Wil92
oriented strand board manufacture (Canada)	99 (C=165)	0.07-0.27 (0.08-0.32)	dust level 0.27 mg/m^3 with MMAD 2.5 μm	Significant lower FEV_1/FVC, and cross-shift reduction of FEV_1 and FVC. Elevated reports of 'asthma' and higher frequency of lower respiratory tract symptoms. No difference in atopy.	Her94
paper mill (India)	22 (C=27)	0.025 8-h TWA (0.03)		Exposed subjects showed more respiratory symptoms and complaints pertaining to gastrointestinal, musculoskeletal and cardiovascular systems. No difference in hematology.	Sri92
chemical company (Norway)	37 (C=37, matched in age, no difference in smoking habits)	0.5 - >2 (0.6 - >2.4)		Exposed group showed more pronounced metaplastic alterations in nasal mucosa. Three of 17 workers exposed to 0.5-2 ppm showed epithelial dysplasia.	Boy90
anatomy laboratory (US)	34 (C=12) all subjects are non-smokers	0.07-2.94 (0.08-3.53) exposure to F at least six weeks. Mean 1.24 ppm (1.49)	embalming fluid consisted of 36% formaldehyde, 8.6% methanol and 1.2% phenol	No difference in basic lung functions between both groups. During shift there was decrease of FVC and FEV_3.	Akb94
histology laboratory (US)	280 all were non-smokers (compared to normal subjects in the same state)	0.2-1.9 (0.24-2.28) with peaks of 5 ppm (6)	co-exposure to chloroform, xylene and toluene	Exposed group showed steeper reduced vital capacity and flows from age 20 to 60.	Kil89

Table 1 Continued.

factory or professions (country)	number of subjects (C=controls)	levels of exposure in ppm (mg/m^3)	confounding factors	effects	ref.
students during anatomy course (US)	24 (no control group)	0.49-0.93 (0.59-1.12) geom. 0.73 (0.88) 3 h/wk, 10 wks		Increase of irritant symptoms, stronger in the beginning. Decline in the PEF rates over the semester. Reports of 'asthma' and throat irritation	Kri93
students anatomy class (Singapore)	150 (C=189, matched for age, sex and ethnic group)	0.41-1.20 (0.49-1.44) mean 0.74 (0.89)		No difference between the groups in FEV_1 and FVC. Significant differences in symptoms of decreased ability to smell, eye irritation, throat irritations and dry mouth.	Chi92

The study by Wilhelmsson and Holmström (Wil92) on 66 workers occupationally exposed to formaldehyde during formaldehyde production is described in section 7.1.2. Beside irritation, the authors were also interested in whether chronic exposure affected exposed people through hyperreactivity in atopic persons, through formaldehyde-induced hyperreactivity in non-atopic persons or through immunologically mediated, immediate type I reactions to formaldehyde itself. Among the 53% of the exposed workers experiencing nasal discomfort through hyperreactivity, atopics were not significantly overrepresented. Two workers with occasional occupational nasal discomfort, and sensitised by long-term inhalation, had a positive radio-allergo-sorbent test for formaldehyde. Of the occupationally exposed group 20% experienced general eye problems. The frequency in the control group was 0%. Thirty six percent of the exposed group had dermatological problems such as eczema or itching, while the corresponding frequency among the control group was 11%. The authors concluded that in certain circumstances formaldehyde can induce an IgE-mediated type 1 reaction in the nose, but in most cases the annoying nasal symptoms are caused by formaldehyde-induced hyperreactivity, which can cause problems in about 50% of a population exposed to formaldehyde at an average level of 0.26 mg/m^3 (0.22 ppm). Another interesting finding was that atopics run approximately the same risk of suffering from this hyperreactivity as non-atopics. However, these results were obtained from a not-published questionaire and therefore the resuls are of limited use.

The cross-sectional study by Herbert *et al.* (Her94) on workers employed in a manufacture of oriented strand board is described in section 7.1.5. The workers showed reduced lung functions and complained more of self-reported asthma and of lower respiratory tract symptoms compared to the reference group.

Boysen *et al*. (Boy90) reported on a study on nasal biopsies of 37 workers occupationally exposed to formaldehyde (chemical company producing formaldehyde and formaldehyde resin). The workers were exposed for more than 5 years, and they were compared to 37 age-matched controls. The level of exposure of the exposed group ranged from 0.6 to more than 2.4 mg/m^3 formaldehyde. The two groups did not differ as to other environmental influences, smoking habits and previous nasal disease. The authors found that the degree of metaplasia of the nasal mucosa cells was more pronounced among the exposed workers than among the controls. Three cases of dysplasia out of 17 workers (18%), all of the squamous type, were observed in the formaldehyde group (zero in cases in the control group). These workers had been exposed daily to formaldehyde concentrations ranging from 0.6 mg/m^3 to more than 2.4 mg/m^3 for more than 22 years. According to the committees the study, however, is too small to draw any conclusions. Since only a small area of the nasal mucosa can be examined histologically, the number of dysplastic lesions found can not be expected to reflect the real prevalence of dysplasia and therefore the committees are of the oopinion that the real prevalence of displasia could even be higher.

Longitudinal / prospective morbidity studies

Nunn *et al*. (Nun90) followed a group of 164 workers exposed daily to formaldehyde during the production of urea-formaldehyde resin, together with 129 workers not exposed to formaldehyde, for 6 years. Exposure was classified as high (TWA more than 2.4 mg/m^3), medium (0.72 to 2.4 mg/m^3) or low (0.12 to 0.6 mg/m^3). Twenty-five percent of the workers had high exposure during several periods and 17% moderate exposure. The annual assessment included lung function testing. The proportion of self-reported respiratory symptoms was similar in the two groups. The initial FEV1 was within 0.5 l of the predicted value (by age and height) in 65% of the exposed and 59% of the unexposed workers, and more than 0.5 l below the predicted value in 9% of the exposed and 11% of the unexposed workers. The mean decline in FEV1 was 42 ml/year in the exposed group and 41 ml/year in the unexposed group. The authors found no association be- tween the rate of decline and indices of exposure to formaldehyde in the exposed group. In interpreting these results it is important to assess any possible bias in the conduct of the study. Workers with adverse respiratory effects from exposure to high concentrations of formaldehyde may have left employment so that only ‘survivors’ are included in the study (healthy worker effect).

The effect of low-level exposure to formaldehyde on oral, nasal and lymphocytic biological markers were studied prospectively by Suruda *et al*. (Sur93) in a group of 29 mortician students who were about to take a course in embalming. During the 85-day study period the subjects performed an average of 69 embalmings and had an average

cumulative formaldehyde exposure of 14.8 ppm.hour, with an average air concentration of 1.7 mg/m^3 (1.4 ppm) formaldehyde during embalming. The calculated 8-hour TWA was 0.40 mg/m^3 (0.33 ppm) on days when embalmings were done. Epithelial cells from the buccal area of the mouth as well as nasal epithelial cells showed an increase of micronucleus frequency. In the lymphocytes the micronucleus frequency increased while sister chromatid exchanges decreased. In this study no control group was used. Each subject had been used as his or her own control. The study was limited due to the small number of measurements, other formaldehyde exposures and due to prior embalming exposure to formaldehyde of subjects.

Retrospective cohort mortality/morbidity studies

A summary of retrospective cohort mortality studies is presented in Table 2.

Most attention was given to a retrospective cohort mortality study on workers of 10 formaldehyde-producing or -using facilities in the US by several authors (Bla86, Bla87, Bla90b, Mar92, Mar94, Ste94, Bla94, Ste95), who came to different conclusions.

The first report of the study was done by Blair *et al.* (Bla86). This historical cohort study evaluated the mortality of 26,561 workers, comprising approximately 600,000 person-years. The cohort consisted of all workers first employed before January 1, 1966. Subjects were traced to January 1, 1980, to determine vital status. Historical exposure to formaldehyde was estimated by job-related monitoring data available from participating plants. There were five ranked categories: (1) trace, (2) less than 0.12 mg/m^3 (0.1 ppm), (3) from 0.12 to 0.6 mg/m^3 (0.1 to <0.5 ppm), (4) from 0.6 to 2.4 mg/m^3 (0.5 to <2.0 ppm) and (5) equal or higher than 2.4 mg/m^3 (2.0 ppm). The standard mortality ratio (SMR) was calculated by comparison with the mortality rates of the total US population, local population and non-exposed workers. No statistically significant increases occurred of specific cancers. Two deaths from nasal cancer occurred (both among the exposed), whereas three were expected. The risk of lung cancer was higher in each exposure category compared to the non-exposed, due to the lower risk among the non-exposed (in comparison to the general population). But no trend of increasing lung cancer risk was seen with cumulative exposure.

Table 2 A summary of retrospective cohort mortality studies of workers occupationally exposed to formaldehyde.

factories or occupations (country)	estimation of exposure	characteristics of cohort	results	ref.
10 formaldehyde production and use facilities (USA)	based on job titles. Using available monitoring data from participating plants. Five ranked categories of exposure.	26,561 workers (approx 600,000 person-years). Follow-up 1966 to 1980. Comparison with US population, local population and non-exposed workers. Information on smoking habits was not available	No significant excesses for specific cancers. SMRs for cancer of the respiratory system are 112 (95% CI 97-128) for white men, 121 (95% CI 52-238) for white women, 68 (95% CI 34-124) for black men. There is no trend of increasing lung cancer risk with cumulative exposure level. Mortality from cancer of the nasal cavity was not excessive. The pattern of nasopharyngeal cancer suggests that simultaneous exposure to formaldehyde and "particulates" may be a risk factor for this tumour.	Bla86 Bla87 Bla90
automotive iron foundry (US)	based on job titles, four categories (high, medium, low and none)	3929 workers. Follow-up period 1960-1989. Comparison with US population and non-exposed workers (n = 2032). Smoking status ascertained in 65.4% of exposed and 55.1% of the unexposed cohort	No association between formaldehyde exposure and deaths from malignant or non-malignant disease of the respiratory system. SMRs for cancer of buccal cavity and pharynx: exposed workers 131 (95% CI 48-286); unexposed workers 169 (95% CI 54-395). SMRs for cancer of trachea, bronchus and lung: exposed workers 120 (95% CI 89-158); unexposed workers 119 (95% CI 84-163).	And95a And95b
chemical and plastic industry (United Kingdom)	based on job titles, four categories (high, moderate, low and background)	7660 men first employed before 1965, and 6357 men first employed after 1964 (total 14017). Follow-up until 1989. Comparison with death rates from England and Wales, also local rates	there were no deaths from cancer of nasophapharynx (expected 1.3). Among earlier group of workers there was no suggestion of a trend in mortality due to lung cancer with increasing exposure. The high exposure group, however, did have the highest SMR (124, 95% CI 107-144), which was largely due to data from one factory. There was no relation between mortality from lung cancer and cumulative dose.	Gar93

In 1987, the authors (Bla87) reported an analysis of the excess mortality from cancers of the nasopharynx and oropharynx. Four of seven workers with nasopharynx cancer and two of five workers with oropharynx cancer occurred in a single plant producing moulding compounds which was a dusty operation. The authors concluded that the patterns for nasopharyngeal cancer suggested that simultaneous exposure to formaldehyde and particulates may be a risk factor for these tumours. For persons exposed to particulates, the risk of death from cancer of the nasopharynx increased with cumulative exposure to formaldehyde from SMR of 192 for 0.6 mg/m^3.years (0.5 ppm.years) to 403 for concentrations between 0.6 and 6.6 mg/m^3.years (0.5 and 5.5 ppm-years) and to 746 for 6.6 mg/m^3.years (5.5 ppm.years). This trend was not significant, however.

In 1990, the same authors (Bla90b) again performed additional analyses to determine whether the association with formaldehyde may have occurred in a subgroup of the cohort and/or to identify other occupational risk factors that might have been involved. This report includes only 20,714 white men, the race-sex group that had an excess of lung cancer. Cumulative exposure was used to assess total dose. The SMRs and standardized rate ratios (SRRs) were estimated. The authors found that, in general, the relative risk for lung cancer (both SMRs and SRRs) 20 or more years after first exposure did not rise with increasing exposure to formaldehyde. There was a lack of consistency among the various plants for risk of lung cancer. Mortality from lung cancer was more strongly associated with exposure to other substances, including phenol, melanine, urea and wood dust than with exposure to formaldehyde.

In 1992, Marsh *et al*. (Mar92) performed an additional analysis from the same data collected from Blair *et al*. (Bla86) by using regression analysis of lung cancer mortality. There were 242 lung cancer deaths in the cohort of 20,067 white male workers. SMRs were computed by plant, age, calendar time and job type for several time-dependent formaldehyde exposures, including formaldehyde exposures in the presence of twelve selected co-exposures to other agents. A 1.6-fold increase in lung cancer risk was found (significant with $P<0.01$), beginning approximately 16 to 20 years after first employment. For workers who were never co-exposed to any of the ten other agents associated with increased lung cancer risk, an inverse relation was found between the estimated lung cancer risk ratios and (cumulative) formaldehyde exposure.

Two years later the same authors (Mar94) performed an enlarged and updated investigation on one of the plants from the study of Blair *et al*. (Bla96) which revealed an excess of nasopharyngeal cancer (four cases). The cohort consisted of 7359 workers first employed between the plant start-up in 1941 and 1984. Vital status was determined on December 31, 1984 for 96% of the cohort and death certificates were obtained for 93% of 1531 deaths. The statistical analyses focused on 6039 white males for the 1945-1984 period. SMRs were calculated based on both US and local county death rates. A significantly increased SMR (550 by local comparison) was found for nasopharyngeal cancer based on the same four cases found earlier. But when the workers were divided into long-term and short-term employed workers, there were no significantly excesses or deficits in the mortality of long-term workers (n=2590). In contrast, the short-term workers (n=3449) had significant elevated SMRs for total mortality, ischemic heart disease, non-malignant respiratory disease and accidents, and for cancers of the lung, skin and CNS. The authors claimed that these increases are difficult to interpret due to the brief employment of the workers. The results provided little evidence that the risk of lung cancer and nasopharyngeal cancer was associated with formaldehyde exposure alone or in combination with particulate or pigment exposures.

In 1994, Sterling and Weinham (Ste94), using the same data from Blair *et al*. (Bla86), compared the more exposed to less exposed workers to compute relative risks for respiratory and lung cancers using a multiple, log-linear model, incorporating factors for job type, cumulative exposure, length of exposure and age. Models were fit for all workers, all males, all workers less than 65 years of age, and for all males less than 65 years of age. The results showed that while only at high levels of cumulative exposure a significant elevation in relative lung cancer risk was observed, trend analyses of the coefficients of log-linear models indicated a significant trend of increasing risk with increasing formaldehyde exposure.

Shortly after this publication, Blair and Stewart (Bla94) stated that it is unclear why the results from Sterling and Weinham's calculations were different from those performed by others using other approaches which failed to note an exposure-response gradient. Blair and Stewart noted that apparently the authors had not considered exposures other than formaldehyde in their analyses and Blair and Stewart disagreed with their conclusions for several reasons: (1) the exposure-response gradient was not confirmed by others, (2) the findings differed from those of other major studies on formaldehyde in several countries and (3) there was a stronger linkage between lung cancer and exposures to agents other than formaldehyde than with formaldehyde itself.

In 1995, Sterling and Weinham (Ste95) replied to the comments. They acknowledged that there were a number of crucial procedural differences between Blair *et al*. and theirs. Their analysis showed a trend in relative lung and respiratory cancer risks with increasing cumulative exposure; Blair's did not. Besides, trend analysis by Blair et al. was performed on white males and on white male wage earners, and theirs on all employees and all males. Sterling and Weinham attributed Blair's failure to find such a trend to failing to adequately adjust for the 'healthy worker effect', to restricting their analysis to white males and white male hourly workers only, and to possible misclassification bias due to their use of less precise exposure computations.

Hansen and Olsen (Han95) studied the risk of cancer morbidity in Denmark during 1970-1984 from standardized proportionate incidence ratios (SPIR) among men in 265 companies in which formaldehyde was used. The longest employment had been held since 1964, at least 10 years before diagnosis of cancer. A total of 126,347 men with cancer, born between 1897 and 1964, were identified in the files of the nationwide Danish Cancer Registry. Individual employment histories were established for the patients through comprehensive data linkage with Supplementary Pension Fund. Only 91,182 male cancer cases (72.2%) were found in the files of the latter, of the rest no record of employment was found. The results did not show an association between formaldehyde exposure and lung cancer (SPIR = 1.0; 95% CI: 0.9-1.1). However, significantly elevated risks were found for cancers of the colon (SPIR = 1.2; 95% CI:

1.1-1.4), kidney (SPIR = 1.3; 95% CI: 1.0-1.6), and sinonasal cavities (SPIR = 2.3; 95% CI: 1.3-4.0). For sinonasal cancer, a relative risk of 3.0 (95% CI: 1.4-5.7) was found among blue collar workers with no probable exposure to wood dust, the major confounder. The authors concluded that formaldehyde may increase the risk of sino-nasal cancer in humans. Because of the rarity of nasopharyngeal cancer, it was not possible to evaluate the risk in this study. According to the committees there are some serious shortcomings in this study. First, the exposure classification was based on the unusual criterion of having been employed at a company that annually used over one kilogram of formaldehyde per employee. Clearly only a small proportion of these employees had been exposed to formaldehyde. Secondly, job histories were only collected for exposed cases and not for exposed controls. Thus an actual comparison of job histories between cases and controls is not possible. In addition, several of the job histories of the 13 'exposed' cases provided no evidence for formaldehyde exposure. For instance it is quite unlikely that a representative of a glue manufacturing company had been exposed to formaldehyde.

Case-control studies

Partanen *et al.* (Par90) performed a nested case-control study in a woodworker cohort in Finland. The cohort consisted of all male production workers who entered and were employed for at least a year in these plants between January 1944 and December 1965. 136 Cases of respiratory cancers were newly diagnosed among the cohort members between 1957 and 1982. Three controls (408 in all) were individually matched to each case according to year of birth. The study size was determined prior to the start in such a way that an odds ratio (OR) of at least 2 would be detected for respiratory cancer and formaldehyde exposure at an alpha of 0.05 (one-sided) and a power of 0.8. The occupational exposure of the cases ranged from less than 0.12 - 3.6 mg/m^3 (0.1 to 3 ppm) formaldehyde. The results showed that the most relevant figure was the OR adjusted for both vital status and smoking with provision for a latency period of at least 10 years. This OR was 1.4 (95% CI: 0.4-4.1) which did not differ significantly from unity (=1). The OR for lung cancer was near unity. The number of cases exposed to repeated peak exposures to formaldehyde was small, and no excess risk was observed. No significant exposure-response relationship was observed.

Luce *at al.* (Luc93) conducted a case-control study of cancer of the nose and paranasal sinuses in France. There were 207 histologically confirmed cases which were diagnosed between January 1986 and February 1988. The controls were obtained from two sources, the first being hospital controls consisting of patients with cancers at other sites, matched for age and sex (control to case ratio 3:2), and the second coming from a list provided by the cases, matched in sex, age and residence (n = 233). Occupational

exposure to formaldehyde and 14 other substances was assessed by an occupational hygienist, the levels of exposure categorized into low, medium and high. The results indicated that the OR estimates for formaldehyde exposure and squamous cell carcinomas of nasal cavities among males, adjusted for exposure to wood dust and glues, did not significantly differ; the highest OR was below 1.5. The ORs decreased when the duration and the cumulative levels of exposure increased. This study confirmed the association between nasal adenocarcinoma and exposure to wood dust. The authors suggested that interaction between formaldehyde and wood dust is plausible, since the action of wood dust, by impairing the nasal mucosa, might enhance the effect of formaldehyde.

Recently, Andjelkovich *et al*. (And94) reported a nested case-control study in the US to identify the determinants of lung cancer mortality in a cohort of 8147 male foundry workers among whom an excess of lung cancer deaths was observed previously. This study consisted of 220 lung cancer deaths that occurred in this cohort between 1950 and 1989. Both living and dead controls, matched on race and attained age, were selected in the ratio 10 : 1 (n = 2200). Smoking history was obtained for about 71% of the study objects. The formaldehyde exposures were categorised into high, medium, low and none. The same was done for silica exposure. The results showed that cigarette smoking was a strong predictor of lung cancer mortality. Neither exposure to formaldehyde nor silica, nor employment in any of the six major work areas within the foundry indicated an association with lung cancer.

A population-based case-control study on cases of bladder cancer was carried out in Montreal, Canada by Siemiatycki *et al*. (Sie94). Between 1979 and 1986, 484 persons with pathologically confirmed cases of bladder cancer and 1879 controls with cancers at other sites were interviewed, as well as a series of 533 controls of the general population. The job histories of the subjects were evaluated by a team of chemist/hygienists for exposure to 294 workplace chemicals, and information on relevant non-occupational compounds was obtained. One of the substances which showed no evidence of an association was formaldehyde. The estimated OR for ‘non-substantial’ exposure to formaldehyde was 1.2 (95% CI: 0.9-1.6) and for ‘substantial’ exposure was 1.2 (95% CI: 0.7-2.0). The results were adjusted for age, ethnicity, socio-economic status, smoking, coffee, and status of the respondent.

From these case-control studies the committees conclude that no clear relations can be found between occupational exposure to formaldehyde and cancer of the respiratory tract, including cancers of the nose, paranasal sinuses, the lung and bladder cancer.

Meta-analysis studies

Three meta-analysis of the carcinogenicity data have been published (Bla90a, Par93 and Col97). The committee decided to use these data as a starting point for the evaluation of the carcinogenicity and completed with more recent epidemiolocal studies (if relevant) which were not discussed in the meta-analysis. The first two meta-analysis took similar approaches to analysing the data.

Blair *et al.* (Bla90a) performed a meta-analysis of 30 epidemiological studies to evaluate cancer risks associated with formaldehyde exposure. In some studies excesses were reported for: leukaemia and cancers of the nasal cavities, nasopharynx, lung and brain. However, no consistent pattern emerged for any given cancer across the 30 studies. Inconsistencies among and within studies impeded assigning formaldehyde a convincing causal role for the excesses of lung cancer found among industrial workers. The authors divided the exposed groups into two categories: the professionals, like embalmers, anatomists, pathologists and funeral professionals, and the industrial workers, subjects employed in the production of formaldehyde, formaldehyde resins, formaldehyde adhesives, paraform and alcoforms. In the analyses, the observed and expected numbers were summed for studies of professional and industrial groups separately to create combined relative risk (CRR) estimates. The summation approach weighs the risks estimates by study size. The authors found that among the professionals significant excesses occurred for leukaemia (CRR 1.6, $P < 0.05$), brain cancer (CRR 1.5, $P < 0.05$) and colon cancer (CRR 1.3, $P < 0.05$). Fewer deaths from lung cancer occurred among the professionals (CRR 0.9, $P < 0.05$). In contrast to the professionals, industrial workers did not show elevated mortality from leukaemia (CRR 1.1) or brain cancer (CRR 0.9). A small but significant excess of lung cancer (CRR 1.1, $P < 0.05$) was seen among industrial workers. A non-significant increase was observed for nasopharyngeal cancer (CRR 1.2), nasal cavity cancer (CRR 1.1) and bladder cancer (CRR 1.1). The risk of nasal cancer was evaluated by exposure level or duration. The results showed no exposure-related response gradient. On the other hand, for nasopharyngeal cancer, the CRR values rose to 2.1 in the high-exposure category (higher than 6.6 mg/m^3.year cumulative exposure), a trend which was significant. The authors concluded that: (1) a causal association between exposure to formaldehyde and lung cancer could not be entirely discounted; (2) a causal role for formaldehyde is most probable for cancers of the nasopharynx; (3) the association with nasal cancer is plausible, but somehow less persuasive than that for nasopharyngeal cancer; (4) the absence of excesses for leukaemia and cancers of colon and brain among industrial workers suggests that the association seen among professional workers may not be due to formaldehyde.

Partanen (Par93) also performed a meta-analysis using the same sources as Blair *et al*. (Bla90a) with some updating. The overlaps between the studies were removed, as in the earlier study. The aggregated risk ratios (RR) were estimated as aggregated observed-to-expected ratios, and the 95% confidence limits were set for the RR values. The main difference between the earlier (original) analysis and the reanalysis was the selection of the input values. In the reanalysis of both sinonasal and nasopharyngeal cancers, a significant increase was associated with 'substantial' exposure category (RR 1.7 for sinonasal cancers and 2.7 for nasopharyngeal cancers). Neither an increased risk nor an exposure-response relation was suggested by the aggregated data for the combined category of oropharynx, hypopharynx, lip, tongue, salivary glands and mouth cancer. Analyses for lung cancer showed a decreased risk for professionals (aggregated RR = 0.3 and 1.0), for industrial workers the aggregated RR was 1.1 (95% confidence interval (CI): 1.0-1.2). Further analyses for industrial workers alone showed an aggregated RR of 1.2 for 'low-medium' exposure and 1.1 for 'substantial' exposure. The authors concluded that it did remain unlikely that workplace exposures to formaldehyde pose any substantial lung cancer hazard among humans. On the other hand, an exposure-response gradient was revealed on sinonasal cancer; risk in the category of substantial exposure was significantly elevated. However, according to both committees, in this meta-analysis the authors did not correct for the unreported studies in which no cases of nasal cancers were found. This method must have led to an overestimation of the overall relative risk for nasopharyngeal cancer.

Collins *et al.* (Col97) reported a review of 47 epidemiologic studies in which the carcinogenic risk after occupational exposure to formaldehyde was studied. These 47 studies included studies of industrial cohorts of exposed workers, of exposed medical specialists and exposed embalmers case-control studies. After correction for underreporting a meta relative risk of 1.0 for nasal cancer was found in the cohort studies and a relative risk of 1.3 for the case-control studies. The authors concluded that the available studies do not support a causal relation between formaldehyde exposure and nasopharyngeal cancer. In addition to the literature review the investigators provide four factors that explain the discrepancy with the two earlier positive literature reviews. Since this well conducted (more recent) meta-analysis includes more studies (positive and negative) than the previous literature reviews and the exposure potential for jobs included in the general population case-control studies was evaluated, the committees give preference to the review of Collins *et al.* over the earlier reviews. In 2000, Vaughan et al (Vau00) published a case-control study at five cancer registries in the United States. Cases (n=196) with nasopharyngeal cancer diagnosed between 1987-1993 and controls (n=244) were questioned. The authors concluded that the results of this study support the hypothesis that occupational exposure to formaldehyde, but not to wooddust, increase the risk of nasophryngeal

cancer (specific for squamous cell carcinomas). However, no actual exposures to formaldehyde was measured, the authors used self reported occupational histories for assessing to exposureconcentration. Thus, misclassification was inevitable.

Finaly, 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.

Genotoxicity

Several studies were identified that described the positive and negative genotoxic effects after exposure to formaldehyde.

Ying *et al.* (Yin97) studied the frequency of micronuclei in the cells of nasal mucosa, oral mucosa and in lymphocytes of 25 students exposed to formaldehyde. The concentration of formaldehyde was 0.508 +/- 0.299 mg/m^3. A higher frequency of micronuclei was observed in nasal and oral exfoliative cells but not in lymphocytes. In 1999, Ying *et al* (Yin99) evaluated the effects of formaldehyde on pheripheral lymphocytes of 23 non smoking students. No significant difference was reported between lymphocyte proliferation and sister chromatid exchange (SCE).

Vasudeva *et al.* (Vas96) examined the effect of formaldehyde in the incidence of chromosome aberrations in peripheral blood lymphocytes of 30 medical students exposed to concentrations of less than 1.2 mg/m^3. There was no difference in incidence of chromosomal aberrations between the exposed and control group.

He *et al.* (He98) examined human peripheral lymphocytes of 13 student exposed to formaldehyde (3.17 mg/m^3) for abnormalities. Lymphocytes of 10 student of the same school without formaldehyde exposure served as controls. The micronuclei rate (6.38 +/- 2.5, $p<0.01$), chromosome aberration rate (5.92 +/- 2.4, $p<0.01$) and sister chromatid exchange rate (3.15 +/- 1.57, $p<0.05$) in the exposed group was increased.

In conclusion, evidence for genotoxic potential of formaldehyde in humans exposed to occupational levels is insufficient and conflicting.

7.2 Animal experiments

7.2.1 Sensory irritation

Kane and Alarie (Kan77) exposed Swiss Webster mice for 10 min to concentrations of formaldehyde ranging from 0.62 to 13.4 mg/m^3 (0.52 to 11.2 ppm) to evaluate sensory

irritation after single exposures. The RD_{50} appeared to be 3.6 ± 0.34 mg/m^3 (3.0 ± 0.28 ppm).

Wood and Coleman (Woo95) studied the irritant properties of formaldehyde in mice (N=8) by observing their behaviour. The animals were initially trained to terminate exposure to ammonia by poking their nose five times into a conical sensor. In this experiment, mice were exposed to a series of concentrations from 1.2 to 12 mg/m^3 (1 to 10 ppm) formaldehyde for a maximum of 60 sec followed by a 60 sec washout period; this cycle was repeated 25 times per session. As the concentration of formaldehyde increased, the timespan after which the animals terminated their exposure shortened. This study showed that formaldehyde was aversive to mice at concentrations which approximate those at which humans reported sensory irritation.

7.2.2 Airway reactivity

Adult male Cynomolgus monkeys (N=9) exposed to an average of 3.1 mg/m^3 (2.6 ppm) formaldehyde for 10 minutes showed significant pulmonary function deficits immediately after the challenge (Bia89). The design of this experiment included a pre-exposure metacholine challenge to determine whether responses to formaldehyde were associated with pre-existing bronchial hyperreactivity. A significant increase of the average pulmonary flow resistance (Rl) was observed 2, 5, and 10 min after formaldehyde challenge.

The hyperreactivity of the respiratory smooth muscle after exposure to formaldehyde was studied by Swiecichowski *et al*. (Swi93). Groups of 5 to 7 guinea pigs were exposed to (I) 1, 4, 11.3 or 37.3 mg/m^3 (0.86, 3.4, 9.4 or 31.1 ppm) formaldehyde for 2 hours, or to (II) 0.1, 0.4, 0.7 or 1.3 mg/m^3 (0.11, 0.31, 0.59 or 1.05 ppm) formaldehyde for 8 hours. The airway reactivity was assessed before exposure to formaldehyde and one and 24 hours after exposure, using *in vivo* and *in vitro* methods. The authors found that the specific pulmonary resistance and airway reactivity (to infused acetylcholine) increased with increasing formaldehyde exposure. Formaldehyde exposure caused bronchoconstriction and hyperreactivity at lower concentrations when exposure was extended from 2 to 8 hours. Exposure to concentrations of formaldehyde higher than 0.37 mg/m^3 for 8 hours was sufficient to produce a significant increase in airway reactivity, while similar effects after 2 hours exposure only occurred at concentrations above 11 mg/m^3. Formaldehyde exposure also heightened airway smooth muscle responsiveness to acetylcholine or carbachol *in vitro*. These effects occurred with no evidence of epithelial damage or inflammation up to 4 days after formaldehyde exposure. From this study the committees conclude that the no-observed-adverse-effect-level (NOAEL) for airway reactivity in guinea pigs is 0.13 mg/m^3 (0.11 ppm) formaldehyde vapour.

7.2.3 Sensitization

Hilton *et al.* (Hil96) studied the sensitizing property of formaldehyde. They reported that the compound elicited strong positive responses in three independent methods: the guinea pig maximization test (N=10), the guinea pig occluded patch test of Buehler (N=10) and the mouse local lymph node assay (N=4). In contrast, formaldehyde was negative in the mouse IgE test (N=6), which is a novel predictive test method for assessment of respiratory sensitisation potential. The authors concluded that, although formaldehyde is a potent contact allergen, it lacks a significant potential to cause sensitisation of the respiratory tract.

Boman *et al.* (Bom96) studied the potency of contact allergens, including formaldehyde, by using the guinea pig maximization test (GPM test). For each chemical five groups of five animals each were treated intradermally with concentrations per group reduced with increments of a factor three from the highest concentration that could be applied intradermally. Two of the five groups were treated topically with the highest non-irritating concentration and the three other groups with a 100 times lower concentration. All groups were challenged and rechallenged with the highest non-irritating concentration. For each chemical a vehicle control group was included for comparison. Measurements were performed in two different laboratories. A highly significant dose response relationship was obtained and the curves were similar at both laboratories and corresponded well with earlier reported test results supporting that multidose design gives reproducible results.

7.2.4 Acute cytotoxic effects on nasal epithelium

In vitro experiments have been performed by Colizzo *et al*. (Col92) to study the alterations of specific ciliated epithelial cell surface components after exposure to formaldehyde levels which decreased respiratory ciliary function. In this experiment bovine trachea was exposed to 0, 16, 33 and 66 mg formaldehyde per cm^2 epithelial surface for 30 min. The results showed that the axoneme proteins (i.e. part of the cilia) decreased with increased formaldehyde concentrations and the biotinylated proteins proportionally increased. Membrane fractions showed little change in protein. The data suggest that increasing formaldehyde exposure reduced both extractable ciliary axonemes and detergent-soluble surface components.

Bhalla *et al*. (Bha91) investigated the distribution of epithelial cells over the turbinates in the rat nasal cavity and their injury following exposure to formaldehyde in a nose-only manner. Rats were exposed to either purified air or to 12 mg/m^3 (10 ppm) formaldehyde for a period of 4 hours. Changes were seen in the various regions of the

turbinates in the form of ciliary destruction and cell separation (especially in the naso- and maxilloturbinates), cellular swelling (throughout the turbinate), mucous release by the goblet cells (in the naso turbinate), and in some cases pores on the cell surface or between adjacent cells (evident in the meates). The authors concluded that the degree of deleterious effects of formaldehyde on the nasal epithelia of rats is dependent upon cell type and location.

7.2.5 *Toxicity during short-term exposure*

Major short-term inhalation toxicity studies of formaldehyde in experimental animals are summarized in Table 3.

Table 3 Short-term inhalation toxicity studies of formaldehyde in rats, mice or monkeys.

study design	NOAEL	LOAEL	critical effect	ref.
Rats and mice (number and sex not specified) exposed to 0, 0.6, 2.4, 7.2, 18 mg/m^3 (0, 0.5, 2, 6, 15 ppm); 6h/d; 3 days	7.2 mg/m^3 (mice)	*mice*: 18 mg/m^3; *rats*: Permanent effects at 7.2 mg/m^3, and transient effects at 0.6 and 2.4 mg/m^3	Increased epithelial cell proliferation in nasal cavity.	Swe83, 86
Groups of 6 male rats exposed to 0, 0.6, 2.4, 7.1 or 17.3 mg/m^3 (0, 0.5, 2, 5.9 or 14.4 ppm); 6 h/day, 5 days/week; 1, 2, 4, 9 or 14 days	2.4 mg/m^3	7.1 mg/m^3	Histopathological effects in nasal cavity. Inhibition of mucociliary clearance.	Mor86A
Groups of 10 male and 10 female rats exposed to 0, 1.2, 11.6 or 23.8 mg/m^3 (0, 1, 9.7 or 19.8 ppm); 6 h/day, 5 days/week; 13 weeks	1.2 mg/m^3; however, doubtful according to authors	11.6 mg/m^3	Histopathological effects in nasal cavity.	Wou87
Groups of 10 male rats exposed to 0, 6, or 12 mg/m^3 (0, 5, 10 ppm); for 8 h/day ("continuous exposure") or to 10 or 20 ppm (12 or 24 mg/m^3) for 8 to 30-min. Exposure periods separated by 30-min. intervals ("intermittent exposure"); 5 days/week; 4 weeks		6 mg/m^3	Histopathological effects and increased cell turnover rates, squamus metaplasia with cellular hyperplasia, minimal to moderate rhinitis. In rats with the same daily cumulative dose, the effects were greater in rats exposed intermittently to the higher concentration.	Wil87
Groups of 50 male and 50 female rats exposed to 0, 0.3, 1 or 3 ppm (0, 0.36, 1.2 or 3.6 mg/m^3); 6 h/day; 5 days/week; 13 weeks. Satellite groups of 5 males and 5 females exposed to the same concentrations for 3 days or 13 weeks	1.2 mg/m^3 (13-week study) 0.36 mg/m^3 (3-day study)	3.6 mg/m^3 (13-week study) 1.2 mg/m^3 (3-day study)	Histopathological changes in nasal cavity and increased epithelial cell proliferation in nasal cavity (13-week study). Increased epithelial cell proliferation in nasal cavity (3-day study).	Zwa88

Table 3 Continued.

study design	NOAEL	LOAEL	critical effect	ref.
Groups of 50 male and 50 female rats exposed to 0, 0.3, 1 or 3 ppm (0, 0.36, 1.2 or 3.6 mg/m^3); 6 h/day; 5 days/week; 13 weeks. Satellite groups of 5 males and 5 females exposed to the same concentrations for 3 days or 13 weeks	1.2 mg/m^3 (13-week study) 0.36 mg/m^3 (3-day study)	3.6 mg/m^3 (13-week study) 1.2 mg/m^3 (3-day study)	Histopathological changes in nasal cavity and increased epithelial cell proliferation in nasal cavity (13-week study). Increased epithelial cell proliferation in nasal cavity (3-day study).	Zwa88
Groups of 10 male rats exposed to 0, 0.1, 1 or 9.4 ppm (0, 0.12, 1.2 or 11.3 mg/m^3); 6 h/day; 5 days/week for 13 weeks	1.2 mg/m^3	11.3 mg/m^3	Histopathological changes in nasal cavity (rhinitis, hyperplasia and metaplasia).	App88
Groups of 3 male Rhesus monkeys exposed to 0 or 6 ppm (0 or 7.2 mg/m^3); 6 h/day; 5 days/week for 1 or 6 weeks		7.2 mg/m^3	Histopathological changes and increased epithelial cell proliferation in upper respiratory tract.	Mon89
Groups of 25 male rats exposed to either 0, 1 or 2 ppm (0, 1.2 or 2.4 mg/m^3) for 8 h/day ("continuous exposure") or to 2 or 4 ppm (2.4 or 4.8 mg/m^3) for 8 30-min. exposure periods separated by 30-min. intervals ("intermittent exposure"); 5 days/week; 13 weeks	2.4 mg/m^3	4.8 mg/m^3	Histopathological changes and increased epithelial cell proliferation in the nasal cavity; squamous metaplasia with basal cell hyperplasia in nasal epithelium .	Wil89
Groups of 10 male rats exposed to 0, 0.3, 1.1 or 3.1 ppm (0, 0.36, 1.3 or 3.7 mg/m^3); 22 h/day for 3 consecutive days	1.3 mg/m^3	3.7 mg/m^3	Histopathological changes and increased epithelial cell proliferation in the nasal cavity.	Reu90
Groups of 36 male rats exposed to 0, 0.7, 2, 6.2, 9.9 or 14.8 ppm (0, 0.8, 2.4, 7.4, 11.9 or 17.8 mg/m^3); 6 h/day; 5 days/week for 1, 4 or 9 days or 6 weeks	2.4 mg/m^3	7.4 mg/m^3	Histopathological changes and nasal epithelial cell necrosis, neutrophil infiltration, epithelial hyperplasia, squamus metaplasia, increased cell proliferation.	Mon91
Groups of 10 male rats exposed to 0, 0.7, 2, 5.9, 10.5 or 14.5 ppm (0, 0.8, 2.4, 7.1, 12.6 or 17.4 mg/m^3); 6 h/day; 5 days/week for 11 weeks	2.4 mg/m^3	7.1 mg/m^3	Histopathological changes and increased epithelial cell proliferation in the nasal cavity.	Cas94
Groups of 5-6 male rats exposed to 0, 1, 3.2 or 6.4 ppm (0, 1.2, 3.8 or 7.7 mg/m^3); 6 h/day 3 consecutive days	1.2 mg/m^3	3.8 mg/m^3	Histopathological changes and increased epithelial cell proliferation in the nasal cavity.	Cas96

The critical effects of short-term exposure to airborne formaldehyde in experimental animals are damage to and increased proliferation of the nasal epithelium. The histopathological changes range from slight hyperplasia and squamous-cell metaplasia of the ciliated and non-ciliated respiratory epithelium in specific areas (found at low effective exposure concentrations, ie. 2.4 to 3.6 mg/m^3) to severe rhinitis, necrosis and extensive hyper/metaplasia of major portions of the nasal epithelium (found at exposure concentrations of about 7.2 mg/m^3) and higher}. Substantial increases in epithelial cell turnover rates occur in rats at exposure concentrations of 7.2 mg/m^3 and higher. Marginally and only transiently increased cell turnover rates have occasionally been found at levels of 0.6 to 2.4 mg/m^3.

Table 3 shows that the majority of NOAELs are between 1.2 to 2.4 mg/m^3 (1 or 2 ppm). Table 3 also reveals that in all studies with a NOAEL of 1.2 mg/m^3 (1 ppm) the LOAEL is higher than 2.4 mg/m^3 (2 ppm), indicating a steep dose-response relation (it is possible that in these studies a NOAEL of 2.4 mg/m^3 might have been obtained if this exposure concentration would have been included in these experiments). However, occasionally (Swe83, 86; Zwa88) increased cell proliferation has been found at exposure levels of 0.6 or 1.2 mg/m^3 (0.5 or 1 ppm), while the findings of Woutersen *et al*. (Wou87) turned out to be inconclusive with respect to 1.2 mg/m^3 (1 ppm) being a NOAEL or a LOAEL.

7.2.6 *Toxicity due to long-term exposure and carcinogenicity*

Major long-term inhalation toxicity and/or carcinogenicity studies in rats and mice are summarized in Table 4.

Critical effects of long-term inhalation exposure to formaldehyde include inflammatory, degenerative and regenerative changes of the nasal mucosa and squamous-cell carcinomas of the nasal respiratory epithelium. The non-neoplastic nasal changes range from a minimal degree of hyperplasia and squamous-cell metaplasia of the nasal respiratory epithelium (occasionally seen at concentrations of approximately 2.4 mg/m^3 or lower) to rhinitis, necrosis and extensive restorative hyperplasia and metaplasia of the nasal respiratory epithelium invariably seen at concentrations of about 7.2 to 18 mg/m^3 (6 to 15 ppm). High incidences of squamous-cell carcinomas have been found in rats at exposure levels of 12 mg/m^3 (10 ppm) or higher.

In most long-term studies, a NOAEL of 1.2 or 2.4 mg/m^3 have been reported (Table 4). However, in one long-term study in rats 2.4 mg/m^3 (2 ppm) appeared to be a LOAEL (Ker83) and in another long-term rat study a LOAEL as low as 0.36 mg/m^3 (0.3 ppm) was reported (Kam97).

Table 4 Long-term inhalation toxicity and/or carcinogenicity studies of formaldehyde in rats, mice.

study design	NOAEL	LOAEL	major effect	ref.
Groups of 119-120 male and 120 female rats, and 119-120 male and 120-121 female mice exposed to 0, 2.0, 5.6 and 14.3 ppm (0, 2.4, 6.7 or 17.2 mg/m^3); 6 h/day; 5 days/week; up to 24 months	2.4 mg/m^3 (mice)	*mice*: 6.7 mg/m^3 *rats*: 2.4 mg/m^3	Histopathological changes in nasal cavity. Nasal squamous-cell carcinoma: 2/17 male mice exposed to 17.2 mg/m^3 and killed at 24 months. Nasal squamous-cell carcinoma: 51/117 male and 52/115 female rats exposed to 17.2 mg/m^3. Nasal polypoid adenoma: 1/232, 8/236, 6/235 and 5/232 rats exposed to 0, 2.4, 6.7 or 17.2 mg/m^3, resp.	Ker83
Three groups of 90-100 male rats exposed to 0, 0 (colony controls) or 14.2 ppm (0, 0 or 17.5 mg/m^3); 6 h/day; 5 days/week for life		17.5 mg/m^3	Histopathological changes in nasal cavity. Nasal squamous-cell carcinoma: 38/100 rats exposed to 17.5 mg/m^3.	Sel85
Groups of 10 male rats exposed to 0, 0.1, 1 or 9.4 ppm (0, 0.12, 1.2 or 11.3 mg/m^3); 6 h/day; 5 days/week; 52 weeks	1.2 mg/m^3	11.3 mg/m^3	Histopathological changes in nasal cavity. No nasal tumours.	App88
Groups of 30 male rats exposed to 0, 0.1 or 9.8 ppm (0, 0.12 or 11.8 mg/m^3); 6 h/day; 5 days/week; 28 months	1.2 mg/m^3	11.8 mg/m^3	Histopathological changes in nasal cavity. No nasal tumours.	Wou89
Groups of 30 male rats exposed to 0, 0.1, 1 or 9.2 ppm (0, 0.12, 1.2 or 11 mg/m^3); 6 h/day; 5 days/week for 3 months and then observed for a further 25 months	1.2 mg/m^3	11 mg/m^3	Histopathological changes in nasal cavity. No nasal tumours.	Wou89
Groups of approximately 90-150 male rats exposed to 0, 0.7, 2, 6, 10 or 15 ppm (0, 0.8, 2.4, 7.2, 12 or 18 mg/m^3); 6 h/day; 5 days/week; up to 24 months	2.4 mg/m^3	7.2 mg/m^3	Histopathological changes in nasal cavity and increased proliferation of nasal epithelial cells. Nasal squamous-cell carcinoma: 20/90 and 69/147 rats exposed to 12 and 18 mg/m^3, resp.	Mon96
Groups of 32 male rats exposed to 0, 0.3, 2 or 15 ppm (0, 0.36, 2.4 or 18 mg/m^3; 6 h/days; 5 days/week; 28 months		0.36 mg/m^3	Histopathological changes in nasal cavity. The effect seen at 0.36 mg/m^3 was not statistically significantly different from that in the controls but was nevertheless considered formaldehyde-related by the authors due to a clear dose-response relationship for these nasal findings. Nasal squamous-cell carcinoma: 13/29 rats exposed to 18 mg/m^3.	Kam97

7.2.7 *Genotoxicity*

The mutagenic properties of formaldehyde have been investigated in many test systems. A summary as presented by the IARC/WHO (IAR95) is shown in Annex E.

After the appearance of the IARC/WHO document (IAR95), more data on the genotoxicity of formaldehyde have been published. Vock *et al*. (Voc99) studied the induction of DNA double-strand breaks in cultured human lung epithelial cells by pulse-field gel electrophoresis, and the viability was evaluated by the MTT (dimethylthiazol-diphenyltetrazolium bromide) cytotoxicity test. They reported induction of DNA double-strand breaks by formaldehyde when cell viability was reduced to less than 60% of the control values, indicating that DNA double-strand breaks were the consequence of extragenomic damage and viability loss.

Merk and Speit (Mer98) studied formaldehyde-induced DNA-protein cross-links in V79 Chinese hamster cells. They observed that formaldehyde, parallel to the induction of cytotoxicity, induced significant numbers of DNA-protein cross-links, sister-chromatid exchanges, and micronuclei in the same range of concentrations. In contrast, treatment of V79 cells with formaldehyde did not induce gene mutations in the HPRT test, even after variations of the treatment protocol. The authors concluded that formaldehyde-induced DNA-protein crosslinks seem to be related to cytotoxicity and clastogenicity, but do not lead to the formation of gene mutations in mammalian cells.

In an *in vivo* experiment Casanova *et al*. (Cas91) reported covalent binding of formaldehyde to DNA in the respiratory tract of rhesus monkeys. The DNA-protein cross-links were formed after exposure by inhalation (head only) to 0.8, 2.4 or 7.2 mg/m^3 (0.7, 2 or 6 ppm) formaldehyde for 6 hours (N=3 per group).

Odeigah (Ode97) performed two short-term *in vivo* mutagenicity tests (sperm head abnormality and dominant lethal mutation assays) in isogenic strains of albino rats. Five daily intraperitoneal injections of formaldehyde resulted in a statistically significant increase of sperm head abnormalities at doses of 0.125 to 0.500 mg/kg b.w. The frequency of dominant lethal mutations in female rats sired by males exposed to formaldehyde was significantly higher than in the control group.

In summary, no adequate data are available on genetic effects of formaldehyde in humans. Formaldehyde is comprehensively genotoxic in a variety of experimental systems, ranging from bacteria to rodents. Formaldehyde given by inhalation or gavage to rats *in vivo* induced chromosomal aberrations in lung cells, micronuclei in the gastrointestinal tract and sperm-head anomalies. Formaldehyde induced DNA-protein cross-links, DNA single-strand breaks, chromosomal aberrations, sister chromatid

exchanges and gene mutations in human cells *in vitro*. It induced cell transformation, chromosomal aberrations, sister chromatid exchanges, DNA strand breaks, DNA-protein cross-links and gene mutations in rodent cells *in vitro*. Administration of formaldehyde to Drosophila *melanogaster* in the diet induced lethal and visible mutations, deficiencies, duplications, inversions, translocations and crossing-over in spermatogonia. Formaldehyde induced mutations, gene conversion, DNA strand breaks and DNA-protein cross-links in fungi, and mutations and DNA damage in bacteria. Inhalation of formaldehyde leads to formation of DNA-protein cross-links in the nasal respiratory mucosa of rats and monkeys. The formation of DNA-protein cross-links is a sublinear function of the formaldehyde concentration in inhaled air from 0.86 to 18.4 mg/m^3 (0.71-15.27 ppm), and the yield of DNA-protein cross-links at a given inhaled concentration is approximately an order of magnitude lower in monkeys than in rats. There is no detectable accumulation of DNA-protein cross-links during repeated exposures.

7.2.8 *Mechanism of formaldehyde nasal carcinogenesis*

From the above data it is clear that formaldehyde is a highly cytotoxic, genotoxic carcinogen capable of inducing nasal carcinomas in rats and possibly in mice. The nasal *toxicity* of formaldehyde is characterized by inhibition of mucociliary function (Mor86A), reaction with small proteins present in nasal mucus (Bog87), reaction with glutathione followed by detoxification by formaldehyde dehydrogenase (Hec84), and, when biotransformation is overwhelmed or even inactivated, rhinitis, degeneration and necrosis followed by regenerative hyperplasia and metaplasia of the respiratory epithelium (Swe83; Mor97). These distinct toxic effects have been invariably found in rats after short- and long-term exposure to concentrations of about 2.4 mg/m^3 (2 ppm) and higher (Ker83; Sel85; Mor86A; Wou87, 89; App88; Mon96).

Formaldehyde appears to be a direct-acting *genotoxicant* capable of inducing DNA-protein cross-links in nasal respiratory epithelium of experimental animals following inhalation exposure (“local genotoxicity”) (Mah88). Cross-linking of DNA with proteins might be expected to lead to DNA damage during cell replication, and potential mechanisms for such effects have been reviewed by Heck *et al.* (Hec90). A series of studies has clearly demonstrated a strong deviation from linearity of the formation of DNA-protein cross-links in the nasal epithelium of rats (Hec87, 89; Cas87). One of the reasons for this non-linearity is inactivation of formaldehyde by glutathione, which apparently is much more effective at low (1,2 to 2.4 mg/m^3) than at high (7.2 to 18 mg/m^3) formaldehyde concentrations (Hec89; 90).

High incidences of *nasal carcinomas* have been found in rats following long-term exposure to concentrations of 12 mg/m^3 (10 ppm) or higher (Ker83; Sel85; Mon96;

Kam97). These tumour data and the aforementioned toxicity data demonstrate that exposure levels causing nasal tumours also cause rhinitis, necrosis and epithelial hyperplasia and metaplasia of the nasal mucosa. Moreover, in a study on the more precise localization of the formaldehyde-induced nasal tumours in rats, Morgan *et al.* (Mor86B) showed that tumours invariably occurred at locations of mucociliary inhibition, and epithelial hyperplasia and metaplasia. The dose-response curve for nasal tumours is very steep and extremely non-linear, while its shape appears to correspond with that of the dose-response curves for DNA-protein cross-links, inhibition of the mucociliary function, increased cell proliferation, and hyperplasia and metaplasia of the nasal respiratory epithelium. Obviously, an association exists between the cytotoxic, genotoxic and carcinogenic effects (Mor97). In other words, the steep non-linear dose-response curve for nasal tumours — indicating a more than proportionate decrease in cancer incidence at low concentrations — is most probably due to the fact that defence mechanisms of the nose (mucociliary clearance, detoxification by dehydrogenase, DNA repair) are very effective at low concentrations, but can be overwhelmed and inactivated at high concentrations; consequently, cell and tissue damage and finally tumours occur at high concentrations only.

These data and considerations suggest that the induction of nasal carcinomas by formaldehyde requires long-term exposure to levels that cause considerable damage to the nasal epithelium followed by restorative hyperplasia. This increased cell replication and subsequent cycles of DNA-synthesis, provoked by long-term exposure to formaldehyde, may strongly enhance the likelihood of relevant DNA-damage, and moreover, may strongly enhance the progression of initiated/preneoplastic cells to cancer. This also means that formaldehyde in concentrations not leading to tissue damage most probably cannot act as a complete carcinogen (causing initiation, promotion and progression), and as a result is very unlikely to induce cancer by itself. Therefore, it is concluded that cytotoxic effects of formaldehyde play a highly significant, if not an essential role, in the formation of nasal tumours by formaldehyde. This conclusion is strongly supported by the results of a long-term inhalation study, in which male rats with a severely damaged or undamaged nasal mucosa were exposed to 0, 0.12, 1.2 or 12 mg/m^3 (0, 0.1, 1.0 or 10 ppm) formaldehyde for 6h/day, 5 days/week, during either 28 months or 3 months followed by a non-exposure, observation period of 25 months (Wou89). The damage to the nasal mucosa was induced by bilateral intranasal electrocoagulation. Treatment-related nasal tumours (squamous-cell carcinomas) only occurred in the 12 mg/m^3 group of rats with a damaged nasal mucosa and exposed to formaldehyde for 28 months. Obviously, severe damage to the nasal mucosa in combination with prolonged exposure to a relatively high cytotoxic concentration of formaldehyde leads to tumour formation. In this study, 12 mg/m^3

formaldehyde induced extensive and severe hyperplasia and metaplasia in the intact nasal mucosa, but no tumours. Clearly, for tumour formation “drastic” conditions seem to be required: severe damage plus a relatively high concentration (dose) of formaldehyde (Fer89).

7.2.9 *Reproductive toxicity*

In 1987, DECOS concluded in its previous document on formaldehyde that, based on studies available at that time, formaldehyde had not been demonstrated to cause adverse reproductive outcomes, even though foetotoxicity but not teratogenic effects had been observed, following administration of high doses of a known precursor of formaldehyde (hexamethylene tetramine). Therefore, it was suggested that additional studies in this field should be conducted. In 1989, the IPCS/WHO (IPC89) concluded that animal experiments did not show any evidence of the embryo, it being unusually sensitive to formaldehyde, and there was no information to show that formaldehyde was teratogenic in rodents when administered orally or applied dermally in non-toxic amounts to the dams. Furthermore, the data did not provide any evidence indicating that formaldehyde caused terata at exposure concentrations that were not toxic for the adult.

Saillenfait *et al.* (Sai89) studied the reproductive toxicity of formaldehyde in Sprague-Dawley rats. Groups of 25 pregnant rats were exposed by inhalation to 0, 6, 12, 24 or 48 mg/m^3 (0, 5, 10, 20 or 40 ppm) formaldehyde, 6 h/day, from day 6 to 20 of gestation. No effect was found on embryonic or foetal lethality, nor significant alterations in the external, visceral or skeletal appearances of the foetuses. Significant concentration-related reduction of foetal body weight occurred at 24 and 48 mg/m^3 (20 and 40 ppm). Maternal toxicity was observed at 48 mg/m^3 (40 ppm), as indicated by reduction of body weight and body weight gain.

Martin (Mar90) exposed groups of 25 mated rats by (whole-body) inhalation to 2.4, 6.0 or 12 mg/m^3 (2, 5 or 10 ppm) formaldehyde 6 hours per day, from day 6 to day 15 of gestation. Two control groups were used. The pregnancy rate in all groups was at least 80%. At the highest dose (12 mg/m^3) there was a significant decrease in maternal food consumption and body weight gain. Pregnancy parameters, including numbers of corpora lutea, implantation sites, live fetuses and resorptions, fetal weights, sex ratios, and preimplantation and postimplantation losses were unaffected by the treatment. The overall incidences of litters and fetuses with major malformations, minor external and visceral anomalies, and minor skeletal anomalies were not affected by treatment with formaldehyde. There was no evidence of maternal toxicity at 2.4 and 6 mg/m^3 (2 and 5 ppm) exposure levels. At the 6 and 12 mg/m^3 (5 and 10 ppm) dose levels, an apparently significant concentration-related decrease in ossification was detected in the fetal bones

of the pelvic girdle, which was associated with larger litter sizes with decreased fetal weights in both these groups. Also the slightly lower fetal weights were considered to be due to the larger litter sizes.

Recently, Majumber and Kumar (Maj95) reported inhibitory effects of formaldehyde on the reproductive system of male rats. In their experiment, adult male rats were treated intraperitoneally with formaldehyde at a dose of 10 mg per kg body weight per day given for 30 days. After the exposure period they found a fall in tissue protein contents of the epididymis and prostate, while these were not affected in testes and seminal vesicles. On the other hand, the DNA content had significantly decreased only in the testes and prostate of treated rats compared to control rats. The sperm count had decreased by 50% in treated rats. The sperm viability was also significantly affected and only 30% of viable sperms in the treated group were motile as compared to 86% in the control group. The authors also performed an *in vitro* study in which equal volumes of sperm suspension of normal rats and different concentrations of formaldehyde were mixed and incubated at ambient temperature for different time intervals. In this study, 80% sperms were viable over a period of 1 hour in the control group. At concentrations of 5 ng/ml formaldehyde only 50% spermatozoa were viable over a period of 30 min. At 500 ng/ml formaldehyde 50% spermatozoa were viable over a period of 6 min and at 2.5 mg/ml the effect was profound and instantaneous, and sperm viability dropped to zero within 10 min. Clearly, direct contact of high concentrations of formaldehyde with sperm affected sperm viability.

From the data the committees conclude that there is no evidence that formaldehyde may induce teratogenicity or may affect reproduction by inhalation exposure.

7.2.10 Other studies

Vargova *et al*. (Var93) studied the immunotoxicity of formaldehyde in male rats. The animals were exposed to doses of 0, 20, 40 and 80 mg/kg body weight/day by oral administration (gastric tube) for 28 days. The body weights of rats exposed to the highest dose were slightly decreased. The lymph node weights were significantly increased, but the cellularity of lymphoid organs was not influenced after 28 days of exposure to formaldehyde. There was a dose-dependent reduction of antibody response (IgG and IgM) at doses of 20, 40 and 80 mg per kg body weight per day. However, there was no significant reduction of the spleen cells producing IgM antibodies in exposed rats. The hepatocytes of the exposed animals showed increased cytoplasmic vacuolization. Histochemistry revealed narrowing of the thymus-dependent zone in the spleen.

7.3 Summary

The odour threshold of formaldehyde varies from 0.06-0.22 mg/m^3 (0.05 and 0.18 ppm) (IPC89).

Human studies

Sensory irritation in man

Sensory irritation in man is first (at low concentrations) experienced in the eyes, then (at higher concentrations) the odour of formaldehyde is perceived, and finally nasal and throat irritation occur (IPC89). After long-term occupational exposure to an average concentration of 0.26 mg/m^3 (0.22 ppm) formaldehyde (range 0.05 to 0.6 mg/m^3) more than 50% of the workers complained of nasal discomfort (Wil92). However, in this (not well controled) study the questionaire used was not published. From cross-sectional morbidity studies it appeared that symptoms of irritation of the upper respiratory tract may occur after acute exposure to formaldehyde levels below 1.2 mg/m^3 (1 ppm) (Wil92; Sri92; Chi92). Also from controlled studies in volunteers it appeared that at exposure levels for a short period lower than 1.2 mg/m^3 (1 ppm) sensory irritation may still occur in a substantial percentage of exposed individuals (And83; Ben83). In one study (And83), 19% of the exposed persons reported eye irritation at an exposure level of 0.29 mg/m^3 (0.24 ppm).

Rhinitis in man

Transient rhinitis has been found in volunteers exposed to 0.48 mg/m^3 (0.4 ppm) formaldehyde for 2 hours (Paz93). A cross-sectional study on workers exposed to formaldehyde levels between 0.6 to 2.4 mg/m^3 (0.5 and 2 ppm) for more than 22 years revealed that 3 of 37 workers (18%) showed *epithelial dysplasia* in nasal biopsies; in all three cases the dysplasia was of the squamous type (Boy90).

Pulmonary function in man

No changes in pulmonary function have been found in humans exposed to formaldehyde concentrations up to 3.6 mg/m^3 (3 ppm) (Wit87; Sau87; Har90).

Sensitization in man

There is no consistent evidence of formaldehyde being capable of sensitizing the respiratory tract. Under certain circumstances formaldehyde induced an IgE-mediated type 1 reaction in the nose, but, in most cases the annoying nasal symptoms were caused by formaldehyde-induced hyperreactivity (Wil92). An interesting finding was that atopics run approximately the same risk of suffering from this hyperreactivity as non-atopics (Wil92). Formaldehyde did not induce transient or permanent bronchial hyperreactivity (Bar91). Symptoms of the lower respiratory tract, like decreases of lung function parameters, were suggested to be related to exposure of workers to respirable particles containing formaldehyde penetrating deep into the airways (Her94).

Skin sensitisation by formaldehyde is induced only by direct skin contact with formaldehyde solutions in concentrations higher than 2% (IPC89). The threshold for induction of delayed hypersensitivity contact dermatitis has not been determined precisely. Formaldehyde-induced allergic contact dermatitis has been estimated to occur in 3 to 6% of the population. Formaldehyde has also been reported to cause contact urticaria, but the mechanism is unknown (Bar91).

Carcinogenic effects in man

An extensive retrospective cohort mortality study consisting of 26,561 workers from 10 formaldehyde-producing or -using facilities in the USA showed no statistically significant excess for specific *cancers* (Bla86). There was no trend of rising lung cancer risk with increasing levels of cumulative exposure to formaldehyde. Further analysis (Bla87) showed that 4 of 7 workers with nasopharynx cancer and 2 of 5 workers with oropharynx cancer occurred in a single plant producing moulding compounds which was a dusty operation. The authors suggested that simultaneous exposure to formaldehyde and particulates may be a risk factor for these tumours. Using the same data (Mar92), other authors calculated there was a 1.6-fold increase in lung cancer risk beginning approximately 16-20 years after first employment. For workers who were never co-exposed to any of the ten substances associated with increased lung cancer risk, the cumulative formaldehyde exposure was inversely related with the estimated lung cancer risk ratios. An update of the investigation by the same authors (Mar94) provided little evidence that the risk of lung cancer and nasopharyngeal cancer was associated either with formaldehyde exposure alone or in combination with particulate or pigment exposures. At the same time, other authors (Ste94) using a different statistical technique on the same data concluded that only high levels of cumulative exposure showed a significant elevation in relative lung cancer

risk. Trend analysis indicated a significant trend of increasing risk of lung cancer and respiratory cancer with increasing formaldehyde exposure.

These results have been strongly opposed by the original investigators (Bla94) who commented that Sterling *et al* (1994) apparently had not considered exposures other than formaldehyde in their analysis. Differences in the outcome might have been attributable to differences in the target population confounded by the healthy worker effect (Ste95).

A cancer morbidity study showed that formaldehyde may increase the risk for sinonasal cancer in humans (Han95). Because of the rarity of nasopharyngeal cancer, it was not possible to evaluate the risks. There were some serious shortcomings in this study. Various case-control studies have been performed using end-points as: respiratory cancer, cancer of the nose and paranasal sinuses, lung cancer and bladder cancer. In these studies no firm relationships could be found between occupational exposure to formaldehyde and these cancers.

A meta-analysis of 30 epidemiological studies (Bla90A) indicated no exposure-related response gradient for the combined relative risk (CRR) on nasal cancer. On the other hand, on nasopharyngeal cancer the CRR value rose to 2.1 in the highest exposure category; the trend was significant. The results of this study were substantiated by another meta-analysis (Par93). However, in this meta-analysis the authors did not correct for the unreported studies in which no cases of nasal cancers were found. It is likely that this may have caused an overestimation of the true relative risk. In a recent meta-analysis of 47 epidemiologic studies (Col97) a correction for underreporting was made. Relatieve risks (RR) for nasal cancers in cohort and case-control studies were 1.0 and 1.3, respectively. The authors concluded that these studies do not support a causal relation between formaldehyde exposure and nasopharyngeal cancer.

Animal studies

Sensitization

For formaldehyde a 10-min RD_{50} in mice of 3.6 ± 0.3 mg/m^3 (3.0 ± 0.28 ppm) has been reported (Kan77).

Studies in mice and guinea pigs produced no evidence of formaldehyde being a respiratory tract sensitizer (Hil96).

Short term exposure

The critical effects of short-term exposure to airborne formaldehyde in experimental animals are damage to and increased proliferation of the nasal epithelium. The histopathological changes range from slight hyperplasia and squamous-cell metaplasia of the ciliated and non-ciliated respiratory epithelium in specific areas, found at low effective exposure concentrations, ie 2.4 to 3.6 mg/m^3 (2 to 3 ppm), to severe rhinitis, necrosis and extensive hyperplasia and metaplasia of major portions of the nasal epithelium, found at exposure concentrations of about 7.2 mg/m^3 (6 ppm) and higher (Mor86a; Wou87; Wil87; Zwa88; App88; Mon89; Wil89; Reu90; Mon91; Cas94,96).

Substantial increases in epithelial cell turnover rates occur in rats at exposure concentrations of 7.2 mg/m^3 (6 ppm) and higher (Swe83,86; Mon89; Mon91; Cas94). The majority of NOAELs found in these short-term studies are 1.2 or 2.4 mg/m^3 (1 or 2 ppm). In all studies with a NOAEL of 1.2 mg/m^3 (1 ppm) the LOAEL was higher than 2.4 mg/m^3 (2 ppm), indicating the possibility that also in these studies a NOAEL of 2.4 mg/m^3 might have been obtained if indeed this exposure level would have been included in these experiments. However, occasionally (marginally and transiently) increased cell proliferation has been found at exposure levels of 0.6 or 1.2 mg/m^3 (0.5 or 1 ppm) (Swe83, 86; Zwa88), while the histopathological changes observed by Woutersen *et al*. (Wou87) turned out to be inconclusive with respect to 1.2 mg/m^3 (1 ppm) being a NOAEL or a LOAEL.

Long term exposure

Critical effects of long-term inhalation exposure to formaldehyde include inflammatory, degenerative and regenerative changes of the nasal mucosa and squamous-cell carcinomas of the nasal respiratory epithelium. The non-neoplastic nasal changes range from a minimal degree of hyperplasia and squamous-cell metaplasia of the nasal respiratory epithelium (occasionally seen at concentrations of approximately 2.4 mg/m^3 (2 ppm) or lower) to rhinitis, necrosis and extensive restorative hyperplasia and metaplasia of the nasal respiratory epithelium invariably seen at concentrations of about 7.2 to 18 mg/m^3 (6 to 15 ppm).

High incidences of squamous-cell carcinomas have been found in rats at exposure levels of 12 mg/m^3 (10 ppm) or higher (Ker83; Sel85; Mon96; Kam97). In most long-term studies, a NOAEL of 1.2 or 2.4 mg/m^3 have been reported. However, in one long-term study in rats 2.4 mg/m^3 (2 ppm) appeared to be a LOAEL (Ker83) and in another long-term rat study a LOAEL of 0.36 mg/m^3 (0.3 ppm) was reported (Kam97).

Genotoxicity

No adequate data were available on genetic effects of formaldehyde in humans. Formaldehyde has been investigated for genotoxic properties in many test systems (IAR95). It is comprehensively genotoxic in a variety of experimental systems, ranging from bacteria to rodents *in vivo*. Formaldehyde given by inhalation or gavage to rats induced chromosomal aberrations in lung cells, micronuclei in gastro-intestinal tract cells and sperm-head anomalies. Inhalation of formaldehyde leads to formation of DNA-protein cross-links in the nasal respiratory epithelium of rats and monkeys. The formation of DNA-protein cross-links is a sublinear function of the formaldehyde concentration in inhaled air from 0.86 to 18.4 mg/m^3 (0.71-15.27 ppm), and the yield of DNA-protein cross-links at a given inhaled concentration is approximately an order of magnitude lower in monkeys than in rats. There is no detectable accumulation of DNA-protein cross-links during repeated exposures (IAR95). In V79 Chinese hamster cells, formaldehyde induced DNA-protein crosslinks, sister-chromatid exchanges and micronuclei, but no gene mutations, in concentrations similar to those inducing cytotoxicity, suggesting that formaldehyde-induced DNA-protein crosslinks are related to cytotoxicity and clastogenicity (Mer98). In cultured human lung epithelial cells, DNA double-strand breaks were induced by formaldehyde only when cell viability was reduced to 60%, indicating that the double-strand breaks were caused by extragenomic damage and viability loss (Voc99). Recio (Rec97) suggested that the nasal inflammation and proliferation induced by formaldehyde exposure may contribute to the induction of genetic alterations through a variety of mechanisms including generation of reactive oxygen species, alterations in nucleotide pools, free radical formation, and clonal expansion with further mutation of genetically altered cells.

With respect to the *mechanism underlying the nasal carcinogenicity* of formaldehyde in rats, there is a large body of data suggesting an association between the cytotoxic, genotoxic and carcinogenic effects of formaldehyde (Hec84; Mor86b; Wou89; Fer89; Hec90; Mor97; CII99). The steep non-linear dose-response curve for nasal tumours — indicating a disproportionate decrease in carcinoma incidence at low concentrations — is most probably due to the fact that defence mechanisms of the nose (mucociliary clearance, detoxification by dehydrogenase, DNA repair) are very effective at low concentrations, but can be overwhelmed and inactivated at high concentrations; consequently, cell and tissue damage and finally tumours occur at high concentrations only. This also means that formaldehyde in concentrations not leading to tissue damage most probably cannot act as a complete carcinogen (causing initiation, promotion and progression), and as a result is very unlikely to induce cancer by itself.

In several animal studies, inhalation of formaldehyde was not found to affect reproduction.

Chapter 8

Existing guidelines, standards and evaluations

8.1 General population

The following recommendation was forwarded by IPCS/WHO (IPC89): 'The formaldehyde air concentration allowed in living, sleeping and working rooms should not be higher than 0.12 mg/m^3 (0.1 ppm), in order to minimize the risk of repeated or continuous low concentration exposure to formaldehyde'.

Using a linear-at-low-dose extrapolation, the United States Environmental Protection Agency (EPA) developed an upper-limit unit-risk estimate of 1.6 x 10^{-2}/ppm continuous exposure to formaldehyde, in 1987 (Con96). This approach was based solely on the dose-response for formaldehyde-induced tumour formation, assuming a five-stage model for carcinogenesis. The EPA subsequently changed its risk estimate using a three-stage model, resulting in an upper-limit risk of 6.1 x 10^{-3}/ppm formaldehyde exposure. In 1991, the EPA further revised its risk estimate using the levels of DNA-protein crosslinks in the rat and monkey as an indicator of delivered formaldehyde dose. The use of this information in a two-stage model, based upon the goodness-of-fit of the data, yielded an upper-limit unit risk estimate of 3.3 x 10^{-4}/ppm. Thus, the use of mechanistic information had resulted in a 50-fold reduction in the estimation of carcinogenic risk to humans from formaldehyde.

In 2002, the WHO/IPCS has published a review on formaldehyde (CICAD) (WHO02). They concluded that based on studies in both animals and humans, formaldehyde is weakly genotoxic, with good evidence of an effect at site of contact. Epidemiological studies taken as a whole do not provide strong evidence for a causal

association between formaldehyde and humane cancer, although the possibility of increased respiratory cancer, cannot be excluded. Therefore, based primarily upon data derived from laboratory studies, the inhalation of formaldehyde under conditions that induce cytotoxicity and sustained regenerative proliferation is considered to present a carcinogenic hazard to humans.

8.2 Working population

Table 5 Occupational exposure standards in various countries.

country - organisation	occupational exposure limit		averaging time	type of exposure limit	note[a]	lit ref[b]	year of adoption[c]
	ppm	mg/m^3					
The Netherlands							
- Ministry	1	1.5	8 h	regulatory		SZW02	1986
	2	3.0	15 min	limit			
- DECOS							
Germany							
- AGS	0.50	0.6			S	TRG98	
- DFG	0.30	0.37	8 h	MAK	4[d] sens	DFG02	unknown
Great Britain							
- HSE	2	2.5	8 h	MEL		HSE00	unknown
	2	2.5	15 min				
Sweden	0.5	0.6	8 h		sens	SNB93	unknown
	1.0	1.2	ceiling		Carc		
Denmark	0.3	0.4	8 h			ARB96	unknown
Finland	0.3	1	8h		S	Sös00	1.998
	1		ceiling				
Norway	0.5	0.6	8 h		S	Dir94	1.996
	1.0	1.2	ceiling		K3[d]		
Iceland	0.3	0.6	8 h		S	Vin99	unknown
	1.0	1.2	ceiling				
USA							
- ACGIH	0.30	0.37	ceiling	TLV	group A_2[d]	ACG01	1992
- OSHA	0.75	0.9	8 h	PEL		OSH92	unknown
- NIOSH							
European Union -SCOEL					carc. cat 3		

[a] S = skin notation; which means that skin absorption may contribute considerably to body burden
sens = substance can cause sensitisation;
classification of carcinogenic properties

[b] Reference to the most recent official publication of occupational exposure limits

[c] Year that this limit was officially adopted

[d] genotoxicity playing no or at most a minor part

8.3 Evaluations of standards

The Netherlands

In 1981, DECOS concluded that formaldehyde is a proven genotoxic carcinogen in experimental animals and that the induction of cancer in humans could not be excluded (WGD81). DECOS estimated that exposure to 0.1 mg/m^3 or 0.5 mg/m^3 formaldehyde, 8 hours per day, 5 days per week for 40 years with a lifespan of 75 years, would result in maximal cancer risks of 1 : 40,000 and 1 : 10,000 respectively.

In 1987, however, DECOS updated the previous document and concluded that an occupational exposure limit not exceeding 1.2 mg/m^3 (1 ppm) formaldehyde, 15 min TWA, virtually should not constitute an increased nasal cancer risk (WGD87). From studies in rats DECOS concluded that at subcytotoxic levels the risk of induction of nasal cancer appears to be negligibly small.

United States

In 1989, the American Conference of Governmental Industrial Hygienists (ACGIH) revised their assessment on formaldehyde. The proposed treshold limit value (TLV) for formaldehyde was 0.37 mg/m^3 (0.3 ppm) as a ceiling, with a notation 'suspected human carcinogen' (A_2) (ACG89). In the opinion of the ACGIH this TLV as a ceiling should reduce the risk of sensory irritation for workers handling formaldehyde or formaldehyde-containing products. They also advised to reduce formaldehyde workplace exposure to the lowest possible level in view of the reported dose-dependent carcinogenic effect in rats and mice, and the inadequate epidemiological data on the cancer risk in man.

In 1992, the Occupational Safety and Health Association (OSHA) responded to a remand by the US Court of Appeals for the DC Circuit (OSH92). The final amendments lowered the permissible exposure level for formaldehyde from 1 ppm as an 8-hour TWA to an 8-hour TWA of 0.75 ppm (0.9 mg/m^3). It should be noted that the former standard had been challenged in US Court by both industry and labour. Four unions had challenged the standard as being insufficiently protective. They contended that the former permissible exposure limit (PEL) was not low enough to eliminate all significant risk of harm, from both cancer and from formaldehyde irritant effects.

The National Institute of Occupational Safety and Health (NIOSH) recommended an exposure limit of 0.02 mg/m^3 (0.016 ppm) (TWA-8h) (REL) and a 0.12 mg/m^3 (0.1 ppm) 15 minutes limit.

Germany

In 2000 the Deutsche Forschungsgemeinschaft set a MAK value of 0.37 mg/m^3 (0.3 ppm) for formaldehyde. Formaldehyde is classified in category 4, which contains substances with carcinogenic potential for which genotoxicity plays no or at most a minor part. No contribution to human cancer risk is expected at the MAK-value. 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 mechanism contributing to carcinogenesis and their characteristic dose-time response relationships are taken into consideration. Furthermore, formaldehyde is classified in germ cell mutagenicity category 5. A risk of damage to developing embryos or fetuses is not to be expected at concentrations below the MAK value. Therefore formaldehyde is classified in group C for compounds which may influence pregnancy.

Sweden

The most current consensus report for formaldehyde by the National Board of Occupational Safety and Health was dated 25-8-1982. It was concluded that the basis for occupational exposure standards should be the irritating effects of formaldehyde on the respiratory organs and eyes. Formaldehyde has been shown to be carcinogenic in animal studies. Epidemiological studies provide inadequate evidence and cannot be used to assess carcinogenic effects on man.

IARC / WHO

The most recent evaluation by the International Agency for Research on Cancer (IARC) on formaldehyde (IAR95) concluded that there was limited evidence in humans for the carcinogenicity of formaldehyde. There is sufficient evidence in experimental animals for the carcinogenicity of formaldehyde. The overall evaluation was that formaldehyde is probably carcinogenic to humans (Group 2A).

European Union

The European Union has classified the carcinogenic effects of formaldehyde in category 3 (*substances which cause concern for man owing to possible carcinogenic effects but in respect of which the available information is not adequate for making a satisfactory assessment*).

Chapter 9

Hazard assessment*

9.1 Assessment of the health hazard

Formaldehyde occurs naturally in the environment and is produced physiologically by mammalian cells during metabolism. It has been used by man for over a century in a variety of products and activities. The human cell can rapidly detoxify lower levels of formaldehyde.

Airborne formaldehyde exposures can occur as vapour or as particles (solids or mists) or as a combination of both. The relative intensities of vapour and particle exposures vary with the industry and the job activities. The anatomic site of tissue contact as well as the intensity of exposure depend on the physical form of the compound. Inhaled formaldehyde vapour is usually efficiently removed by the nose, mouth and trachea, but in analogy with sulphur dioxide, some vapour probably penetrates into the lower airways with mouth breathing during moderately heavy or heavy work (Hig88). Inhaled particles containing formaldehyde are deposited in the respiratory system as a function of their aerodynamic characteristics and, given an appropriate aerodynamic diameter, may result in exposures deep within the respiratory tract. The biological behaviour of formaldehyde deposited in particulate form is unknown. However, the DECOS assumes that the effects of particle bound formaldehyde will be prevented by a HBROEL for formaldehyde vapour.

* For the recommendation of a health-based occupational exposure limit only DECOS (and not the NEG) takes responsibility.

From the toxicological data base on formaldehyde it is evident that the critical effects of formaldehyde are sensory irritation and cytotoxicity-induced regenerative hyperplasia (increased cell proliferation/increased cell turnover rates) and metaplasia of the nasal respiratory epithelium accompanied by nasal carcinomas in rats and possibly in mice after long-term exposure to high cytotoxic concentrations. Therefore, DECOS is of the opinion that the HBR-OEL of formaldehyde should be low enough to prevent the occurrence of both sensory irritation and cytotoxicity-induced hyperproliferation of the nasal epithelium in workers exposed to formaldehyde.

Symptoms of formaldehyde exposure in humans start with sensory irritation first experienced in the eyes, followed by perception of the odour and then irritation of the nose and throat, accompanied by discomfort, lachrymation, sneezing, coughing, nausea and dyspnoea. A panel of independent experts convened by the Industrial Health Foundation (IHF) studied all available data on sensory irritation related to formaldehyde exposure (Pau97). This IHF-panel concluded that for most persons eye irritation does not occur until at least 1.2 mg/m^3 (1.0 ppm) formaldehyde. This panel also observed that from controlled studies in volunteers, it appears that moderate to severe eye, nose and throat irritation does not occur for most individuals until exposure concentrations of formaldehyde exceed 2.4 - 3.6 mg/m^3 (2.0-3.0 ppm). The panel further concluded that an occupational exposure limit of less than 0.6 mg/m^3 (0.5 ppm) may be needed to prevent sensory irritation in a diverse working population, and therefore recommended for formaldehyde an occupational exposure limit of 0.36 mg/m^3 (0.3 ppm) as an 8-hour time weighted average with a ceiling value of 1.2 mg/m^3 (1.0 ppm) (Pau97). However, according to the committees (DECOS and NEG) the database on sensory irritation of formaldehyde reveals that at lower exposure levels sensory irritation may still occur in substantial percentages of exposed individuals. For instance, in a not well documented study, more than 50% of occupationally exposed workers complained of nasal discomfort after longterm exposure to an average concentration of 0.26 mg/m^3 (0.22 ppm; range 0.05 to 0.6 mg/m^3 or 0.04 to 0.5 ppm) (Wil92). Moreover, from a controlled study in volunteers (And83) it appeared that 19% (n=3) of the exposed subjects (n=16) reported eye irritation at an exposure concentration of 0.29 mg/m^3 (0.24 ppm). However, according to the IHF-panel such a response is often considered of doubtful toxicological significance because irritation responses of 15-20% may be obtained in unexposed volunteers (Pau97) as well.

In experimental animals, irritation of eyes, nose, throat and lungs were observed at exposure concentrations higher than 2.4 mg/m^3 (2.0 ppm). Kane and Alarie (Kan77) determined in mice a 10-min RD_{50} for formaldehyde of 3.6 +/- 0.43 mg/m^3 (3.0 ppm +/- 0.28 ppm). Compared to humans experimental animals seem to be less sensitive to stimulation of the trigeminal nerve by formaldehyde. Moreover, in view of the wealth of reliable data on sensory irritation in humans, the irritation data on formaldehyde in

experimental animals are considered of secundary importance in terms of both hazard identification and risk assessment.

Overall, weighing the total body of data on sensory irritation, DECOS estimates that 0.3 mg/m^3 (0.25 ppm) formaldehyde is the lowest exposure concentration at which sensory irritation may occur in low but significant percentages of exposed workers. A factor of two is applied to compensate for the extrapolation from LOAEL to a NAEL. The committee considers a factor 2 sufficient because (I) the critical effect (sensory irritation) is a local, non systemic effect, (II) the incidence of the effect at 0.3 mg/m^3 is low (19%) and may not be different from background incidences in controls, and (III) minimal sensory irritation such as seen in some individuals at 0.3 mg/m^3 may rapidly subside due to 'accommodation' (Pau97). Therefore, based on sensory irritation only, DECOS recommends a HBR-OEL for formaldehyde of 0.15 mg/m^3 (0.12 ppm), providing a margin of safety, which the committee considers large enough to prevent significant sensory irritation in workers exposed to formaldehyde.

Having concuded this on the basis of sensory irritation, the key question is whether an exposure limit of 0.15 mg/m^3 (0.12 ppm) would be low enough to protect workers against cytotoxicity-induced hyperproliferation of the nasal respiratory epithelium, and consequently also against the potential risk of nasal cancer. To answer this question, first the evidence for the carcinogenicity of formaldehyde in experimental animals is briefly discussed.

Nasal carcinomas in rats have only been found at high, cytotoxic exposure concentrations causing rhinitis, necrosis and regenerative hyperplasia and squamous metaplasia of the nasal respiratory epithelium (Ker83; Sel85; Mon96; Kam97). The crucial role of tissue damage followed by hyperplasia and metaplasia of the nasal respiratory epithelium in formaldehyde carcinogenesis has been demonstrated in a convincing way (Wou89; Fer89a,b) and has meanwhile been widely recognized (Pau97; WHO00) and should therefore be included in human cancer risk assessment (CII99). Despite differences in anatomy and physiology of the nose between rats and humans, the upper respiratory tract defence systems are similar in both species (Mor97). It is, therefore, reasonable to conclude that the response of the respiratory tract to formaldehyde will be qualitatively similar in rats and humans. If in humans exposure of formaldehyde were to be accompanied by recurrent tissue damage at the site of contact, formaldehyde may be assumed to have carcinogenic potential in man. Correspondingly, if the respiratory tract tissue is not recurrently injured, exposure of humans to relatively low, non-cytotoxic levels of formaldehyde can be assumed to be associated with a negligible cancer risk.

The committees observe that the majority of short- and long-term inhalation toxicity studies with formaldehyde in experimental animals reveal a NOAEL of 1.2 or 2.4 mg/m^3 (1 or 2 ppm). However, in all studies with a NOAEL of 1.2 mg/m^3 (1 ppm) the LOAEL was higher than 2.4 mg/m^3 (2 ppm), indicating the possibility that also in these studies 2.4 mg/m^3 might have been a NOAEL if indeed this exposure level would have been included in these experiments. However, in one 24-month inhalation study in rats, 2.4 mg/m^3 (2 ppm) formaldehyde (lowest level tested) induced mild squamous metaplasia of the epithelium lining the nasal turbinates (Ker83). Moreover, a 13-week inhalation toxicity study with formaldehyde 1.2 mg/m^3 (1 ppm) in rats was inconclusive with respect toits effects on the nasal respiratory epithelium (Wou87). Furthermore, in two short-term inhalation studies in rats, slightly (and only transiently) increased cell proliferation of the respiratory epithelium was seen in a specific area of the nasal mucosa at formaldehyde exposure concentrations of 0.6 or 1.2 mg/m^3 (0.5 or 1 ppm) (Sve83; 86; Zwa88). Finally, in one recently published long-term inhalation toxicity/carcinogenicity study on formaldehyde in rats (Kam97), a low incidence of hyperplasia with or without squamous metaplasia of the nasal respiratory epithelium was found at 0.36 mg/m^3 (0.3 ppm). This low incidence (4/32) was not statistically significantly different from that in controls (0/32), but was nevertheless considered toxicologically relevant (i.e. formaldehyde-induced) because there was a clear dose-response relationship with the increased incidences at the higher exposure levels being statistically significantly different from that in controls.

The data in humans are less clear. Three meta-analyses of epidemiological studies have shown inconsistent results. In two of them a significant relation between exposure to formaldehyde and nasopharyngeal cancer risk was observed. The association between formaldehyde exposure and nasal cancer was ambiguous (Bla90a, Par93). However, according to the committees in these meta-analyses the authors did not correct for the unreported studies in which no cases of nasal cancers were found. This most likely led to an overestimation of the overall relative risk of nasopharyngeal cancer. In the third, more recent, published meta-analysis, relative risks of 1.0 and 1.3 were found for nasal cancer in cohort and case-control studies, respectively (Col97). In this meta-analysis a correction was made for underreporting. Moreover, the authors evaluated the exposure potential for jobs included in the general population case-control studies. The authors concluded that there was no support for a causal relation between formaldehyde exposure and nasopharyngeal cancer. The committees (both DECOS and NEG) endorse this conclusion and further conclude that the currently available epidemiological database does not provide support for a nasal cancer risk at the exposure levels lower than 0.3 mg/m^3. Also from the epidemiological database it seems unlikely that exposure to formaldehyde affects lung cancer risk (And95a, And95b, Bla90a, Bla90b, Gar93, Han95, Par93). Overall, both committees

conclude that the currently available epidemiological database on formaldehyde does not provide evidence for a respiratory tract cancer risk at the experienced exposure levels. In correspondence to the previous evaluation of formaldehyde by DECOS in 1987, the committee endorses the earlier conclusion from 1987 that with prevention of cytotoxicity, carcinogenic effects wil not occur. However, the present committee is of the opinion that the exposure limit should prevent cytotoxicity.

In view of the aforementioned observations in experimental animals and humans, and a thorough and critical appraisal of the available data, the committee answers the above key question (ie. does an exposure limit of 0.15 mg/m^3 protect workers against cytotoxicity-induced hyperproliferation of the nasal respiratory epithelium, and consequently also against the potential risk of nasal cancer) as positive. This implies that the DECOS considers a health based occupational exposure level (HBR-OEL) of 0.15 mg/m^3 (0.12 ppm) (see page 69) formaldehyde low enough to protect workers against nasal tissue damage, and as a consequence, also against the potential risk of nasal cancer*.

To avoid peak exposures possibly entailing cytotoxicity-induced hyperproliferation and metaplasia of the nasal respiratory epithelium, DECOS recommends for formaldehyde a short-term exposure limit (STEL), using data from the review of Paustenbach and the study of Bender *et al* (Ben83). In this latter study, volunteers were exposed to formaldehyde by inhalation for periods of 6 minutes. At exposure levels up to approximately 1.0 mg/m^3 only slight irritation of the eyes was observed. The review of Paustenbach suggested that at 1.2 mg/m^3 sensory effects might occur. The committee concluded that the total body of evidence indicates that 0.5 mg/m^3 is an exposure level which is low enough to avoid significant sensory irritation from short term exposures and thus, more importantly, also will be low enough to avoid nasal cytotoxicity from such short exposures. In conclusion, the committee considers a factor of 2 sufficient for the extrapolation from LOAEL to NAEL. Therefore, the committtee recommends a short term exposure limit (STEL) of 0.5 mg/m^3 (0.42 ppm).

9.2 Groups at extra risk

The recommended occupational exposure limit does not protect workers from specific sensitisation after direct skin contact with formaldehyde solutions higher than 2%.

* This conclusion is strongly supported by the results of a recently published quantitative cancer risk assessment of airborne formaldehyde, using a very sophisticated biologically-based model that predicts for occupational exposure (40 years beginning at the age of 18, 8 hours/day, 5 days/week) to 0.12 mg/m^3 (0.1 ppm) formaldehyde an increased lifetime risk for cancer of 10^{-7} for smokers and 4.1 x 10^{-9} for non-smokers (CII99), which the committees regard as negligibly small risks.

Allergic dermal sensitisation to formaldehyde in man occurs in 3 to 6% of the general population. It is not possible to identify individuals with elevated risk for allergic sensitization *a priori* with a simple screening test. Skin sensitization constitutes a health risk in workers occupationally exposed to formaldehyde.

9.3 Health-based recommended occupational exposure limit

DECOS recommends a health-based occupational exposure limit of 0.15 mg/m^3 (0.12 ppm) formaldehyde, as an 8 hour time-weighted average, and a short term exposure limit, 15 minutes TWA, of 0.5 mg/m^3 (0.42 ppm).

References

ACG89 ACGIH. Documentation for threshold limit values for chemical substances and physical agents. ACGIH 1989, Cincinnati, Ohio.

ACG01 Threshold limit values for chemical substances and physical agents, 2001, ACGIH, Cincinnati, Ohio.

Akb94 Akbar Khanzadeh F, Vaquerano M, Akbar-Khanzadeh M and Bisesi MS. Formaldehyde exposure, acute pulmonary response and exposure control options in gross anatomy laboratory. Am J Ind Med 1994; 26: 61-75.

And83 Andersen I, Molhave l. Controlled human studies with formaldehyde. In: Formaldehyde toxicity, Gibson JE (ed.), 1983, Hemisphere, Washington, pp.154-165.

And94 Andjelkovich DA, Shy CM, Brown MH *et al*. Mortality of iron foundry workers III. Lung cancer case-control study. J. Occup Med 1994, 36: 1301-1309.

And95a Andjelkovich DA, Janszen DB, Brown MH *et al*. Mortality of iron foundry workers: IV. Analysis of a subcohort exposed to formaldehyde. J Occup Med 1995; 37: 826-837.

And95b Andjelkovich DA, Janszen DB, Conolly RB and Miller FJ. Formaldehyde exposure not associated with cancer of the respiratory tract in iron foundry workers: a synopsis of CIIT epidemiologic findings. CIIT Activities 1995; 15: 1-9.

App88 Appelman LM, Woutersen RA, Zwart A *et al*. One-year inhalation toxicity study of formaldehyde in male rats with damaged or undamaged nasal mucosa. J Appl Toxicol 1988; 8: 85-90.

Arb96 Arbejdstilsynet. Exposure limit values for substances and materials. N 3.1.0.2, 1996.

Bal92 Ballarin C, Sarto F, Giacomelli L *et al*. Micronucleated cells in nasal mucosa of formaldehyde-exposed workers. Mut Res 1992; 280: 1-7.

Bar91 Bardana Jr EJ, Montanaro A. Formaldehyde: an analysis of its respiratory, cutaneous, and immunologic effects. Ann Allergy 1991; 66: 441-452.

Ben83 Bender JR, Mullin LS, Graepel GJ and Wilson WE. Eye irritation response of humans to formaldehyde. Am Ind. Hyg Assoc J 1983; 44: 463 - 465.

Bha91 Bhalla DK, Mahavni V, Nguyen T, McClure T. Effects of acute exposure to formaldehyde on surface morphology of nasal epithelia in rats. J Toxicol Environ Health 1991; 33: 171-188.

Bia89 Biagini RE, Moorman WJ, Knecht EA, ClarkJC. Acute airway narrowing in monkeys from chalenge with 2.5 ppm formaldehyde generated from formalin. Arch Environ Health 1989; 44: 12-17.

Bla86 Blair A, Stewart P, O'berg M *et al*. Mortality among industrial workers exposed to formaldehyde. J Nat Cancer Inst 1986; 76: 1071-1084.

Bla87 Blair A, Stewart PA, Hoover RN *et al*. Cancers of the nasopharynx and oropharynx and formaldehyde exposure. J Nat Cancer Inst 1987; 78: 191-193.

Bla90a Blair A, Saracci R, Stewart PA *et al*. Epidemiologic evidence on the relationship between formaldehyde exposure and cancer. Scand J Work Environ Health 1990; 16: 381-393.

Bla90b Blair A, Stewart PA, Hoover RN. Mortality from lung cancer among workers employed in formaldehyde industries. Am J Ind Med 1990; 17: 683-699.

Bla94 Blair A, Stewart PA. Comments on the Sterling and Weinham analysis of data from the National Cancer Institute Formaldehyde study. Am J Ind Med 1994; 25: 603-606.

Bog87 Bogdanffy MS, Randall HW, Morgan KT. Biochemical quantitation and histochemical localization carboxylesterase in the nasal passages of the Fischer-344 rat and B6C3F1 mouse. Toxicol Appl Pharmacol 1987; 88:183-194.

Bom96 Boman A., Dyring Jacobsen S., Klastrup S. *et al*. Potency evaluation of a contact allergens. Dose-response studies using the guinea pig maximization test. Dept. Occupational Dermatology, National Institute of Occupational Health, Solna, Sweden. TemaNord 1996: 570.

Boy90 Boysen M, Zadig E, Digernes V *et al*. Nasal mucosa in workers exposed to formaldehyde: a pilot study. Br J Ind Med 1990; 47: 116-121.

Cas87 Casanova M, Heck Hd'A. Further studies of of the metabolic incorporation and covalent binding of inhaled 3H- and 14C-formaldehyde in Fischer-344 rats: effects of glutathione depletion. Toxicol Appl Pharmacol 1987; 89: 105-121

Cas91 Casanova M, Morgan KT, Steinhagen WH *et al*. Covalent binding of inhaled formaldehyde to DNA in the respiratory tract of Rhesus Monkeys: pharmacokinetics, rat-to-monkey interspecies scaling, and extrapolation to man. Fundam Appl Toxicol 1991; 17: 409-428.

Cas94a Casanova M, Morgan KT, gross EA *et al*. DNA-protein cross-links and cell replications at specific sites in the nose of F 344 rats exposed subchronically to formaldehyde. Fund Appl Toxicol 1994; 23: 525-536.

Cas94b Cassee FR, Feron VJ. Biochemical and histopathological changes in nasal epithelium of rats after 3-day intermittent exposure to formaldehyde and ozone alone or in combination. Toxicol Let 1994; 72: 257-268.

Cas95 Cassee FR. Upper respiratory tract toxicity of mixtures of aldehydes. In vivo and in vitro studies. Dissertation 1995 in University of Utrecht.

Chi92 Chia SE, Ong CN, Foo SC, Lee HP. Medical students exposure to formaldehyde in a gross anatomy dissection laboratory. J Am Coll Health 1992; 41: 115-119.

CII95 CIIT. Formaldehyde exposure of foundry workers was not associated with cancer of the respiratory tract. Impact 1995. CIIT publication September 1995.

CII99 Chemical Industry Institute of Toxicology (CIIT). Formaldehyde: hazard characterization and dose-response assessment for carcinogenicity by the route of inhalation. Revised edition. September 28, 1999, Research Triangle Park, NC, USA.

CKB97 Chemiekaartenboek. 12e editie, 1997. NIA-TNO, Samson HD Tjeenk Willink, Alphen aan de Rijn.

Col92 Colizzo F, Krantz MJ, Fish JE, Hastie AT. Ciliated respiratory epithelial surface change after formaldehyde exposure. J. Toxicol Environ Health 1992; 35: 221-234.

Col97 Collins JJ, Acquavella JF, Esmen NA. An updated meta-analysis of formaldehyde exposure and upper respiratory tract cancers. JOEM 1997; 39: 639-651.

Con93 Conolly RB, Andersen ME. An approach to mechanism-based cancer risk assessment for formaldehyde. Environ Health Perspect 1993; 101 (suppl 6): 169-176.

Con96 Conaway CC, Whysner J, Verna LK, Williams GM. Formaldehyde mechanistic data and risk assessment: endogenous protection from DNA adduct formation. Pharmacol Ther 1996; 71: 29-55.

Cro91 Cronin E. Formaldehyde is a significant allergen in women with hand eczema. Contact Dermatitis 1991; 25: 276-282.

Dal92 Dallas CE, Scott MJ, Ward Jr JB, Theiss JC. Cytogenetic analysis of pulmonary lavage and bone marrow cells of rats after repeated formaldehyde inhalation. J Appl Toxicol 1992; 12: 199-203.

Dav92 Davis RA. Current issues in formaldehyde: an overview (letter to editor). Comments Toxicology 1992; 4: 265 - 267.

DFG02 Deutsche Forschungsgemeinshaft. MAK- und BAT-Werte List 2002.

Din93 Dinsdale D, Riley RA, Verschoyle RD. Pulmonary cytochrome P450 in rats exposed to formaldehyde vapour. Environ Res 1993; 62: 19-27.

Dir94 Direktoratet for arbeidstilsynet. Administrative normer for forurensning i arbeidsatmosfarer. Veiledning til arbeidsmiljoloven 1994 (Bestillungsnr. 361).

ECE95 ECETOC. Technical Report no 65. Formaldehyde and human cancer risk. May 1995, Brussel.

Fer88 Feron VJ, Bruyntjes JP, Woutersen RA *et al*. Nasal tumours in rats after short-term exposure to a cytotoxic concentration of formaldehyde. Cancer Let 1988; 39: 101-111.

Fer89a Feron VJ, Woutersen RA (1989). Role of tissue damage in nasal carcinogenisis. In: VJ Feron and MC Bosland (eds). Nasal carcinogenisis in rodents: relevance to human health risk. Pudoc Wageningen, pp 76-84.

Fer89b Feron VJ, Wilmer JWGM, Woutersen RA, Zwart A. Inhalation toxicity and carcinogenicity of formaldehyde in animals: significance for assessment of human health risk. In: Assessment of Inhalation Hazards. Mohr (ed. -in- chief), 1989. Springer Verlag Berlin, pp. 131-138.

Fly92 Flyholm M-A, Menne T. Allergic contact dermatitis from formaldehyde. Contact Dermatitis 1992; 27: 27-36.

Gar93 Gardner MJ, Pannett B, Winter PD, Cruddas AM. A cohort study of workers exposed to formaldehyde in the British chemical industry: an update. Br J Ind Med 1993; 50: 827-834.

Gar99 Garrett MH, Hooper MA, Hooper BM, Rayment PR and Abramson MJ. Increased risk of allergy in children due to formaldehyde exposure in homes. Allergy 1999; 54, 330-337.

Gra90 Grammer LC, Harris KE, Shangnessy MA *et al*. Clinical and immunologic evaluation of 37 workers exposed to gaseous formaldehyde. J Allergy Clin Immunol 1990; 86: 177-181.

Gra93a Grafström RC, Hsu I-C, Harris CC. Mutagenicity of formaldehyde in chinese hamster lung fibroblasts: synergy with ionizing radiation and N-nitroso-N-methylurea. Chem-Biol Int 1993; 86: 41-49.

Gra93b Grammer LC, Harris KE, Cugell DW *et al*. Evaluation of a worker with possible formaldehyde-induced asthma. J Allergy Clin Immunol 1993; 92: 29-33.

Gui85 Guicherit R, Schulting FL. The occurrence of organic chemicals in the athmosphere of the Netherlands. Sc Total Environ 1985; 43: 193-219.

Han92 Hansen J, Olsen JH. Formaldehyde and cancer morbidity among male employees in Denmark. Canc Causes Contr 1995; 6: 354-360.

Har90 Harving H, Korsgaard J, Pedersen OF *et al*. Pulmonary function and bronchial reactivity in asthmatics during low-level formaldehyde exposure. Lung 1990; 168: 15-21.

He98 He JL, Jin LF, Jin HY. Detection of cytogenetic effects in peripheral lymphocytes of students exposed to formaldehyde with cytokinesis blocked micronucleus assay. Biomdeical and environmental sciences 1998; 11, 87-92.

Hec84 Heck Hd'A, Casanova-Schmitz M. Biochemical toxicology of formaldehyde. Rev BiochemToxicol 1984; 6: 155-189.

Hec87 Heck Hd'A, Casanova M. Isotope effects and their implications for the covalent binding of inhaled 3H- and 14C-formaldehyde in the rat nasal mucosa. Toxicol Appl Pharmacol 1987; 89: 122-134.

Hec89 Heck Hd'A, Casanova M, Steinhagen WH, Everitt JI, Morgan KT, Popp, JA. Formaldehyde toxicity -DNA-protein cross-linking studies in rats and nonhuman primates. In: Nasal Carcinogenesis in Rodents: Relevance to Human Health Risk, VJ Feron and MC Bosland (eds.), 1989, Pudoc Wageningen, pp. 159-164.

Hec90 Heck Hd'A, Casanova M, Starr TB. Formaldehyde toxicity -New understanding. Crit Rev Toxicol 1990; 20: 397-426.

Her94 Herbert FA, Hessel PA, Melenka LS *et al*. Respiratory consequences of exposure to wood dust and formaldehyde of workers manufacturing oriented strand boards. Arch Environ Health 1994; 49: 465-470.

Hig88 Higginson J, Jensen OM, Kinlen L *et al*. Epidemiology of chronic occupational exposure to formaldehyde: report of the ad hoc panel on health aspects of formaldehyde. Toxicol Ind Health 1988; 4: 77-90.

Hil96 Hilton J, Dearman RJ, Basketter DA *et al*. Experimental assesment of the sensitising properties of formaldehyde. Food Chem Toxicol 1996; 34: 571-578.

HSE00 Health and Safety Executive. EH 40/2000 Occupational exposure limits 2000.

Hol91 Holmstrom M, Lund VJ. Malignant melanomas of the nasal cavity after occupational exposure to formaldehyde. Br J Ind Med 1991; 48: 9-11.

Hor88 Horvath EP, Andersson H, Pierce WE, Hanrahan L, Wendlick JD. Effects of formaldehyde on the muscous membranes and lungs.: A study of an industrial population. J Am Med Assoc. !988; 259, 701-707.

IARC95 IARC. IARC monographs of the evaluation of carcinogenic risks to humans. Wood dust and formaldehyde. Volume 62, 1995.

INR86 INRS. Valeurs limites pour les concentrations des substances dangereuses. Cahiers de notes documentaires no 125, 4e trimester 1986.

IPC89 IPCS/WHO. Environmental Health Criteria 89. Formaldehyde. WHO-Geneva, 1989.

Kam97 Kamata E, Nakadate M, Uchida O *et al*. Results of a 28-month chronic inhalation toxicity study of formaldehyde in male Fischer-344 rats. J Toxicol Sc 1997; 22: 239-254.

Kan77 Kane LE, Alarie, Y. Sensory irritation to formaldehyde and acrolein during single and repeated exposure in mice. Am Ind Hyg Asoc J 1977; 38: 509-522.

Ker83 Kerns WD, Pavkov KL, Dougphrio DJ, Gralla EJ, Swenberg. Carcinogenicity of formaldehyde in rats and mice after long-term inhalation exposure. Cancer Res 1983; 43, 4382-92.

Kil89 Kilburn K, Warshaw R, Thornton JC. Pulmonary function in histology technicians compared with women from Michigan: effects of chronic low dose formaldehyde on a national sample of women. Br J Ind Med 1989; 46: 468-472.

Kil94 Kilburn KH. Neurobehavioral impairment and seizures from formaldehyde. Arch Environ Health 1994; 49: 37-44.

Kim97 Kimbell JS, Gross EA, Richardson RB *et al*. Correlatioin of regional formaldehyde flux predictions with the distributioin of formaldehyde-induces squamous metaplasia in F344 rat nasal passages. Mutation Res 1997; 380: 143-154.

Kit76 Kitchens JF, Casner RE, Edwards GS, Harward WE, Macri BJ. Investigation of selected potential environmental contaminants: formaldehyde. Washington DC, US EPA 1976.

Kri92 Krivanek ND and Imbus HR. Formaldehyde - Studies on irritation at low levels. Comments Toxicology 1992; 4: 315 - 330.

Kri93 Kriebel D, Sama SR, Cocanour B. Reversible pulmonary responses to formaldehyde. Am Rev Respir Dis 1993; 148: 1509-1515.

Krz90 Krzyzanowski M, Quackenboss JJ, Lebowitz MD. Chronic respiratory effects of indoor formaldehyde exposure. Environ Res 1990; 52: 117-125.

Lid93 Liden S, Scheynius A, Fischer T *et al*. Absence of specific IgE antibodies in allergic contact sensitivity to formaldehyde. Allergy 1993; 48: 525-529.

Liu91 Liu K-S, Huang F-Y, Hayward SB *et al*. Irritant effects of formaldehyde exposure in mobile homes. Environ Health Perspect 1991; 94: 91-94.

Lod86 Lodén M. The in vitro permiability of human skin to benzene, ethylene glycol, formaldehyde and n-Hexane. Acta Pharmacol Toxicol 1986; 58: 382-389.

Luc93 Luce D, Gerin M, Leclerc A *et al*. Sinonasal cancer and occupational exposure to formaldehyde and other substances. Int J Cancer 1993; 53: 224-231.

Mah88 MaTH, Harris, MH. Review of the genotoxicity of formaldehyde. Mut Res 1988; 196: 37-59.

Maj95 Majumber PK, Kumar VL. Inhibitory effects of formaldehyde on the reproductive system of male rats. Indian J Physiol Pharmacol 1995; 39: 80-82.

Mar90 Martin, WJ. A teratology study of inhaled formaldehyde in the rat. Repro. Toxicol. 1990; 4: 237-239.

Mar92 Marsh GM, Stone RA, Henderson VL. Lung cancer mortality among industrial workers exposed to formaldehyde: a poisson regression analysis of the National Cancer Institute study. Am Ind Hyg Assoc J 1992; 53: 681-691.

Mar94 Marsh GM, Stone RA, Esmen NA, Henderson VL. Mortality pattern among chemical plant workers exposed to formaldehyde and other substances. J. Nat. Cancer Inst. 1994; 86: 384.

Mer88 Merk O, Speit G. Significance of formaldehyde-induced DNA-protein crosslinks for mutagenesis. Environ Mol Mutag 1998; 32: 260-268.

Mon96 Monticello TM, Swenberg JA, Gross EA *et al*. Correlation of regional and nonlinear formaldehyde-induces nasal cancer with proliferating populations of cells. Cancer Res 1996; 56: 1012-1022.

Mor86a Morgan KT, Gross EA, Patterson DL. Distribution, progression, and recovery of acute formaldehyde-induced inhibition of nasal mucociliary function in F-344 rats. Toxicol Appl Pharmacol 1986; 86: 448-456.

Mor86b Morgan KT, Jiang XZ, Starr TB, Kerns WD. More precize localization of nasal tumors associated with chronic exposure of F-344 rats to formaldehyde gas. Toxicol Appl Pharmacol 1986; 82: 264-271.

Mor91 Morgan KT, Kimbell JS, Monticello TM *et al*. Studies of inspiratory airflow patterns in the nasal passages of the F344 rat and rhesus monkey using nasal molds: relevance to formaldehyde toxicity. Toxicol Appl Pharmacol 1991; 110: 223-240.

Mor97 Morgan KT. A brief review of formaldehyde carcinogenesis in relation to rat nasal pathology and human health risk assessment. Toxicol Pathol 1997; 25: 291-307.

Nun90 Nunn AJ, Craigen AA, Darbyshire JH *et al*. Six years follow up of lung function in man occupationally exposed to formaldehyde. Br J Ind Med 1990; 47: 747-752.

Ode97 Odeigah PGC. Sperm head abnormalities and dominant lethal effects of formaldehyde in albino rats. Mutation Res 1997; 389: 141-148.

ODo93 O'Donovan MR, Mee CD. Formaldehyde is a bacterial mutagen in a range of Salmonella and Escherichia indicator strains. Mutagenenis 1993; 8: 577-581.

OSH92 OSHA. Occupational exposure to formaldehyde. Federal Register 1992; 57: 22290-22338 (present as computer disc).

Par90 Partanen T, Kauppinen T, Hernberg S *et al*. Formaldehyde exposure and respiratory cancer among wood workers - un update. Scand J Work Environ Health 1990; 16: 394-400.

Par93 Partanen T. Formaldehyde exposure and respiratory cancer - a meta-analysis of the epidemiologic evidence. Scand J Work Environ Health 1993; 19: 8-15.

Pau97 Paustenbach D., Alarie Y, Kulle T *et al*. A recommended occupational exposure limit for formaldehyde based on irritation. J Toxicol Environ Health 1997; 50: 217 - 263.

Paz93 Padzrak K, Górski P, Krahowiah A, Ruta U. Changes in nasal lavage fluid due to formaldehyde inhalation. Int Arch Occup Environ Health 1993; 64: 515-519.

Rec97 Recio L. Oncogene and tumor suppressor gene alterations in nasal tumors. Fundam Mol Mech Mutagen 1997; 380: 27-31.

Rei93 Reid CM, Rycroft RJG. Allergic contact dermatitis from multiple sources of MCI/MI biocide and formaldehyde in a printer. Contact Dermatitis 1993; 28: 252-253.

Roe93 Roemer E, Anton HJ, Kindt R. Cell proliferation in the respiratory tract of the rat afater acute inhalation of formaldehyde or acrolein. J Appl Toxicol 1993; 13: 103-107.

Ros90 Rossiter E. Pulmonary function in histology technicians compared with women from Michigan: effects of chronic low dose formaldehyde exposure on a national sample of women. Br J Ind Med 1990; 47: 358-360.

Sal89 Saillenfait AM, Bonnet P, de Ceaurriz J. The effects of maternally inhaled formaldehyde on embryonal and foetal development in rats. Food Chem Toxicol 1989; 27: 545-548.

Sal91 Salkie ML. The prevalence of atopy and hypersensitivity to formaldehyde in pathologists. Arch Pathol Lab Med 1991; 115: 614-616.

Sau87 Sauder LR, Green DJ, Chatham MD, Kulle TJ. Acute pulmonary response of astmatics to 3.0 ppm formaldehyde. Toxicol Indust Health 1987; 3: 569-78.

Sel85 Sellakumar AR, Snyder CA, Solomon JJ, Albert RE. Carcinogenicity of formaldehyde and hydrogen chloride in rats. Toxicol Appl Pharmacol 1985; 81: 401-406.

Sie94 Siemiatycki J, Dewar R, Nadon L, Gerin M. Occupational risk factors for bladder cancer: results from a case-control study in Montreal, Quebec, canada. Am J Epidemiol 1994; 140: 1061-1080.

SNB93 Swedish National Board of Occupational Safety and Health. Occupational exposure limit values, 1993.

Sos00 Sosiaali-ja terveysministeri, HTP-arvot 2000, Työsuojelusäädöksiä 3,200

Sri92 Srivastava AK, Gupta BN, Bifrari V *et al*. Clinical studies of employees in a sheet-forming process at a paper mill. Vet Hum Toxicol 1992; 34: 525-527.

Sta90 Starr TB. Quantitative cancer risk estimation for formaldehyde. Risk Analysis 1990; 10: 85-91.

Stc90 St Clair MB, Gross EA, Morgan KT. Pathology and cell proliferation induced by intranasal instillation of aldehydes in the rat: comparison of glutaraldehyde and fomaldehyde. Toxicol Pathol 1990; 18: 353-361.

Ste94 Sterling TD, Weinham JJ. Mortality among respiratory cancers (including lung cancers) among workers employed in formaldehyde industries. Am J Ind Med 1994; 25: 593-602.

Ste95 Sterling TD, Weinham JJ. Comments on the Blair and Stewart comments on the Sterling and Weinham analysis of data from the National Cancer Institute formaldehyde study. Am J Ind Med 1995; 27: 301-305.

Sun90 Sun HW, Feigal RJ, Messer HH. Cytotoxicity of glutaraldehyde and formaldehyde in relation to time of exposure and concentration. Ped Dent 1990; 12: 303-307.

Sur93 Suruda A, Schulte P, Boeniger M *et al*. Cytogenetic effects of formaldehyde exposure in students of mortuary science. Cancer Epid Biomarkers Prev 1993; 2: 453-460.

Swe83 Swenberg JA, Gross EA, Randall HW, Barrow CS. The effect of formaldehyde exposure on cytotoxicity and cell proliferation. In: Formaldehyde Toxicology, Epidemiology,Mechanisms. JJ Clary, JE Gibson, RS Waritz (eds.), 1983, Marcel Dekker, Inc., New York and Basel, pp. 225-236.

Swe86 Swenberg JA, Gross EA, Randall, HW. Localization and quantitation of cell proliferation following exposure to nasal irritants. In: Toxicology of the Nasal Passages, CS Barrow (ed.), 1986, Hemisphere Publishing Corporation, Washington/New York/London, pp. 291-300.

Swi93 Swiecichowski AL, Long, KJ, Miller ML, Leikauf GD. Formaldehyde induced airway hyperreactivity in vivo and ex vivo in Guinea pigs. Environ Res 1993; 61: 185-199.

SZW02 Ministerie van Sociale Zaken en Werkgelegenheid. De nationale MAC lijst 2002.

Thr90 Thrasher JD, Broughton A, Madison R. Immune activation and autoantibodies in humans with long-term inhalation exposure to formaldehyde. Arch Environ Health 1990; 45: 217-223.

TRG98 Technical rule for hazardous substances 900, B Arb Bl 1998; 10: 71-74.

Var93 Vargova M, Wagnerova J, Liskova A. *et al*. Subacute immunoatoxicity study of formaldehyde in male rats. Drug Chem Toxicol 1993; 16: 255-275.

Vas96 Vasudeva N and Annand C. Cytogenetic evaluation of medical students exposed to formaldehyde vapor in te gross anatomy dissection laboratory. J Am Coll Health 1996; 44, 177-179.

Vau00 Vaughan TL, Stewart PA, Teschke K, Lynch CF, Swanson GM, Lyon JL, Berwick M. Occupational exposure to formaldehyde and woorddust and nasopharyngeal cancer. Occup. Environ. Med. 2000; 57, 376-384.

Ven92a Venkatakrishna H, Panchal GM. Behavioral change in rats due to chronic oral and systemic formaldehyde. Indian J Physiol Pharmacol 1992; 36: 270-272.

Ven92b Venkatakrishna-Bhatt H, Panchal GM. In vitro study of rat uterus after chronic formaldehyde exposure. Indian J Exp Biol 1992; 30: 901-903.

Vin99 Vinnueftirlit Rikisins. Mengunarmörk og adgerdir til ad draga úr mengun. 1999.

Voc99 Vock EH, Lutz WK, Ilinskaya O, Vamvakas S. Discrimination between genotoxicity and cytotoxicity for the induction of DNA double-strand breaks in cells treated with aldehydes and diepoxides. Mutation Res 1999; 44: 85-93.

Web77 Weber-Tschopp A, Fischer T, Grandjean E. Reizwirkung des Formaldehyds (HCHO) auf den Menschen. Int Arch Occup Environ Hlth 1977; 39: 207 - 218.

WGD81 Werkgroep van Deskundigen van de Nationale MAC-commissie. Rapport inzake formaldehyde RA 4/81, Voorburg, 1981.

WGD87 Dutch Expert Committee on Occupational Standards. Health-based recommended occupational exposure limits for formaldehyde. Directorate-General of Labour RA 3/87, 1987.

WHO00 World Health Organization. Formaldehyde. Final consultation, Updating and Revision of the Air Quality Guidelines for Europe, Meeting of the Final Consultation Group, Bilthoven, 28-31 October 1996. WHO Regional Office for Europe, Copenhagen.', 2000, in press.

WHO02 World Health Organization. Concise International Chemical Assessment Document 40, Formaldehyde. Geneva 2002.

Wil89 Wilmer JWGM, Woutersen RA, Appelman LM *et al*. Subchronic (13 week) inhalation toxicity study of formaldehyde in male rats: 8-hour intermittent versus 8-hour continuous exposures. Toxicol Let 1989; 47: 287-293.

Wil92 Wilhelmsson B, Holström M. Possible mechanisms of formaldehyde induced discomfort in the upper airways. Scand J Work Environ Health 1992; 18: 403-407.

Wit87 Witek Jr TJ, Schachter EN, Tosun T *et al*. An evaluation of respiratory effects following exposure to 2.0 ppm formaldehyde in asthmatics: lung function, symptoms, and airway reactivity. Arch Environ Hlth 1987; 42: 230 - 237.

Woo95 Wood RW, Coleman JB. Behavioral evaluation of the irritant properties of formaldehyde. Toxicol Appl Pharmacol 1995; 130: 67-72.

Wou87 Woutersen RA, Appelman LM, Wilmer JWGM, Falke HE, Feron VJ. Subchronic (13-week) inhalation toxicity study of formaldehyde in rats. J Appl Toxicol 1987; 7: 43-49.

Wou89 Woutersen RA van, Garderen-Hoetmer A, Bruijntjes JP *et al*. Nasal tumours in rats after severe injury to the nasal mucosa and prolonged exposure to 10 ppm formaldehyde. J Appl Toxicol 1989; 9: 39-46.

Yin97 Ying CJ, Yan WS, Zhao MY, Ye XL, Xie H, Yin SY, Zhu XS. Micronuclei in nasal mucosa, oral mucosa and lymphocytes in students exposed to formaldehyde vapour in anatomy class. Biomedical and environmental sciences (1997); 10, 541-455.

Yin99 Ying CJ, Ye XL, Xie H, Yan WS, Zhao MY, Xia T, Yin SY. Lymphocyte subsets and sister chromatid exchanges in the students exposed to formaldehyde vapor. Biomedical and environmental sciences (1999); 12, 88-94.

Zwa88 Zwart A, Woutersen RA, Wilmer JW *et al*. Cytotoxic and adaptive effects in rat nasal epithelium after 3-day and 13-week exposure to low concentrations of formaldehyde vapour. Toxicology 1988; 51: 87-99.

Annexes

Annex **A**

Request for advice

In a letter dated October 11, 1993, ref DGA/G/TOS/93/07732A, to, the State Secretary of Welfare, Health and Cultural Affairs, the Minister of Social Affairs and Employment wrote:

Some time ago a policy proposal has been formulated, as part of the simplification of the governmental advisory structure, to improve the integration of the development of recommendations for health based occupation standards and the development of comparable standards for the general population. A consequence of this policy proposal is the initiative to transfer the activities of the Dutch Expert Committee on Occupational Standards (DECOS) to the Health Council. DECOS has been established by ministerial decree of 2 June 1976. Its primary task is to recommend health based occupational exposure limits as the first step in the process of establishing Maximal Accepted Concentrations (MAC-values) for substances at the work place.

In an addendum, the Minister detailed his request to the Health Council as follows:

The Health Council should advice the Minister of Social Affairs and Employment on the hygienic aspects of his policy to protect workers against exposure to chemicals. Primarily, the Council should report on health based recommended exposure limits as a basis for (regulatory) exposure limits for air quality at the work place. This implies:

- A scientific evaluation of all relevant data on the health effects of exposure to substances using a criteria-document that will be made available to the Health Council as part of a specific request for advice. If possible this evaluation should lead to a health based recommended exposure limit, or, in

the case of genotoxic carcinogens, a ‘exposure versus tumour incidence range’ and a calculated concentration in air corresponding with reference tumour incidences of 10^{-4} and 10^{-6} per year.

- The evaluation of documents review the basis of occupational exposure limits that have been recently established in other countries.
- Recommending classifications for substances as part of the occupational hygiene policy of the government. In any case this regards the list of carcinogenic substances, for which the classification criteria of the Directive of the European Communities of 27 June 1967 (67/548/EEG) are used.
- Reporting on other subjects that will be specified at a later date.

In his letter of 14 December 1993, ref U 6102/WP/MK/459, to the Minister of Social Affairs and Employment the President of the Health Council agreed to establish DECOS as a Committee of the Health Council. The membership of the Committee is given in annex B.

Annex **B**

The committees

Dutch Expert Committee on Occupational Standards

- GJ Mulder, *chairman*
  professor of toxicology; Leiden University, Leiden
- RB Beems
  toxicologic pathologist; National Institute of Public Health and the Environment, Bilthoven
- PJ Boogaard
  toxicologist; Shell International Petroleum Company, Den Haag
- PJ Borm
  toxicologist, Heinrich Heine Universität Düsseldorf, Germany
- JJAM Brokamp, *advisor*
  Social and Economic Council, Den Haag
- DJJ Heederik
  epidemiologist; Agricultural University, Wageningen
- LCMP Hontelez, *advisor*
  Ministry of Social Affairs and Employment, Den Haag
- TM Pal
  occupational physician; Netherlands Centre for Occupational Diseases, Amsterdam
- IM Rietjens
  professor of toxicology, Wageningen University, Wageningen

- H Roelfzema, *advisor*
  Ministry of Health, Welfare and Sports, Den Haag
- T Smid
  occupational hygienist; KLM Health Safety & Environment, Schiphol and professor of working conditions, Free University, Amsterdam
- GMH Swaen
  epidemiologist; University Limburg, Maastricht
- RA Woutersen
  toxicologic pathologist; TNO Nutrition and Food Research, Zeist
- P Wulp
  occupational physician; Labour Inspectorate, Groningen
- JM Rijnkels, *scientific secretary,*
  Health Council of the Netherlands, Den Haag
- ASAM van der Burght, *scientific secretary*
  Health Council of the Netherlands, Den Haag

Nordic Expert Group

- G Johanson *chairman*
  toxicologist; National Institute for Working Life, Solna (Sweden)
- V Kristjansson
  occupational hygienist; Administration of Occupational Safety and Health, Reykjavik (Iceland)
- K Savolainen
  Finnish Institute of Occupational Health, Helsinki (Finland)
- V Skaug
  National Institute of Occupational Health, Oslo, Norway
- J Jarnberg, *scientific secretary*
  National Institute for Working Life, Solna (Sweden)

The first draft of the present report was prepared by dr AAE Wibowo, Coronel Institute, Academic Medical Centre, University of Amsterdam by contract with the Ministry of Social Affairs and Employment.

Both committees greatly acknowlegde prof dr VJ Feron, a former member of the DECOS, for his extensive contribution to this report.

Secretarial assistance was provided by M Javanmardi and A Aksel.
Lay-out: M Javanmardi and J van Kan.

Annex C

Comments on the public draft

A draft of the present report was released for public review in 2001 (a first draft was relaeased in 1998). The following organisations and persons have commented on the draft document.

- Dr WF ten Berge
  DSM, The Netherlands
- A Aalto
  Tampere, Finland
- dr RD Zumwalde
  National Institute for Occupational Safety and Health, USA
- dr H Greim
  Senatskommission der Deutschen Forschungsgemeinschaft, Germany
- mr J Landman
  Vereniging Academische Ziekenhuizen, Utrecht, The Netherlands
- mrs C Jeukenne
  Formaldehyde Sector Group, CEFIC, Belgium

Annex **D**

Formaldehyde monitoring data in occupational settings (IPC89)

D Formaldehyde monitoring data in occupational settings (IPC89)

Industry	Job or work area	Exposure levels mg/m^3 (ppm) range	mean	median	Area or personal monitor-	Number of observations	Method[b]	Reference
Formaldehyde production	production operator	-	1.68 (1.4)	-	personal	-	CT, IC	NIOSH (1980a)
	laboratory technician	-	1.57 (1.31)	-	personal	-	CT, IC	NIOSH (1980a)
Resin and plastic materials production	production operator	-	1.67 (1.39)	-	personal	-	CT, IC	NIOSH (1980a)
	resin plant	0.06-0.44 (0.05-0.37)	0.29 (0.24)	-	area	8	BI, CT, GC	NIOSH (1976a)
	resin plant	0.11-0.20 (0 09-0.17)	0.16 (0.13)	-	area	2	BI, CO	NIOSH (1978a)
	UF resin production (2 plants)	0.14-0.66 (0.12-0.55)	-	-	area	-	SS, IC	Herrick et al. (1983)
		0.22-6.48 (0.18-5 4)	-	-	area	-	SS, IC	Herrick et al. (1983)
		0.24-0 89 (0.2-0.74)	-	-	area	-	SS, IC	Herrick et al. (1983)
		0.72-0.41 (0.6-0.34)	-	-	area	-	SS, IC	Herrick et al. (1983)
	UF resin production	0.14-6.48 (0.12-5.4)	1.08 (0.90)	-	personal	18	BI, CA	NIOSH (1980b)
		0.24-0.89 (0.20-0.74)	0.47 (0.39)	-	personal	5	BI, CA	NIOSH (1980b)
		0 72-0.41 (0.06-0 34)	0.23 (0.19)	-	personal	5	BI, CA	NIOSH (1980b)
Textile finishing	textile warehouse	0.05-0.88 (0.04-0.73)	0.37 (0.31)	-	area, personal	11	CT, SP	NIOSH (1979a)
		0 10-0.61 (0.08-0 51)	0.30 (0.25)	-	area, personal	11	BI, SP	NIOSH (1979a)
	textile facilities	< 0.12-1.56 (< 0.1-1.3)	-	0.96 (0.8)	area, personal	28	-	NIOSH (1979b)
		< 0.12-1.68 (< 0 1-1.4)	-	0.84 (0.7)	area, personal	15	-	NIOSH (1979b)
	textile manufacture	0.13-1 60 (0.11-1.33)	0.83 (0 69)	0.77 (0.64)	personal	6	-	NIOSH (1981)
		0.18-1.44 (0 15-1.2)	0.64 (0.53)	0.54 (0 54)	area	13		NIOSH (1981)
Clothing production	permanent press	0.18-0.46 (0.15-0 38)	0.37 (0.31)	-	area	9	BI, I	US DHEW (1966)
		0-3.24 (0-2.7)	0.89 (0.74)	-	area	32	BI, I	US DHEW (1968)
	warehouse	0.13-0.68 (0.11-0.57)	0.47 (0.39)	0.44 (0.37)	personal	13	-	NIOSH (1979a)
		0.05-0.23 (0 04-0.19)	0.14 (0.12)	0.18 (0.15)	area	9	-	NIOSH (1979a)
	sewing machine operators	0.61-1.09 (0.51-0.91)	0.86 (0.72)	0.85 (0.71)	personal	16	-	NIOSH (1979a)
		0.36-2 16 (0.3-1.8)	1.44 (1.2)	1.44 (1.2)	personal	41	-	NIOSH (1979a)
	clothing pressers	0.006-1.14 (0.005-0.95)	0.08 (0.07)	0.065 (0.054)	personal	40	-	NIOSH (1976a)
Plywood particleboard production	all workers	-	1.2-3.0 (1-2.5)	-	area	-	-	NIOSH (1979b)
Wood furniture manufacture	particle board veneering	0.01-0.3 (0.008-0.25)	0.14 (0.12)	-	area	11	BI, CA	Herrick et al. (1983)
		1.08-7.68 (0.9-6.4)	3.30 (2.75)	-	area	-	BI, CA	Herrick et al. (1983)
		0.24-0.66 (0.2-0.55)	0.48 (0.40)	-	area	9	BI, CA	Herrick et al. (1983)
		0 24-3.0 (0.2-2.5)	0.84 (0.70)	-	area	13	BI, CA	Herrick et al. (1983)

Industry	Job or work area	Exposure levels mg/m^3 (ppm) range	mean	median	Area or personal monitor-	Number of observa- tions	Method[b]	Reference
Plastic moulding	injection mold	0 01-0.12 (0.01-0.1)	0.044 (0 037)	-	personal	9	CA	NIOSH (1973a)
	area samples	0.01-0.64 (0 01-0.53)	0.24 (0 20)	-	area	8	CA	NIOSH (1973a)
	operators	< 2.4 (< 2)	< 2.4 (< 2)	< 2.4 (< 2)	personal	28	DT	NIOSH (1973a)
	near grinder hopper	2.4-4.8 (2-4)	3.6 (3)	3.6 (3)	area	3	DT	NIOSH (1973a)
	sand mould production	0.12-0.84 (0.1-0.7)	0.37 (0.31)	0.24 (0.2)	personal	28	-	NIOSH (1976a)
		ND-1.32 (ND-1.1)	0.20 (0.17)	0.12 (0.1)	area	29	-	NIOSH (1976a)
Paper and paper-board manufacture	paper treatment (resin impregnated)	0.05-0.19 (0.04-0.16)	0.10 (0.08)	-	personal	15	BI, CT CA	NIOSH (1976b)
		0.04-0.08 (0.03-0.07)	0.07 (0.06)	-	area	7	BI, CT, CA	NIOSH (1976b)
		0.01-0.28 (0.01-0.23)	0.06 (0.05)	-	personal	30	BI, CT, CA	NIOSH (1976b)
Paper and paper-board manufacture (contd).		0.02-0.34 (0.02-0.28)	0.06 (0.05)	-	personal	10	BI, CT, CA	NIOSH (1976b)
	treated paper products	0.17-1.19 (0.14-0.99)	-	0.70 (0.59)	area	64	-	NIOSH (1979b)
		0.17-1.08 (0.14-0.90)	-	0.41 (0.34)	personal	37	-	NIOSH (1979b)
	coating preparation	< 0.01-3.6 (< 0.01-3)	1.2 (1.0)	0.01 (0.01)	area	7	-	NIOSH (1980a)
		0.96-0.50 (0.8-0.42)	0.61 (0.51)	0.50 (0.42)	area	4	-	NIOSH (1980a)
Foundries (steel, iron, and non-ferrous)	bronze foundry, core machine operators	0.29-0.96 (0.24-0.80)	0.64 (0.53)	0.66 (0.55)	personal	4	BI, CA	NIOSH (1976c)
		0.14-0.83 (0.12-0.69)	0.47 (0.39)	0.47 (0.39)	area	11	BI, CA	NIOSH (1976c)
	iron foundry, core machine operators	< 0.02-22.0 (0.02-18.3)	-	0.52 (0.43)	personal	14	-	NIOSH (1979b)
		0.08-0.40 (0.07-0.33)	0.19 (0.16)	-	personal	3	BI, CA	NIOSH (1973b)
	moulding	0.04-0.16 (0.03-0.13)	0.11 (0.09)	-	personal	6	BI, CO	NIOSH (1977a)
		0.08-0.94 (0.07-0.78)	0.25 (0.21)	-	area	6	BI, CO	NIOSH (1977a)
Rubber hose production	-	ND-0.05 (ND-0.04)	0.05 (0.04)	-	personal	10	BI, CO	NIOSH (1977b)
Asphalt shingle production	producers	0.04-0.08 (0.03-0.07)	0.06 (0.05)	0.06 (0.05)	area	2	BI, CO	NIOSH (1978b)
Fibreglass insulation	installers	0.008-0.04 (0.007-0.033)	0.028 (0.023) (TWA)[c]	0.023 (0 019)	personal	13	-	NIOSH (1980a)
Urea-formaldehyde foam insulation dealing and installation	suburban shopping centre insulated with UF foam	0.08-2.4 (0.07-2)	-	-	-	-	IC	Herrick et al. (1983)
		0.96-1.92 (0.8-1.6)	1.26 (1.05)	-	area	36	BI, CA	NIOSH (1979b)
		0.36-3.72 (0.3-3.1)	1.73 (1.44)	-	area	30	CT, IC	NIOSH (1979b)
		< 0-6.36 (< 0.5-3)	1.87 (1.56)	-	area	16	DT	NIOSH (1979b)
Fertilizer manufacturing		0.24-2.28 (0.2-1.9)	1.08 (0.9)	-	personal, area	11	-	NIOSH (1979b)
Mushroom farming		< 0.61-12+ (0.51-10+)	3.22 (2.68)	-	area	12	DT	NIOSH (1980b)
		ND-3.24 (ND-2.7)			personal	3	CT, IC	NIOSH (1980b)
		ND-5.92 (ND-4.93)	-	-	area	3	CT, IC	NIOSH (1980b)
Funeral homes	embalmers	0.1-6.3 (0.09-5.26)	0.89 (0.74)	-	area	187	CA	Kerfoot & Mooney (1975)
		0.24-4.79 (0.20-3.99)	1.32 (1.1)	0.65 (0.54)	area personal	8	CT	NIOSH (1980c)
		1.56-4.72 (1.30-3.99)	3.24 (2.7)	2.99 (2.49)	area personal	5	CT	NIOSH (1980c)

Industry	Job or work area	Exposure levels mg/m^3 (ppm) range	mean	median	Area or personal monitor-	Number of observa- tions	Method[b]	Reference
Pathology	autopsy room	0.07-9.5 (0.06-7.9)	5.76 (4.8)	-	area	10	BI, CA	Covino (1979)
		2.64-9.5 (2.20-7.9)	5.22 (4.35)	-	area	6	-	NIOSH (1979b)
Garment manufac- turing (contd)								
		0.06-1.34 (0.05-1.2)	0.55 (0.46)		area	42	CEA	Blade (1983)
Chemical manu- facturing	-	0.05-1.92 (0.04-1.6)	0.66 (0.55)	-	personal	3	BI	Blade (1983)
		0.04-0.52 (0.03-0.43)	0.20 (0.17)	-	area	5	BI	Blade (1983)
Glass manufac- facturing	-	0.50 (0.42)	0.50 (0.42)	-	personal	1	CT	Blade (1983)
		0.54-0.80 (0.45-0.64)	0.65 (0.54)	-	area	2	CT	Blade (1983)
Hospital work	-	0.44-0.88 (0.37-0.73)	0.66 (0.56)	-	area	2	BI	Blade (1983)
Paraformaldehyde packaging	-	< 0.30-1.02 (< 0.25-0.85)	0.66 (0.55)	-	personal	10	CA	Blade (1983)
		0.34-4.08 (0.28-3.4)	1.40 (1.17)	-	area	[illegible]	CEA	Blade (1983)
Office work (3 locations)	-	0.02-0.14 (0.02-0.12)	0.07 (0.06)	-	area	39	BI	Blade (1983)
		< 0.05 (< 0.04)	< 0.05 (< 0.04)	-	area	9	CT	Blade (1983)
Biology teaching	laboratory	3.30-17.76 (2.75-14.8)	8.2)	-	area	8	BI, CA	US EPA (1981)
Hospital	laboratory	2.64-2.76 (2.2-2.3)	2.70 (2.25)		personal	2	BI	Blade (1983)
		2.28 (1.9)			personal	1	CT	Blade (1983)
		2.64 (2.2)	2.4 (2)		area	2	CT	Blade (1983)
Government	laboratory	2.88 (2.4)			personal	1	CT	Blade (1983)
		0.96 (0.8)			area	1	CT	Blade (1983)
Hospital	dialysis unit	ND-1.08 (ND-0.90)	0.50 (0.42)		area	9	CT	Blade (1983)
		0.32-0.76 (0.27-0.63)	0.49 (0.41)		personal	5	CT	Blade (1983)
		0.05-0.60 (0.04-0.50)	0.61 (0.51)		area		CEA	Blade (1983)
Animal dissection	laboratory	< 0.46-1.25 (< 0.38-1.04)			personal	15	CA	Blade (1983)
		0.06-0.48 (0.05-0.40)	0.18 (0.15)		area	6	BI	Blade (1983)
		0.13-0.22 (0.11-0.29)	0.22 (0.18)		area	3	CEA	Blade (1983)
Garment manufac- turing (3 plants)	-	< 0.17-0.76 (< 0.14-0.63)	0.28-0.40 (0.23-0.33)		personal	40	CT	Blade (1983)
		< 0.04-0.48 (< 0.03-0.40)	0.23-0.31 (0.19-0.26)		area	43	CT	Blade (1983)
		0.04-0.48 (0.03-0.40)	0.25 (0.21)		area	43	BI	Blade (1983)
Autopsy rooms	resident	-	1.90[d] (1.58)		personal	10	CA	Makar et al. (1975)
	pathologist	-	1.50[d] (1.24)		personal	9	CA	
	technician	-	0.68[d] (0.57)		personal	2	CA	Makar et al. (1975)
	assistants	0.16-16.28 (0.13-13.57)	0.86 (0.72)		area	23	CA	

[a] From: Consensus Workshop on Formaldehyde (1984)

[b] *Abbreviations for analytical procedures:*

AA = acetylacetone.
BI = bisulfite impingers.
CA = chromotropic acid procedure.
CL = chemiluminescence procedure.
CO = colorimetric analysis.
CT = charcoal tubes.
SS = solid sorbents.
DT = Draeger tubes.
FS = Fourier transform spectrometer.
GC = gas chromatography.
IC = ion chromatography.
MB = MBTH procedure.
SP = spectrophotometric procedure.
CEA = CEA instruments Model 555.

[c] TWA = time-weighted average.

[d] Average.

Annex **E**

Genetic and related effects of formaldehyde (IAR95)

Zie bijlage D.

E Genetic and related effects of formaldehyde (IAR95)

Test system		Result[a]		Dose[b] (LED/HID)	Reference
		Without exogenous metabolic system	With exogenous metabolic system		
•	Misincorporation of DNA bases into synthetic polynucleotides *in vitro*	+	0	30	Snyder & Van Houten (1986)
PRB	Prophage induction, SOS repair test, DNA strand breaks, cross-links or related damage	+	0	0.0075	Kuykendall & Bogdanffy (1992)
PRB	Prophage induction, SOS repair test, DNA strand breaks, cross-links or related damage	+	0	20	Le Curieux *et al.* (1993)
ECB	*Escherichia coli* (or *E. coli* DNA) strand breaks, cross-links or related damage; DNA repair	+	0	600	Wilkins & MacLeod (1976)
ECB	*Escherichia coli* (or *E. coli* DNA) strand breaks, cross-links or related damage; DNA repair	+	0	60	Poverenny *et al.* (1975)
ECD	*Escherichia coli* K12 KS160-KS66 *pol*A1, differential toxicity	+	0	10	Leifer *et al.* (1981)
ECL	*Escherichia coli* K12 KS160-KS66 *pol*A1, differential toxicity	+	0	60	Poverenny *et al.* (1975)
ECK	*Escherichia coli* K12, forward or reverse mutation	+	0	60	Zijlstra (1989)
ECK	*Escherichia coli* K12, forward or reverse mutation	+	0	18.8	Graves *et al.* (1994)
ECK	*Escherichia coli* K12, forward or reverse mutation	+	0	120	Crosby *et al.* (1988)
ECK	*Escherichia coli* K12, forward or reverse mutation	+	+	10	Temcharoen & Thilly (1983)
SAF	*Salmonella typhimurium*, forward mutation	(+)	0	25	Mamett *et al.* (1985)
SA0	*Salmonella typhimurium* TA100, reverse mutation	-	-	30	Gocke *et al.* (1981)
SA0	*Salmonella typhimurium* TA100, reverse mutation	-	+	16.6	Haworth *et al.* (1983)
SA0	*Salmonella typhimurium* TA100, reverse mutation	(+)	+	30 (toxic above 125 µg/plate)	Connor *et al.* (1983)
SA0	*Salmonella typhimurium* TA100, reverse mutation	+	0	7.5	Takahashi *et al.* (1985)
SA0	*Salmonella typhimurium* TA100, reverse mutation	+	+	4.5	Pool *et al.* (1984)
SA0	*Salmonella typhimurium* TA100, reverse mutation	+	0	9.3	O'Donovan & Mee (1993)
SA0	*Salmonella typhimurium* TA100, reverse mutation	(+)	+	3	Schmid *et al.* (1986)
SA0	*Salmonella typhimurium* TA100, reverse mutation	+	0	10	Mamett *et al.* (1985)
SA2	*Salmonella typhimurium* TA102, reverse mutation	+	0	10	Le Curieux *et al* (1993)
SA2	*Salmonella typhimurium* TA102, reverse mutation	+	0	35.7	O'Donovan & Mee (1993)
SA2	*Salmonella typhimurium* TA102, reverse mutation	+	0	10	Mamett *et al.* (1985)
SA4	*Salmonella typhimurium* TA104, reverse mutation	-	-	30	Gocke *et al.* (1981)
SA5	*Salmonella typhimurium* TA1535, reverse mutation	-	-	50	Haworth *et al.* (1983)
SA5	*Salmonella typhimurium* TA1535, reverse mutation	0	-	9	Pool *et al.* (1984)
SA5	*Salmonella typhimurium* TA1535, reverse mutation	-	0	143	O'Donovan & Mee (1993)
SA5	*Salmonella typhimurium* TA1535, reverse mutation	-	-	30	Gocke *et al.* (1981)
SA7	*Salmonella typhimurium* TA1537, reverse mutation	-	-	50	Haworth *et al.* (1983)
SA7	*Salmonella typhimurium* TA1537, reverse mutation	-	0	143	O'Donovan & Mee (1993)
SA7	*Salmonella typhimurium* TA1537, reverse mutation	-	-	30	Gocke *et al.* (1981)
SA8	*Salmonella typhimurium* TA1538, reverse mutation	-	0	143	O'Donovan & Mee (1993)
SA8	*Salmonella typhimurium* TA1538, reverse mutation	+	0	5	Mamett *et al.* (1985)
SA9	*Salmonella typhimurium* TA98, reverse mutation	-	-	30	Gocke *et al.* (1981)
SA9	*Salmonella typhimurium* TA98, reverse mutation	-	(+)	16.6	Haworth *et al.* (1983)
SA9	*Salmonella typhimurium* TA98, reverse mutation	-	(+)	30 (toxic above 100 µg/plate)	Connor *et al.* (1983)
SA9	*Salmonella typhimurium* TA98, reverse mutation	0	(+)[c]	3	Pool *et al.* (1984)
SA9	*Salmonella typhimurium* TA98, reverse mutation	+	0	17.9	O'Donovan & Mee (1993)
SA9	*Salmonella typhimurium* TA98, reverse mutation	+	0	5	Mamett *et al.* (1985)
SA5	*Salmonella typhimurium* TA97, reverse mutation	-	-	100 (toxic at 250 µg/ml)	Connor *et al.* (1983)
SA5	*Salmonella typhimurium* (other miscellaneous strains), reverse mutation	+	0	15	Takahashi *et al.* (1985)
ECW	*Escherichia coli* WP2 *uvr*A, reverse mutation	+	0	17.9	O'Donovan & Mee (1993)
ECW	*Escherichia coli* WP2 *uvr*A(pKM101), reverse mutation				

Test system		Result[a]		Dose[b] (LED/HID)	Reference
		Without exogenous metabolic system	With exogenous metabolic system		
EC2	*Escherichia coli* WP2, reverse mutation	+	0	1.2	Nishioka (1973)
EC2	*Escherichia coli* WP2(pKM101), reverse mutation	+	0	35.7	O'Donovan & Mee (1993)
EC2	*Escherichia coli* WP2, reverse mutation	+	0	60	Takahashi *et al.* (1985)
ECR	*Escherichia coli* (other miscellaneous strains), reverse mutation	+	0	900	Panfilova *et al.* (1966)
ECR	*Escherichia coli* (other miscellaneous strains), reverse mutation	+	0	80	Demerec *et al.* (1951)
ECR	*Escherichia coli* (other miscellaneous strains), reverse mutation	+	0	30	Takahashi *et al* (1985)
SSB	*Saccharomyces* species, DNA strand breaks, cross-links or related damage	+	0	990	Magaña-Schwencke *et al.* (1978)
SSB	*Saccharomyces* species, DNA strand breaks, cross-links or related damage	+	0	500	Magaña-Schwencke & Ekert (1978)
SSB	*Saccharomyces* species, DNA strand breaks, cross-links or related damage	+	0	500	Magaña-Schwencke & Moustacchi (1980)
SCH	*Saccharomyces cerevisiae*, gene conversion	+	0	540	Chanet *et al.* (1975)
SCH	*Saccharomyces cerevisiae*, homozygosis by mitotic recombination or gene conversion	+	0	18 5	Zimmermann & Mohr (1992)
NCF	*Neurospora crassa*, forward mutation	+	0	100	de Serres *et al.* (1988)
NCR	*Neurospora crassa*, reverse mutation	-	0	732	Dickey *et al.* (1949)
NCR	*Neurospora crassa*, reverse mutation	+	0	37 500	Jensen *et al* (1952)
NCR	*Neurospora crassa*, reverse mutation	-	0	300	Kölmark & Westergaard (1953)
PLM	Plants (other), mutation	+	0	0 0	Auerbach *et al.* (1977)
DMG	*Drosophila melanogaster*, genetic crossing over or recombination	+		2700	Ratnayake (1970)
DMG	*Drosophila melanogaster*, genetic crossing over or recombination	+		420	Alderson (1967)
DMG	*Drosophila melanogaster*, genetic crossing over or recombination	+		1260	Sobels & van Steenis (1957)
DMX	*Drosophila melanogaster*, sex-linked recessive lethal mutations	+		420	Alderson (1967)
DMX	*Drosophila melanogaster*, sex-linked recessive lethal mutations	(+)		1940	Ratnayake (1968)
DMX	*Drosophila melanogaster*, sex-linked recessive lethal mutations	+		2380	Ratnayake (1970)
DMX	*Drosophila melanogaster*, sex-linked recessive lethal mutations	+		1940	Auerbach & Moser (1953)
DMX	*Drosophila melanogaster*, sex-linked recessive lethal mutations	+		1080	Kaplan (1948)
DMX	*Drosophila melanogaster*, sex-linked recessive lethal mutations	+		420	Khan (1967)
DMX	*Drosophila melanogaster*, sex-linked recessive lethal mutations	+		270	Stumm-Tegethoff (1969)
DMX	*Drosophila melanogaster*, sex-linked recessive lethal mutations	+		1260	Sobels & van Steenis (1957
DMH	*Drosophila melanogaster*, heritable translocation	+		2700	Ratnayake (1970)
DMH	*Drosophila melanogaster*, heritable translocation	+		420	Khan(1967)
DML	*Drosophila melanogaster*, dominant lethal mutation	+		1940	Auerbach & Moser (1953)
DML	*Drosophila melanogaster*, dominant lethal mutation	+		1400	Šrám (1970)
•	*Caenorhabditis elegans*, recessive lethal mutations	+		700	Johnsen & Baillie (1988)
DIA	DNA strand breaks, cross-links or related damage, animal cells *in vitro*	+	0	6	Ross & Shipley (1980)
DIA	DNA strand breaks, cross-links or related damage, animal cells *in vitro*	+	0	3.75	Ross *et al* (1981)
DIA	DNA strand breaks, cross-links or related damage, animal cells *in vitro*	+	0	22.5	Demkowicz-Dobrzanski & Castonguay (1992)
DIA	DNA strand breaks, cross-links or related damage, animal cells *in vitro*	+	0	7 5	O'Connor & Fox (1987)
G9H	Gene mutation, Chinese hamster V79 cells, *hprt* locus	+	0	9	Grafström *et al.* (1993)
SIC	Sister chromatid exchange, Chinese hamster cells *in vitro*	+	0	1	Obe & Beek (1979)
SIC	Sister chromatid exchange, Chinese hamster cells *in vitro*	+	+	3 2	Natarajan *et al.* (1983)
SIC	Sister chromatid exchange, Chinese hamster cells *in vitro*	+	+	1 8	Basler *et al* (1985)
CIC	Chromosomal aberrations, Chinese hamster cells *in vitro*	+	+	6 5	Natarajan *et al.* (1983)
CIC	Chromosomal aberrations, Chinese hamster cells *in vitro*	+	0	18	Ishidate *et al* (1981)

Test system		Result[a]		Dose[b] (LED/HID)		Reference
		Without exogenous metabolic system	With exogenous metabolic system			
TCM	Cell transformation, C3H10T1/2 mouse cells	+	0	0.5		Ragan & Boreiko (1981)
DIH	DNA strand breaks, cross-links or related damage, human cells *in vitro*	+	0	24		Fornace *et al.* (1982)
DIH	DNA strand breaks, cross-links or related damage, human cells *in vitro*	+	0	1.5		Craft *et al.* (1987)
DIH	DNA strand breaks, cross-links or related damage, human cells *in vitro*	+	0	3		Grafström *et al* (1986)
DIH	DNA strand breaks, cross-links or related damage, human cells *in vitro*	+	0	3		Snyder & Van Houten (1986)
DIH	DNA strand breaks, cross-links or related damage, human cells *in vitro*	+	0	3		Saladino *et al.* (1985)
DIH	DNA strand breaks, cross-links or related damage, human cells *in vitro*	+	0	3		Grafström *et al.* (1984)
DIH	DNA strand breaks, cross-links or related damage, human cells *in vitro*	+	0	12		Grafström (1990)
DIH	DNA strand breaks, cross-links or related damage, human cells *in vitro*	-	0	3 (> 0.1 mmol/L was lethal)		Doolittle *et al* (1985)
UIH	Unscheduled DNA synthesis, human bronchial epithelial cells *in vitro*	+	0	3		Grafström *et al.* (1985)
GIH	Gene mutation, human cells *in vitro*	+	0	3 9		Goldmacher & Thilly (1983)
GIH	Gene mutation, human cells *in vitro*	+	0	0 9		Craft *et al* (1987)
GIH	Gene mutation, human cells *in vitro*	+	0	4 5		Crosby *et al* (1988)
GIH	Gene mutation, human cells *in vitro*	+	0	4 5		Liber *et al.* (1989)
GIH	Gene mutation, human cells *in vitro*	+	0	3		Grafström (1990)
GIH	Gene mutation, human cells *in vitro*	+	0	6		Grafström *et al.* (1984)
RIH	DNA repair exclusive of unscheduled DNA synthesis, human cells *in vitro*	+	0	5 4		Obe & Beek (1979)
SHL	Sister chromatid exchange, human lymphocytes *in vitro*	+	0	5		Kreiger & Garry (1983)
SHL	Sister chromatid exchange, human lymphocytes *in vitro*	+	+	3 75		Schmid *et al.* (1986)
SHL	Sister chromatid exchange, human lymphocytes *in vitro*	+	0	60		Levy *et al.* (1983)
CHF	Chromosomal aberrations, human fibroblasts *in vitro*	+	0	10		Miretskaya & Shvartsman (1982)
CHL	Chromosomal aberrations, human lymphocytes *in vitro*	+	+	7 5		Schmid *et al* (1986)
CHL	Chromosomal aberrations, human lymphocytes *in vitro*	+	0	3 75		Dresp & Bauchinger (1988)
CHL	Chromosomal aberrations, human lymphocytes *in vitro*	+		1 5 inhal 6 h		Casanova-Schmitz *et al* (1984b)
DVA	DNA–protein cross-links, rat cells *in vivo*	(+)		1 5 inhal. 6 h		Lam *et al* (1985)
DVA	DNA–protein cross-links, rat cells *in vivo*	+		0.25 inhal 3 h		Heck *et al* (1986)
DVA	DNA–protein cross-links, rat cells *in vivo*	+		0.25 inhal. 3 h		Casanova & Heck (1987)
DVA	DNA–protein cross-links, rat cells *in vivo*	+		0 08 inhal. 6 h		Casanova *et al* (1989)
DVA	DNA–protein cross-links, rat cells *in vivo*	+		0.05 inhal 6 h		Heck *et al* (1989)
DVA	DNA–protein cross-links, rhesus monkey nasal turbinate cells *in vivo*	+		0.05 inhal. 6 h		Casanova *et al.* (1991)
DVA	DNA–protein cross-links, rhesus monkey nasal turbinate cells *in vivo*	+		2 mg/ml instil.		Costa *et al.* (1988)
DVA	DNA–protein cross-links, rat tracheal implant cells *in vivo*	+		3.9 inhal. 6 h/d × 5		Kligerman *et al.* (1984)
SVA	Sister chromatid exchange, rat cells *in vivo*	-		5 µg/ml, 12 d		Siboulet *et al* (1984)
•	Micronucleus induction, newt (*Pleurodeles waltl*) *in vivo*	-		25 ip × 1		Natarajan *et al.* (1983)
MVM	Micronucleus induction, mouse *in vivo*	-		30 ip × 1		Gocke *et al.* (1981)
MVM	Micronucleus induction, mouse *in vivo*	+		200 po × 1		Migliore *et al.* (1989)
MVR	Micronucleus induction, rat (gastrointestinal tract) *in vivo*	+		25 ip × 1		Natarajan *et al.* (1983)
CBA	Chromosomal aberrations, mouse bone-marrow cells *in vivo*	+		0.07 inhal. 4 h/d, 4 months		Kitaeva *et al.* (1990)
CBA	Chromosomal aberrations, rat bone-marrow cells *in vivo*	+		3.9 inhal 6 h/d × 5, 8 weeks		Dallas *et al.* (1992)
CBA	Chromosomal aberrations, rat bone-marrow cells *in vivo*	+				

Test system		Result[a]		Dose[b] (LED/HID)	Reference
		Without exogenous metabolic system	With exogenous metabolic system		
CLA	Chromosomal aberrations, rat leukocytes *in vivo*	-		3.9 inhal. 6 h/d × 5	Kligerman *et al.* (1984)
CCC	Chromosomal aberrations, mouse spermatocytes treated *in vivo*, spermatocytes observed	-		50 ip × 1	Fontignie-Houbrechts (1981)
CVA	Chromosomal aberrations, mouse spleen cells *in vivo*	-		25 ip × 1	Natarajan *et al.* (1983)
CVA	Chromosomal aberrations, rat pulmonary lavage cells *in vivo*	+		3.9 inhal. 6 h/d × 5	Dallas *et al.* (1992)
GVA	Gene mutation, rat cells in vivo (p53 point mutations in nasal carcinomas)	+		3.9 inhal. 6 h/d, 2 years	Recio *et al.* (1992)
MST	Mouse spot test	-		3.9 inhal. 6 h/d × 3	Jensen & Cohr (1983) [Abstract]
DLM	Dominant lethal mutation, mouse	(+)		50 ip × 1	Fontignie-Houbrechts (1981)
DLM	Dominant lethal mutation, mouse	-		20 ip × 1	Epstein *et al.* (1972)
DLR	Dominant lethal mutation, rat	(+)		0.2 inhal. 4 h/d × 120	Kitaeva *et al.* (1990)
DLM	Dominant lethal mutation, mouse	-		20 ip × 1	Epstein & Shafner (1968)
MVH	Micronucleus formation, human lymphocytes *in vivo*	(+)		0.06[c] inhal. 8-h TWA	Suruda *et al.* (1993)
MVH	Micronucleus formation, human cells (buccal epithelium) *in vivo*	+		0.06[c] inhal. 8-h TWA	Suruda *et al.* (1993)
MVH	Micronucleus formation, human cells (nasal epithelium) *in vivo*	-		0.06[c] inhal. 8-h TWA	Suruda *et al.* (1993)
MVH	Micronucleus formation, human cells (nasal epithelium) *in vivo*	+		0.06[c] inhal. 8-h TWA	Ballarin *et al.* (1992)
SLH	Sister chromatid exchange, human lymphocytes *in vivo*	-		0.5 inhal. 8-h TWA	Thomson *et al.* (1984)
SLH	Sister chromatid exchange, human lymphocytes *in vivo*	-		0.5 inhal. 8-h TWA	Bauchinger & Schmid (1985)
SLH	Sister chromatid exchange, human lymphocytes *in vivo*	+		0.2 inhal. 8-h TWA	Yager *et al.* (1986)
SLH	Sister chromatid exchange, human lymphocytes *in vivo*	-		0.06[c] inhal. 8-h TWA	Suruda *et al.* (1993)
CLH	Chromosomal aberrations, human lymphocytes *in vivo*			0.5 inhal. 8-h TWA	Thomson *et al.* (1984)
CLH	Chromosomal aberrations, human lymphocytes *in vivo*	-		0.8 inhal. 8-h TWA	Fleig *et al.* (1982)
CLH	Chromosomal aberrations, human lymphocytes *in vivo*	+		0.5 inhal. 8-h TWA	Bauchinger & Schmid (1985)
CLH	Chromosomal aberrations, human lymphocytes *in vivo*	-		0.4 inhal.	Vargová *et al.* (1992)
SPR	Sperm morphology, rats *in vivo*	+		200 po × 1	Cassidy *et al.* (1983)
SPM	Sperm morphology, mice *in vivo*	-		100 po × 5	Ward *et al.*[f] (1984)
SPH	Sperm morphology, humans in vivo	-		0.2 inhal. 8-h TWA	Ward *et al.* (1984)

•Not on profile

[a] +, positive, (+) weak positive; -, negative; 0, not tested, ?, inconclusive (variable response in several experiments within an adequate study)

[b] In-vitro tests, µg/ml; in-vivo tests, mg/kg bw

[c] Tested with S9 without co-factors

[d] Positive only in presence of 12-*O*-tetradecanoylphorbol 13-acetate (TPA)

[e] Based on a mean 8-h time-weighted average of 0.33 ppm (range, 0.1–0.96 ppm), peak exposures up to 6.6 ppm

Summary table of genetic and related effects of formaldehyde

Non-mammalian systems					Mammalian systems																									
Pro-karyotes	Lower eukaryotes	Plants		Insects	*In vitro*														*In vivo*											
					Animal cells								Human cells						Animal							Humans				
D G	D R G A	D G C		R G C A	D G S M C A T I								D G S M C A T I						D G S M C DL A							D S M C A			
+	+ + +	+		+ + +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	.	+	?	?	?	?	?	?	?	?	?

A, aneuploidy; C, chromosomal aberrations; D, DNA damage; DL, dominant lethal mutation; G, gene mutation; I, inhibition of intercellular communication; M, micronuclei; R, mitotic recombination and gene conversion; S, sister chromatid exchange; T, cell transformation

In completing the table, the following symbols indicate the consensus of the Working Group with regard to the results for each end point

+ considered to be positive for the specific end-point and level of biological complexity

+[1] considered to be positive, but only one valid study was available to the Working Group

. considered to be negative

.[1] considered to be negative but only one valid study was available to the Working Group

? considered to be equivocal or inconclusive (e.g. there were contradictory results from different laboratories there were confounding exposures, the results were equivocal)

Annex **F**

Classification of substances with respect to carcinogenicity

Guideline 93/21/EEG of the European Community

4.2 Criteria for classification, indication of danger, choice of risk phrases

4.2.1 Carcinogenic substances

For the purpose of classification and labelling, and having regard to the current state of knowledge, such substances are divided into three categories:

Category 1:

Substances known to be carcinogenic to man.

There is sufficient evidence to establish a causal association between human exposure to a substance and the development of cancer.

Category 2:

Substances which should be regarded as if they are carcinogenic to man.

There is sufficient evidence to provide a strong presumption that human exposure to a substance may result in the development of cancer, generally on the basis of:

- appropriate long-term animal studies
- other relevant information.

Category 3:

Substances which cause concern for man owing to possible carcinogenic effects but in respect of which the available information is not adequate for making a satisfactory assessment.

There is some evidence from appropriate animal studies, but this is insufficient to place the substance in Category 2.

4.2.1.1 The following symbols and specific risk phrases apply:

Category 1 and 2:

T; R45 May cause cancer

However for substances and preparations which present a carcinogenic risk only when inhaled, for example, as dust, vapour or fumes, (other routes of exposure e.g. by swallowing or in contact with skin do not present any carcinogenic risk), the following symbol and specific risk phrase should be used:

T; R49 May cause cancer by inhalation

Category 3

Xn; R40 Possible risk of irreversible effects

4.2.1.2 Comments regarding the categorisation of carcinogenic substances

The placing of a substance into Category 1 is done on the basis of epidemiological data; placing into Categories 2 and 3 is based primarily on animal experiments.

For classification as a Category 2 carcinogen either positive results in two animal species should be available or clear positive evidence in one species; together with supporting evidence such as genotoxicity data, metabolic or biochemical studies, induction of benign tumours, structural relationship with other known carcinogens, or data from epidemiological studies suggesting an association.

Category 3 actually comprises 2 sub-categories:

a) substances which are well investigated but for which the evidence of a tumour-inducing effect is insufficient for classification in Category 2. Additional experiments would not be expected to yield further relevant information with respect to classification.
b) substances which are insufficiently investigated. The available data are inadequate, but they raise concern for man. This classification is provisional; further experiments are necessary before a final decision can be made.

For a distinction between Categories 2 and 3 the arguments listed below are relevant which reduce the significance of experimental tumour induction in view of possible human exposure. These arguments, especially in combination, would lead in most cases to classification in Category 3, even though tumours have been induced in animals:

- carcinogenic effects only at very high levels exceeding the 'maximal tolerated dose'. The maximal tolerated dose is characterized by toxic effects which, although not yet reducing lifespan, go along with physical changes such as about 10% retardation in weight gain;
- appearance of tumours, especially at high dose levels, only in particular organs of certain species is known to be susceptible to a high spontaneous tumour formation;
- appearance of tumours, only at the site of application, in very sensitive test systems (e.g. i.p. or s.c. application of certain locally active compounds); if the particular target is not relevant to man;
- lack of genotoxicity in short-term tests *in vivo* and *in vitro*;
- existence of a secondary mechanism of action with the implication of a practical threshold above a certain dose level (e.g. hormonal effects on target organs or on mechanisms of physiological regulation, chronic stimulation of cell proliferation;
- existence of a species - specific mechanism of tumour formation (e.g. by specific metabolic pathways) irrelevant for man.

For a distinction between Category 3 and no classification arguments are relevant which exclude a concern for man:

- a substance should not be classified in any of the categories if the mechanism of experimental tumour formation is clearly identified, with good evidence that this process cannot be extrapolated to man;
- if the only available tumour data are liver tumours in certain sensitive strains of mice, without any other supplementary evidence, the substance may not be classified in any of the categories;
- particular attention should be paid to cases where the only available tumour data are the occurrence of neoplasms at sites and in strains where they are well known to occur spontaneously with a high incidence.

G

Abbreviations

bp	boiling point
EC_{50}	concentration at which a described effect is found in 50% of the exposed animals or at which the effect is decreased up to 50% of the control value
HBR-OEL	health based recommended occupational exposure limit
h	hour
IC_{50}	concentration at wAbbreviationshich inhibition of a certain function is found up to 50% of the control value
LC_{50}	lethal concentration for 50% of the exposed animals
LC_{lo}	lowest lethal concentration
LD_{50}	lethal dose for 50% of the exposed animals
LD_{lo}	lowest lethal dose
LOAEL	lowest observed adverse effect level
MAC	maximaal aanvaarde concentratie (maximal accepted concentration)
MAEL	minimal adverse effect level
MAK	Maximale Arbeitsplatz Konzentration
MOAEL	minimal observed adverse effect level
MTD	maximum tolerated dose
NAEL	no adverse effect level
NEL	no effect level

NOAEL	no observed adverse effect level
OEL	occupational exposure limit
PEL	permissible exposure limit
ppb	parts per billion (v/v)10^{-9}
ppm	parts per million (v/v)10^{-6}
RD_{50}	concentration at which a 50% decrease of respiratory rate is observed
REL	recommended exposure limit
STEL	short term exposure limit
tgg	tijd gewogen gemiddelde
TLV	threshold limit value
TWA	time weighted average
V_{max}	maximal reaction velocity of an enzyme

Organisations

ACGIH	American Conference of Governmental Industrial Hygienists
CEC	Commission of the European Communities
DECOS	Dutch Expert Committee on Occupational Standards
DFG	Deutsche Forschungsgemeinschaft
EPA	Environmental Protection Agency (USA)
FDA	Food and Drug Administration (USA)
HSE	Health and Safety Executive (UK)
IARC	International Agency for Research on Cancer (WHO)
INRS	Institut National de Recherche et de Sécurité (France)
NIOSH	National Institute for Occupational Safety and Health (USA)
NTP	National Toxicology Programme (USA)
OECD	Organisation for Economic Cooperation and Development
OSHA	Occupational Safety and Health Administration (USA)
RTECS	Registry of Toxic Effects of Chemical Substances
SER	Social and Economic Council (Sociaal-Economische Raad NL)
WATCH	Working Group on the Assessment of Toxic Chemicals (UK)
WHO	World Health Organisation

Toxicological terms

bid	*bis in diem* (twice per day)
bw	body weight

CARA	chronic non-specific respiratory diseases
CHD	coronary heart disease
CNS	central nervous system
ECG	electrocardiogram
EEG	electro encephalogram
FCA	Freunds Complete Adjuvans
FEV	forced expiratory volume
FSH	follicle stimulating hormone
GD	gestation day(s)
GPMT	guinea pig maximisation test
GSH	glutathione
HLiA	hamster liver activated
IHD	ischaemic heart disease
im	intramuscular
ip	intraperitoneal
ipl	intrapleural
it	intratracheal
iv	intravenous
LH	lutheinising hormone
MAC	minimal alveolar concentration
MFO	mixed function oxidase
NA	not activated
PNS	peripheral nervous system
po	*per os* (= oral)
RBC	red blood cells
RLiA	rat liver activated
SCE	sister chromatid exchange
sc	subcutaneous
UDS	unscheduled DNA-synthesis

Statistical terms

GM	geometric mean
OR	Odds Ratio
RR	Relative Risk
SD	standard deviation

SEM	standard error of mean
SMR	standard mortality ratio

Analytical methods

AAS	atomic absorption spectroscopy
BEEL	biological equivalent exposure limit
BEI	biological exposure index
BEM	biological effect monitoring
BM	biological monitoring
ECD	electron capture detector
EM	environmental monitoring
FID	flame ionisation detector
GC	gas chromatography
GLC	gas liquid chromatography
GSC	gas solid chromatography
HPLC	high performance liquid chromatography
IR	infrared
MS	mass spectrometry
NMR	nuclear magnetic resonance
PAS	personal air sampling
TLC	thin layer chromatography
UV	ultraviolet

Additional abbreviations in the present report

CI	confidence interval
CRR	combined relative risk
FEF	mean forced expiratory flow during the middle half ofthe FVC
FEV_1	Forced expitation volume in 1 second
FRC	Functional residual capacity
FVC	Forced vital capacity
NK	natural killer
$MEF_{50\%}$	Maximal flow at 50% of VC
PEFR	peak expitation flow rate
PHA	phytohemagglutinin
R_{aw}	Airway resistance

RD_{50}	The concentration associated with a 50% decrease in respiratory rate
RV	Retidual volume
SG_{aw}	Specific airway conductance ($SG_{aw} = SR_{aw}$)
SPIR	standardized proportionate incidence ratio
SR_{aw}	Specific airway resistance
SRR	standardized rate ratio
TLC	Total lung capacity
VC	Vital capacity