Hardwood and softwood dust

Evaluation of the carcinogenicity and genotoxicity

Aan de Staatssecretaris van Sociale Zaken en Werkgelegenheid

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Mijnheer de staatsecretaris,

Op 12 november 1998 verzocht uw Directeur Arbeidsomstandigheden, R. Laterveer, namens u om advies over de wijze waarop toxicologische advieswaarden voor blootstelling aan hardhout- en zachthoutstof moeten worden afgeleid (brief nr. ARBO/AMIL/9834631).

Hierbij bied ik u - gehoord de Beraadsgroep Gezondheid en Omgeving - het advies 'Hardwood and softwood dust, evaluation of the carcinogenicity and genotoxicity' aan, dat is opgesteld door de Commissie Beoordeling carcinogeniteit van stoffen.

Hoogachtend,
w.g.
prof. dr JJ Sixma

Hardwood and softwood dust

Evaluation of the carcinogenicity and genotoxicity

Committee on the Evaluation of the carcinogenicity of chemical substances

to:

the Minister and State Secretary of Social Affairs and Employment

Nr 2000/08OSH, The Hague, 18 July 2000

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Contents

Samenvatting

Hardhoutstof is voor mensen kankerverwekkend: inademing ervan kan leiden tot het optreden van adenocarcinoom van de neus en de neusbijholten. Onduidelijk is nog of er ook sprake is van verhoogde kansen op andere vormen van kanker, in het bijzonder nasofarynxcarcinoom, dieper in de luchtwegen. Uitkomsten van meta-analyses geven wél aanwijzingen in die richting. Voor zachthoutstof gaat de evidentie voor kankerverwekkendheid nog niet verder dan een verdenking: epidemiologische gegevens doen vermoeden dat dit agens plaveiselcelcarcinoom van de neus en de neusbijholten kan veroorzaken. Het bestaan van een causaal verband tussen hardhoutstof en nasofarynxkanker en tussen zachthoutstof en plaveiselcelcarcinoom van de neus en de neusbijholten is noch als bewezen noch als uitgesloten te beschouwen. Deze ongewisheid is waarschijnlijk vooral het gevolg van onzekerheid over de aard van de blootstelling (hardhout óf zachthout óf een mengsel van beide) en van een tekortschietend statistisch onderscheidingsvermogen van het verrichte onderzoek.

Onderzoek met proefdieren heeft tot dusver geen informatie opgeleverd over de eventuele kankerverwekkendheid van houtstof. Slechts van één langdurig inhalatie-experiment met hardhoutstof bij proefdieren zijn de uitkomsten gepubliceerd. Zij duiden niet op carcinogeniteit. Over de oorzaken van de discrepantie tussen de uitkomsten van onderzoek bij mensen en bij proefdieren is niets met zekerheid te zeggen.

Het is onmogelijk om de genotoxiciteit van houtstof rechtstreeks te onderzoeken. Daarom is gewerkt met extracten of condensaten als vervangende agentia. Uit de resultaten is het beeld naar voren gekomen dat de genotoxiciteit van hard- en zachthoutstof vergelijkbaar is, wat betreft zowel de potentie — *in casu*: zwak — als de

aard. Onbekend is echter in hoeverre de eigenschappen van de vervangende agentia representatief zijn voor die van hard- of zachthoutstof. De commissie betwijfelt of de gevonden genotoxiciteit betekenis heeft voor de (mogelijke) carcinogeniteit. Andere gegevens die plausibel kunnen maken dat hier de genotoxiciteit een cruciale rol speelt in het proces dat tot kanker leidt, bijvoorbeeld gegevens over het optreden van specifieke mutaties bij mensen die aan houtstof blootgesteld zijn geweest, zijn verre van eensluidend.

Er zijn ook bevindingen die erop duiden dat houtstof ontstekingsreacties kan veroorzaken en cytotoxisch is. De betekenis van deze bevindingen voor de carcinogeniteit — te weten: hogere incidenties van functionele en histologische veranderingen in de neus en de neusbijholten van aan houtstof blootgestelde mensen — is, net als die van de bevindingen inzake genotoxiciteit, nog onduidelijk. Wél kan men spreken van indicaties voor het bestaan van een (plaatselijke) weefselbeschadigende werking. De waargenomen effecten zijn zwak. Omdat de waarnemingen betrekking hebben op mengblootstellingen valt niet te zeggen of beide typen houtstof de genoemde effecten kunnen veroorzaken. In dierexperimenteel onderzoek (met hardhoutstof) naar plaatselijke cytotoxiciteit en regeneratieve celproliferatie zijn praktisch geen effecten waargenomen. Juist voor een agens als houtstof, dat matig vatbaar is voor degradatie door het immuunsysteem, zou men veel sterkere effecten verwachten dan hetgeen tot dusver is waargenomen. Er is geen verklaring voor het feit dat de ontstekingsbevordende en de cytotoxische eigenschappen van houtstof zich uitsluitend lijken te manifesteren als bescheiden histologische en functionele afwijkingen in de neus en de neusbijholten. Zowel bij mensen als bij proefdieren zijn de aangeduide waarnemingen gedaan na (semi-)chronische blootstelling. Dit bemoeilijkt hun interpretatie: uitsluitend het vroege optreden van de genoemde verschijnselen zou de commissie tot de overtuiging kunnen brengen dat houtstof niet langs genotoxische weg kankerverwekkend is, maar dat het ontstaan van tumoren door toedoen van dit agens voornamelijk berust op cytotoxiciteit en de regeneratieve hyperplasie die op weefselbeschadiging volgt. Was dit laatste het geval dan zou kanker goeddeels te voorkomen zijn door weefselbeschadiging te verhinderen.

Evenzeer tot dusver onbeantwoord is de vraag welke bestanddelen van houtstof verantwoordelijk zijn voor de waargenomen effecten. Is dat het stof als zodanig, of zijn het opzettelijk aan het hout toegevoegde stoffen of verontreinigingen, zoals conserveermiddelen respectievelijk schimmels? Ook de rol van de fysische kenmerken, zoals deeltjesgrootte, is onduidelijk.

De commissie meent dat toxicologische advieswaarden voor hard- en zachthoutstof op gelijke wijze moeten worden afgeleid, ook al staat voor hardhoutstof de

kankerverwekkendheid bij mensen vast en is zachthoutstof in dit opzicht als verdacht te bestempelen. Doorslaggevend is de overeenkomst in genotoxische eigenschappen.

Gezien de geschetste onduidelijkheden met betrekking tot genotoxiciteit en functionele of histologische veranderingen kan de commissie niet aangeven om welke van de volgende, voor de keuze van de methode bepalende, mogelijkheden het gaat:

- hard- en zachthoutstof zijn rechtstreeks genotoxisch carcinogeen, met een hoofdrol voor de genotoxiciteit
- hard- en zachthoutstof zijn indirect genotoxisch carcinogeen, met een hoofdrol, zo niet een essentiële rol, voor ontstekingsachtige of regeneratieve hyperplastische veranderingen
- hard- en zachthoutstof zijn niet-genotoxisch carcinogeen, met en essentiële rol voor regeneratieve hyperplasie na herhaaldelijk opgetreden weefselbeschadiging.

Het voorgaande houdt in dat het niet mogelijk is om te beslissen of bij de afleiding van gezondheidskundige bovengrenzen voor beroepsmatige blootstelling aan houtstof wel of niet moet worden uitgegaan van het bestaan van een drempelwaarde waarbeneden zich geen gezondheidsschade voordoet. In het verleden is het voorstel gehonoreerd om in geval van ongewisheid over het bestaan van een drempelwaarde aan te nemen dat zo'n grens niet bestaat en — derhalve — de methode van lineaire extrapolatie toe te passen. In dit rapport is een dienovereenkomstige berekening toegevoegd.

Executive summary

Hardwood dust is a human carcinogen; upon inhalation it can cause sinonasal adenocarcinoma. Whether it is able to induce other tumours, especially nasopharyngeal carcinoma, a cancer deeper down the airways, is unresolved, but the outcome of a meta-analysis suggests that it is. Softwood, on the other hand, is *suspected of* carcinogenic properties. The epidemiological data available suggest that it can cause sinonasal squamous-cell carcinoma. The data do not prove or disprove a causal relationship between hardwood dust and nasopharyngeal carcinoma, nor between softwood dust and sinonasal squamous-cell carcinoma. This may mainly be due to uncertainty as to the nature of the exposure (hardwood, softwood or mixed) and to lack of statistical power of the studies concerned.

The animal experiments do not provide any clues as to the questions of the types of tumour caused by the two species of wood dust. From only one long-term inhalation experiment, with hardwood dust, the results have been published. It did not provide any indication of carcinogenicity. The cause of the discrepancy between the human and animal findings as regards carcinogenicity is unknown.

The genotoxicity of the wood dusts cannot be and has not been tested directly. Preparations like extracts and condensates have been used as substitutes. The picture emerging from the results of the genotoxicity tests is that hardwood and softwood both possess genotoxic properties and that their genotoxicity is similar, with regard to nature and strength (weak). It is unknown, however, to what extent the properties of the dust surrogates represent those of the original material. According to the Committee, the relevance of the genotoxicity observed for the (possible) carcinogenicity of the dusts is

questionable. Other lines of evidence that could lend plausibility to the assumption that the genotoxicity is crucial to the carcinogenic process, such as specific mutations in adenocarcinomas from individuals with a history of wood dust exposure, are inconclusive.

Doubt as to their significance for carcinogenicity also holds true for the findings pointing to inflammatory and cytotoxic potential *in vivo, viz.* higher incidences of functional and histological changes in the sinonasal cavities of wood dust-exposed individuals. Due to the mixed nature of the exposure it has not been possible to determine whether both dusts can cause these effects. Together the findings are taken as indications of local tissue damage. The effects observed are weak, however. Correspondingly, animal experiments, with hardwood dust, aimed at detection of local cytotoxicity and regenerative cell proliferation (hyperplasia), were negative or virtually negative. A much stronger *in vivo* response than that observed is expected from an agent like wood dust, that is relatively resistant to degradation by the immune system. Why the inflammation and cytotoxicity are weak, only reflected in diminished nasal function and mild histological abnormalities, is enigmatic. The observations on local tissue damage, in humans and animals, have all been made upon semi-chronic and chronic exposure. It is not known whether they occur earlier upon exposure. This hampers interpretation, because only early presentation of such phenomena would convince the Committee that the wood dust does not cause tumours through genotoxicity, but promotes tumour formation predominantly by cytotoxicity and ensuing regenerative hyperplasia, and that tumours can largely be prevented by preventing tissue damage.

Another unresolved matter is that of the constituents to be held responsible for the effects observed: the wood dust itself, or components added to the wood deliberately or contaminating it, such as preservatives or moulds, respectively. Perhaps the physical characteristics, particle size for example, also play a role.

According to the Committee toxicology-based recommended exposure limits for hardwood and softwood dust should be derived identically, bearing in mind that hardwood dust is a proven, softwood dust a suspected carcinogen. The decisive factor here was the similarity of their genotoxicity.

In view of the dubious significance of both the genotoxicity findings and the functional and histological findings the Committee cannot answer the question whether the wood dusts are

- direct genotoxic carcinogens with a major role for their genotoxicity
- indirect genotoxic carcinogens with a major, if not an essential role for inflammatory or regenerative hyperplastic changes
- non-genotoxic carcinogens with an essential role for regenerative hyperplasia following recurrent tissue damage.

Consequently, the decision how toxicology-based occupational exposure limits should be derived, with a threshold or linear model, cannot be made. In the past the suggestion to apply linear extrapolation to carcinogens with unresolved mechanism has been honoured. Therefore, calculations along this line have been added.

Chapter 1

Introduction

Recently, the Dutch Expert Committee on Occupational Standards (DECOS), a committee of the Health Council of the Netherlands, assessed the health effects of exposure to wood dust (DEC98). This evaluation was restricted to the carcinogenic properties. It was performed according to the classification system of the EU, that uses the strength of the evidence, and it was based on a monograph from the International Agency for Research on Cancer (IARC), supplemented with more recent publications (IAR95). Hardwoods and softwoods were separately assessed. The terms ‘hardwood’ and ‘softwood’ refer to angiosperm and gymnosperm trees, respectively, and not necessarily to the hardness of the wood. According to DECOS hardwood dust has been found to be carcinogenic to humans and to possess genotoxic properties. They concluded that softwood dust, on the other hand, had been insufficiently investigated and proposed to classify it as a suspected human carcinogen.

In a previous report, DECOS had assessed the health effects of exposure to wood dust *as a whole* and derived a toxicology-based recommended exposure limit based on a threshold, a level below which adverse effects are expected not to occur (DEC91). This limit was based on prevention of irritation.

The classification outcome prompted the State Secretary of Social Affairs and Employment to request the Health Council for assessment of its consequences for the exposure limit in force, that applies to wood dust as such (see Annex A). Because of their specialised knowledge, the President of the Health Council asked the Committee on the Evaluation of the Carcinogenicity of Chemical Substances — further referred to as: the Committee — to answer the questions.

For its judgement the Committee has relied on the reviews of IARC and DECOS, as well as on papers published more recently than the latter. These were drawn from the databases Biosis, Embase, Elsevier Biobase, IAC Health, Pascal, Medline and Toxline up until March 2000. If considered necessary the original papers included in the reviews were checked. The report starts with separate evaluations of hardwood and softwood dust. It does not mention the species of tree investigated, because species-wise evaluation is not possible, as exposure involves dust from several species combined (in the case of epidemiological data), or species-specific data are too scarce (the other data). In the final chapter the health hazards of the two types of dust are compared. This is crucial for the decision whether to propose different methods for estimation of toxicology-based recommended exposure levels, levels that do not pose a health risk higher than a predetermined one.

Chapter 2

Hardwood

2.1 Genotoxicity and interaction with DNA

To investigate wood dust for compounds with genotoxic properties two preparative methods have been applied that are common for assessing the health hazards of materials consisting of insoluble high-molecular components, such as cellulose and lignin, and low-molecular ones, like terpenes. The material is heated and the fumes set free are collected and condensated; alternatively it is extracted with a solvent.

In vitro genotoxicity tests were performed with both types of preparation. The majority were tests with bacteria, that detect gene mutations. Both condensates and extracts from hardwoods have been shown to cause mutations in bacteria, albeit weakly (Kur90, Moh86, Moh90). Addition of a metabolic activation system was not required to demonstrate this activity. Not all experiments of this type performed demonstrated mutagenicity; some were negative, with and without metabolic activation (Kub88, Sin95, Wei92). In one study a third method, microbial degradation, was applied to a hardwood dust (Moh90). The preparation proved to be genotoxic.

Additionally, hardwood preparations were investigated for the ability to cause chromosomal aberrations. An extract proved positive in a test with a cell line of human origin, the positivity being moderate (Zho95). A condensate, on the other hand, was found negative in a test with human peripheral blood lymphocytes (Mar95a).

With hardwood one *in vivo* genotoxicity test was performed. Intranasal application of a hardwood extract to rats significantly increased the frequency of micronuclei in the

nasal tissue (Nel93). Also the local formation of DNA adducts was checked by ^{32}P-postlabelling; none was observed.

Hardwood extracts and condensates have not been investigated for interaction with DNA *in vitro*.

Furthermore, four papers describe observations suggestive of genotoxicity in humans. The peripheral blood of workers employed in the plywood industry on average demonstrated more chromosomal aberrations than controls, the difference being small but statistically significant (Kur93). Similarly the peripheral blood lymphocytes of smoking workers exposed to hardwood dust in the furniture industry appeared to contain significantly more DNA breaks than unexposed smoking colleagues (Pal98). It should be noted, however, that there had been exposure to hard- and softwood in both cases. In the third paper the investigators confirmed these findings in non-smoking workers in a furniture plant, exposed to dust from unspecified wood (Pal99).

The fourth paper describes a different approach: a molecular analysis of the DNA modifications in sinonasal adenocarcinomas, the type of tumour undoubtedly caused by hardwood dust (see 2.2) (Sab98). A particular mutation was observed in the k-*ras* oncogene in sinonasal adenocarcinomas from patients who had been exposed to (an unspecified type of) wood dust. The investigators suggest that this points to genotoxic properties. The Committee considers this doubtful, because the suggestion is based on two subjects only and the mutation described has also been observed in several types of animal and human tumour not associated with wood dust exposure (Cap91). More papers document mutations in sinonasal adenocarcinoma. Mutations in h-*ras* and k-*ras* were observed in five and one, respectively, out of 31 cases; n-*ras* was not mutated (Per99). Others found mutations in *p53*, but not k-*ras*, in 2 out of 11 tumours (Wu96). The h-*ras* mutations were identical; the adenocarcinomas they were detected in, came from patients with and without a history of exposure to wood dust. In the case of the *p53* mutations it is not known whether the patients had been exposed to wood dust previously.

2.2 Carcinogenicity

2.2.1 Animals

The available animal data have been examined for indications of carcinogenicity and effects that may be causally related to tumour formation: local cytotoxicity and histological abnormalities, suggestive of regeneration of the tissue following a cytotoxic insult. Such lesions are for instance hyper- and metaplasia.

Since the publication of the IARC review no new relevant data obtained in toxicity studies with animals have been reported. This means that only one experiment has been

carried out in which animals have been exposed to hardwood dust chronically. It is a two-year inhalation study in rats (Hol89). The animals demonstrated no enhanced risk of tumours in the nose or lungs, the organs investigated, at the end of the experiment, only a significantly increased histological score in the nasal tissue corresponding to (unspecified) light histological changes.

From another long-term inhalation study only some preliminary results have been published. Female rats were exposed to dust from hardwood, untreated or preserved with certain chemicals, or to the chemicals themselves (Wol98a). Findings concerning part of the animals have been reported. As they are incomplete, the Committee does not take them into account.

The remainder of the data reviewed by IARC originate from experiments with rats, mice and hamsters, of varying designs, and sharing a shorter duration (minimally six months). They provide evidence neither for carcinogenicity, nor for histological abnormalities, except minor ones.

Cytotoxicity and histological changes have not been addressed at short-term exposures (28 days or less).

There is evidence from one animal study that hardwood dust carries carcinogenic properties. The experiment has been carried out with a genotoxic extract of hardwood dust, applied dermally for three months (Moh89). It proved to be carcinogenic, to cause a significant and dose-dependent increase of tumours, most of which occurred at the site of application, the skin, and none in the nasal cavities. These findings demonstrate that tumours can be induced locally and suggest that the genotoxicity of the extract is associated with the carcinogenic effect observed.

2.2.2 Humans

Hardwood dust is a proven human carcinogen; it can cause a specific type of cancer of the nasal cavities and paranasal sinuses: sinonasal adenocarcinoma (DEC98, IAR95). A sufficient number of well-performed studies on cohorts with exposure to hardwood dust alone or as the major source of the wood dust has demonstrated this in separate and pooled analyses. Support comes from various case-control studies.

The individual studies had produced inconsistent findings with regard to other cancers. To address this issue two meta-analyses, taken into account by IARC (Dem95a) and DECOS (Dem95b), were performed. In these analyses the type of wood dust was not specified and crude measures of exposure to wood dust were applied. Industry and job titles provided information as to involvement of each type.

The primary aim of a combined analysis of five cohorts (about 28 000 persons) was to detect association of wood dust with any cancer other than sinonasal adenocarcinoma (Dem95b). The suspected cancer sites, the respiratory, digestive and hematopoietic

system, had been indicated by the previous studies. Additionally the combined analysis sought to quantify the risk of sinonasal cancer. 'Sinonasal cancer' was addressed instead of 'sinonasal adenocarcinoma', presumably because some of the contributing datasets lacked histological specification of the sinonasal tumours. The aggregated data show statistically significant increases of sinonasal cancer (SMR 3.2 [95%-CI 1.6-5.6]) and nasopharyngeal cancer (2.4 [1.1-4.5]).

The data were also analysed by decade of first employment, number of years since first employment and type of industry — all surrogate measures of exposure. Analysis by industry title confirmed that the sinonasal and nasopharyngeal cancers are significantly enhanced in the furniture industry (4.3 [2.2-7.8] and 2.9 [1.2-5.9], respectively). In the plywood industry they are raised, though not significantly, but show large confidence intervals with high upper bounds (0.0 [0.0-11.5] and 4.6 [0.6-16.4]). The furniture makers had been exposed to hardwood primarily, the plywood workers to unknown wood species.

Using the other exposure measures mentioned the relative risks of sinonasal and nasopharyngeal cancer were shown to be significantly increased, like in the full cohort, and the relative risk of multiple myeloma to be suggestively, but non-significantly augmented. The relative risk of both sinonasal and nasopharyngeal cancer increases with exposure; the data on multiple myeloma do not show this type of consistency in exposure-response relationship.

A recent cohort study also addressed the issue of other cancers than those of the sinonasal cavities (Ste98). The risk of cancer of various origins was examined in a group of 45,399 US. men that had been exposed to wood dust (of unspecified type). Their follow-up was six years and exposure varied from less than 10 to more than 20 years. They showed statistically significant excesses of all malignancies combined and tumours of the lung, prostate and brain. The investigators offer confounding by, among others, asbestos and formaldehyde as explanation, at least partially. A peculiarity is that the cohort does not demonstrate an excess of sinonasal tumours. This is in line with the (unexplained) observations that the hardwood dust-associated risk of sinonasal tumours is raised in Europe, but not in North America (see for instance the review by Blot and co-workers (Blo97)).

Twelve case-control studies on sinonasal cancer and wood dust have also been subjected to pooled analysis (Dem95a). The purpose of this evaluation was to gain more insight into the type of sinonasal tumour associated with wood dust. Occupation and industry titles were used to construct a job exposure matrix. The exposures were ascribed to three categories: high, moderate or low. The histological characterisation of the tumours was crucial. In the analysis 625 of the 930 sinonasal cancers included were specified as either adenocarcinoma (195 cases) or squamous-cell carcinoma (430 cases), the

remainder as tumours of other or unspecified histology. The analysis was performed for all sinonasal cancers together, adenocarcinoma, and squamous-cell carcinoma.

The risk of all sinonasal cancer was found to be significantly elevated when either all jobs or all exposure categories were combined. Analyses by exposure category and by duration of exposure demonstrated that the risk increases with the exposure. For adenocarcinoma a similar pattern emerged, with higher relative risks though. The risk of squamous-cell carcinoma, however, did not appear to be significantly raised in any of these analyses. These conclusions are based on the data from the men in the study. The outcome regarding squamous-cell carcinoma does not appear to be the consequence of a lack of statistical power, since the number of exposed cases is about half that of exposed cases of adenocarcinoma. Generally the women showed a pattern of relative risks similar to that of the men, although with trends instead of significant effects, probably a reflection of the considerably lower number of female cases compared to male ones (one tenth or less). There is one exception: the women exposed for more than five years in all jobs combined and those exposed equally long to moderate to high dust concentrations demonstrated a statistically significant excess risk of squamous-cell carcinoma (5.6 [1.1.-28] and 8.9 [1.6-48.4], respectively).

Recently, the eight European case-control studies included in the above-mentioned analysis were subjected to another pooled analysis, taking into account occupation, smoking and gender (Man99). In general the conclusions of the larger study are confirmed, with OR's and confidence intervals reflecting the difference in size.

Furthermore, some epidemiological investigations are worth mentioning, because they may shed light on the mechanism by which the sinonasal cancers develop. They concern histological changes in the sinonasal epithelium and indications of functional impairment.

IARC reviewed the results from nasal biopsies up until 1995. Higher frequencies of various morphological changes in the nasal epithelium have been noted in nasal biopsies from wood-dust exposed persons as compared to controls. Similar findings were described in a more recent publication (Pis95). Some of the changes noted have also been detected in the tumour-free nasal tissue of patients with sinonasal adenocarcinomas. In most cases the source of the wood dust the subjects had been exposed to was uncertain. It may or may not have been hardwood only. Only one of the studies reviewed by IARC does not suffer from lack of insight into the exposure (Wolf *et al*., 1994 in IAR95; see also Wol98b). Various histological scoring systems were used and two pathways leading to tumours were suggested. One from metaplasia of the normal (low-cuboidal) sinonasal epithelium through high-cuboidal epithelium, squamous metaplasia, squamous dysplasia to squamous cell carcinoma. The other from normal

through high-cuboidal epithelium, high-cuboidal epithelium with dysplasia to adenocarcinoma.

IARC also reviewed the available results from tests of nasal function in humans exposed to wood dust, mostly employees of furniture factories exposed to both dust species (IAR95). Diminished mucociliary transport rates were noted, indicating that nasal clearance can be partly or fully inhibited in wooddust-exposed individuals. In one study the groups exposed to unprocessed wood did not exhibit statistically significant reduction of nasal clearance, whereas those additionally exposed to preservatives did, suggesting that these chemicals play an important role (IAR95, see also Wol98b).

Additionally it was reported that woodwork teachers show slightly decreased nasal function, but no indications of inflammation (Ahm95, Ahm96). However, the data are incomplete with regard to the exposure: the type of wood was unknown, the wood was a mixture of hard- and softwood, or additional exposure to metal dust had occurred.

Workers coating wood surfaces were examined for signs of inflammation in cells obtained by nasal lavage (Gra98). Only the groups that had been exposed to coatings and wood dust showed raised numbers of macrophages and inflammatory cells, of which only the former was significant. Information as to the type of wood was not provided.

Without any exception the data on nasal histology and function have been collected from groups exposed to hardwood dust for upon average ten years or more, individual exposures lasting minimally one year.

2.3 Evaluation

The Committee concludes that there is consistent evidence from epidemiological studies that hardwood dust can cause sinonasal adenocarcinoma. They agree with IARC and DECOS that the epidemiological data on wood dust and cancer allow this inference. It is primarily based on the facts that it concerns a tumour that is rare in the general population and that many cohorts have been investigated that leave no doubt as to the association with hardwood. The combined analysis of case-control studies confirms that the adenocarcinomas stand out, as expected from the single studies (Dem95a). Why the association in the cohort studies is found in the European, but not the American ones, is enigmatic. The outcome of the pooled cohort analysis provides evidence that exposure to wood dust can also lead to cancer at an other site in the airways, the nasopharyngeal region, as demonstrated by a statistically significant excess risk in the same order of magnitude as that of the adenocarcinomas (Dem95b). The inconsistency of the individual studies with regard to the presence or absence of excess risk had precluded this conclusion before. The cohort-derived findings do not point to an association of (hard)wood with any other cancers than those of the sinonasal and nasopharyngeal region.

Whereas the cohort meta-analysis has not addressed the specificity of the sinonasal tumours, the case-control meta-analysis has. It provides some evidence that wood dust may also be able to cause squamous-cell carcinoma, the second sinonasal type of tumour frequently mentioned as possible consequence of exposure to wood dust. In this respect a statistically significant excess risk of squamous-cell carcinoma demonstrated in highly-exposed women is striking. The investigators offer several explanations, among them sex-related differences in susceptibility or exposure. They also suggest that these tumours are caused by softwood, not hardwood dust. The Committee agrees with these suggestions.

Further epidemiological findings demonstrate that wood dust has histologically and functionally detectable adverse effects on the nose. As regards the former the Committee does not support the interpretation, given by several investigators, that specific morphological changes in the nasal lining represent early stages in the development of certain cancers. Although occurring significantly more frequent in wood dust-exposed persons, the background prevalence of some of them was quite high. Additionally the assessment of their relevance is complicated by differences and inadequacies in histological typing and by the fact that the exposures were mostly of mixed nature. Many of them, if correct and relevant, would point to squamous-cell carcinoma rather than adenocarcinoma. This combined with the uncertainty as to the type of wood, the high background prevalence of the tissue lesions, the abundance of these lesions in patients with nasal complaints of unknown cause or arising spontaneously and the speculative character of the sequence of histological events preceding a tumour renders their significance, especially as indicator of specific types of tumour, dubious.

The interpretation of the reduced nasal clearance of course also suffers from the limitations imposed upon them by the exposure characteristics.

Together, the histological and functional findings nevertheless demonstrate that wood dust can have a cytotoxic effect on the cells lining the sinonasal cavities. Whether this effect can be ascribed to hardwood dust, remains to be determined, however.

There is a discrepancy between the epidemiological and the experimental findings. In the one animal species exposed via inhalation no carcinogenic effect in the airways has been detected. The estimated exposure concentration in the cohort with the highest relative risk of sinonasal adenocarcinoma, a group of British furniture workers, was 4.2 (range 0.3-53) mg per m^3 in 1983 and 7.8 (range 2.0-32) mg per m^3 in 1976 and 1977, whereas the rats had been inhaling 25 mg per m^3 (Hol89, IAR95, Jon86). Therefore the nonresponsiveness of the animals does not seem to be the consequence of too low a dose. Additionally, the animals that had been inhaling hardwood dust show at most weak signs of cytotoxicity and tissue regeneration in the sinonasal cavities. These observations were

made after semi-chronic or chronic exposure. In the one experiment demonstrating carcinogenicity in animals an extract with genotoxic properties was applied dermally and shown to induce tumours locally (Moh89). Thus, the route of exposure (dermal) was different from that experienced by humans (inhalation) and cannot be used as such to imply that hardwood dust is a (genotoxic) carcinogen by inhalation. Together, the scarce animal data available do not provide evidence that points to carcinogenicity by inhalation.

There is sufficient evidence that hardwood extracts and condensates can cause gene mutations and chromosomal aberrations *in vitro*. Therefore, this material is considered genotoxic *in vitro*. The genotoxicity is weak, however. Whether hardwood preparations are also genotoxic *in vivo* has not been investigated properly. According to the Committee the only test, performed with an extract, does not allow any inferences, because small numbers of cells were scored (Nel93). The epidemiological studies of genotoxicity are inconclusive as to the type of wood dust or have produced results of doubtful relevance, as in the case of the k-*ras* mutation (Sab98).

Chapter 3

Softwood

3.1 Genotoxicity and interaction with DNA

Softwood has been investigated for genotoxic properties in the same manner as hardwood: as condensates and extracts. With regard to *in vitro* tests the majority of experiments has been performed with bacterial systems. Condensates isolated from softwoods were demonstrated to be mutagenic, the mutagenicity being weak, but observable with and without metabolic activation (Kur90, Sin95). Other investigators found negative results, however, even after metabolic activation (Kub88, Wei92).

Three softwood condensates were tested for induction of chromosomal aberrations and sister chromatid exchanges *in vitro*. Two appeared to be able to cause these cytogenetic effects in human as well as animal cells (Mar95b, Mar95c, Mar95d). The third was tested only in animal cells and found positive as well (Mar95e). Like the mutagenicity the cytogenetic effects were weak. Additionally, an extract was tested for the capacity to induce chromosomal aberrations and found negative in a human cell line (Zho95).

The effects *in vitro* on DNA and the *in vivo* genotoxicity of softwood condensates or extracts have not been investigated.

Some epidemiological observations regarding occupational exposure of softwood dust suggest that it carries genotoxic properties. Among them are the observations already mentioned in the previous chapter, concerning people that had been in contact with hardwood and softwood dust (Kur93, Pal98, Pal99). An additional finding pointing in

the same direction is that employees of a match factory, exclusively exposed to softwood dust, carry more micronuclei in their peripheral blood lymphocytes than a control group (Jia94). Unfortunately it was not reported whether their smoking habits were comparable to those of the controls. As tobacco smoke is known to cause DNA breaks, differences in smoking behaviour may have confounded the outcome.

3.2 Carcinogenicity

3.2.1 Animals

The health effects of inhalation of softwood dust have not been investigated in animals, neither in chronic, nor in subchronic studies.

3.2.2 Humans

Whether inhalation of softwood dust can lead to cancer is controversial. However, sinonasal adenocarcinomas hardly figure in the discussions; the focus is on other tumours. It is assumed that the adenocarcinomas that seem to be caused by softwood dust, in fact are due to co-exposure to hardwood. According to the Committee this is plausible.

The predominant type under discussion is squamous-cell carcinoma of the sinonasal tissues. One of the major difficulties when interpreting the data is the uncertainty as to the nature of the wood from which the dust originates. Of course this also applies to hardwood, but there the high carcinogenic potency of the agent combined with the specificity of the tumours made inferences relatively easy, at least for the adenocarcinomas. Only few of the relevant epidemiological data concern people that had been exposed to softwood exclusively; and even in some of these cases some co-exposure to hardwood cannot be ruled out, according to Demers and co-workers, who reviewed the data (Dem97). The remainder, however, concern unequivocal co-exposure to hardwood.

The review by Demers and colleagues describes which studies presumably concern softwood predominantly, the species of trees harvested locally serving as criterium (Dem97). The Committee endorses this analysis of the matter, except for exclusion of a cohort of construction workers (see below). Relevant are five case-control, several cohort and two other studies, one lacking a control group and the other investigating the morphology of the sinonal tissue instead of nasal cancer (Boysen *et al*., 1986 in IAR95, see 3.2.3). The case-control studies were directed at squamous-cell carcinomas (two studies) and sinonasal cancers (three studies), reflecting the absence or presence of histological information, respectively. Together, they concern 86 squamous-cell

carcinomas and 235 sinonasal cancers. Two out of three studies showed statistically significant raises of sinonasal cancer, two statistically significant increases of squamous-cell carcinoma in subgroup analyses. The SMRs for sinonasal tumours were 2.5 ($p < 0.03$), 3,4 (1.1-10.3) and 0.7 (0.3-2.0). Those for squamous-cell carcinoma overall were 2.4 (0.8 - 6.7) and 1.7 ('not significant', 95%-CI not given). In the subgroups with the highest exposure they were significantly raised for at least one of the measures used for this purpose: 7.3 (1.4 - 34.3) for more than 10 years of exposure and 2.5 (1.1.-6.0) for exposure started in 1945 or earlier, respectively. According to the authors of the review only three cohort studies were sufficiently specific for softwood to be included: two small ones (2283 and 1283 persons exposed) and a large one (26 487 persons exposed). The small studies demonstrated some significantly raised excesses of tumour risk, among them no cancers of the respiratory system, but the figures were considered unreliable due to variation associated with very small numbers. The larger cohort will be discussed below separately (Her97). According to the reviewers the cohort studies lacked the statistical power to address the risk of sinonasal cancer, without specifying the relative risk they had in mind, however. They prudently conclude from the overall data that softwood exposure possibly increases the risk of squamous-cell carcinoma. With regard to association of softwood with any other type of cancer they see no consistency among the cohort studies.

The results of two retrospective cohort studies have been reported after IARC published its monograph (Don95, Her97). One concerns construction workers in the United Kingdom, the other saw mill employees in British Columbia, Canada. Neither paper discusses the type(s) of wood involved. Data on wood production from the United Nations Food and Agriculture Organisation indicate that the wood produced in British Columbia is almost exclusively softwood and in the UK for about 80% (cited in Dem97). As saw mills and the industries supplied by them use wood produced locally, the Committee assumes that both studies concern softwood exclusively or predominantly (IAR95), whereas Demers and colleagues apparently regard only the saw mill workers as exposed to softwood dust (Dem97).

The cohort of construction workers in the UK (15 007 persons) shows a small but significantly enhanced risk of death by cancer of any type (proportional mortality rate 1.21, 95% confidence interval 1.18-1.25), and of specific types: mesothelioma and cancer of the stomach, pancreas, bladder and lung, but not the nasal cavities (Don95). The last category was not subdivided any further. In the cohort more than 20 different job titles were represented. The authors do not provide any information as to the wood dust exposure in the various jobs held. Analysis by job titles showed a significantly enhanced risk of cancer in general for many of the jobs; the corresponding PMRs vary from 1.11 to 1.56. With regard to the duration of the exposure it was mentioned that the

median length of reckonable service was 4.9 years and that 15% had over 20 years of service.

The other cohort reported upon consists of 26 487 sawmill workers in British Columbia, Canada, of which 23 829 had been exposed to wood preserved with chlorophenate fungicides and 2658 to unpreserved wood (Her97). It was set up for investigation of the relation between chlorophenates and (various types of) cancer. The group exposed to preserved wood was compared with that exposed to unpreserved wood and with the general population. The two groups are characterised by 9.8 and 7.3 years of employment on average, respectively. Their mean follow-up was 24.5 and 15.5 years, respectively. The comparison with the general population, detecting in fact the effect of chlorophenates plus softwood, showed no statistically significant increases in risk of any kind of cancer. The majority of cancer types investigated showed no increase at all. Cancers of the nasopharynx and of the nose and nasal cavities, however, showed increases that are non-significant and do not correlate with exposure duration. The same holds true for soft tissue sarcoma and non-Hodgkin's lymphoma, the primary target of study.

With regard to observations on nasal histology and inflammation there are two investigations reviewed by IARC concerning groups that had exclusively been exposed to softwood. The first is the group that had been exposed to softwood only without additives for at least 15 years in the study already mentioned in the previous chapter, the findings of which, a non-significantly higher frequence of cuboid metaplasia, are subject to the same objections (Wolf *et al.*, 1994 in IAR95, see also Wol98b). The other is a group of 44 persons who had been exposed for 10 to 43 years and whose nasal biopsies showed a significantly higher incidence of dysplasia than biopsies taken from controls (Boysen *et al.*, 1986 in IAR95).

The most recent data on nasal histology and function have already been mentioned under hardwood, because they concern combined exposure to hardwood and softwood (Ahm95, Ahm96, Gra98, Pis95). In addition to the questionable relevance of the findings, as already discussed in 2.3, they pose the problem of exposure to a mix of wood species. The only finding not mentioned there is that of normal nasal function in individuals that had been exposed to softwood dust only (Wolf *et al.*, 1994 in IAR95, see also Wol98b).

3.3 Evaluation

The epidemiological data on softwood are harder to interpret than those on hardwood, because they are fewer and a large variety of cancers reported incidentally are associated with excess risks that are generally lower than those of the adenocarcinomas associated

with hardwood. The adenocarcinomas observed in the various studies on softwood probably are due to co-exposure to hardwood. The ones with exclusive, or almost certainly exclusive exposure to softwood do not show an enhanced risk of adenocarcinomas. However, some of them demonstrate enhanced risk of sinonasal tumours, without histological characterisation (Dem97). As the major question is whether softwood exposure can lead to sinonasal squamous-cell carcinoma, this lack of specificity complicates the matter considerably.

The overall evidence does not show a consistent association of softwood dust with other types of cancer — neither with squamous-cell carcinoma of the sinonasal cavities, nor with any other. As such the epidemiological studies do not provide consistent evidence that softwood dust possesses carcinogenic properties. On the other hand, at least high-exposed subgroups in some of the case-control studies suggest that it does and indeed point in the direction of squamous-cell carcinoma. Moreover, the cohort studies carried out lack the statistical power to resolve the matter. According to the Committee this holds true for all the cohorts investigated, the ones in the review by Demers and colleagues (that includes the saw mill workers, discussed separately in 3.2 (Her97)) and the construction workers (Don95). Thus, the data leave open the possibility that softwood can cause sinonasal squamous-cell carcinoma. In the opinion of the Committee the data have neither proven nor refuted association of softwood with squamous-cell cancer. Like DECOS the Committee regards softwood dust as a suspected human carcinogen (DEC98).

The nasal histology in humans that have been exposed to softwood dust is poorly documented. As far as it has been carried out, it shows an augmented incidence of changes upon long-term exposure of which the meaning is elusive. These histological changes merely indicate that softwood dust possesses cytotoxic potential.

Decreased nasal function was observed in groups that had been experiencing mixed exposure (see 2.2 and 2.3). The only study addressing nasal function in individuals with a history of exposure to softwood only, showed normal clearance.

Softwood dust has also been investigated less thoroughly in the laboratory. Verification of carcinogenic potential in animals has not been carried out. And as far as genotoxicity testing is concerned, the testing of preparations has been restricted to *in vitro* experiments. Softwood extracts and condensates have been investigated for genotoxicity *in vitro* as thoroughly as hardwood though. They appear to possess identical properties: the abilities to cause gene mutations, chromosomal aberrations and sister chromatid exchanges. So, like hardwood dust surrogates they are clearly genotoxic *in vitro*. Moreover, the similarity extends to the strength of the genotoxicity: both surrogates are weak genotoxins. But as far as other aspects of the genotoxicity profile are concerned, interaction with DNA and *in vivo* genotoxicity testing, data are lacking. Overall, the Committee feels that softwood dust extracts and condensates should be

regarded as genotoxic; an opinion differing from that of DECOS and based on several publications not considered by them, obtained by searching additional databases.

Chapter 4

Health hazard assessment

Hardwood dust is a human carcinogen with weak genotoxic properties and equivocal cytotoxic capacity *in vivo*. Softwood dust possesses similar genotoxic and cytotoxic power, but is possibly carcinogenic. The Committee reached these conclusions taking into account that hardwood co-exposure figures in the dataset on softwood and *vice versa*, and that the former is the stronger one.

Hardwood dust possesses the capacity to induce sinonasal adenocarcinoma in humans. This is the only consensus finding so far from the overall studies of a series of groups of individuals exposed occupationally to dust from hardwood, softwood or, as in most cases, both. An unresolved, but important issue is why only the European cohorts investigated show an excess risk.

The possible causal relationship between hardwood dust and other types of tumours, in the sinonasal cavities and elsewhere in the body, is subject to debate. With regard to a causal relationship between softwood dust and any cancer the situation is similarly unresolved. The outcomes of the meta-analyses suggest that the relative risk of nasopharyngeal tumours and squamous-cell tumours of the nose is elevated by exposure to hardwood and softwood dust, respectively, the uncertainty being partly due to the mixed exposure.

There are several explanations for the difference in the epidemiological findings on hardwood and softwood in addition to that of sample size; they are not mutually exclusive. First that the follow-up in the softwood studies is shorter on average — and shorter than the tumour latency period. This appears to be the case: only the hardwood-exposed groups contain subgroups that had been exposed for more than 30

years and sufficiently large to demonstrate a significant excess of adenocarcinoma (Dem95a).

An alternative explanation is that the cumulative exposure, the integral of concentration and duration of exposure, of softwood dust-exposed groups is lower than that of hardwood dust-exposed ones. This issue cannot be resolved, because most of the studies have very little information, or none at all, about dust concentrations and exposure duration. They allow inferences only from industry and job titles, occasionally supplemented with the number of years spent in a job; the study on British furniture workers presents a favourable exception.

A third explanation is that the carcinogenic potency of softwood dust is smaller than that of hardwood dust, as a consequence of, for instance, a difference in average particle size. Airway deposition is known to depend strongly on particle characteristics. The physical properties of hardwood and softwood differ and it is probable that this difference together with that in woodworking processes they undergo, leads to dissimilarity in particle size. Differences in chemical properties may also play a role (Bia94).

Finally, there is the matter of treated *versus* untreated wood. The relevance of this issue has clearly been demonstrated by Wolf and colleagues who analysed wood samples presumed to be untreated and found a variety of preservatives (Wol98b).

Unfortunately, proof or refutation is lacking for all of these theories. Therefore the Committee, like DECOS, prudently considers softwood to be a suspect carcinogen in humans. Why the animal experiment performed to detect carcinogenicity upon inhalation did not show evidence of carcinogenic properties is a question the Committee cannot answer.

Several lines of evidence need to be evaluated to answer the question of the methods appropriate to derive toxicology-based occupational exposure limits for each of the dusts. These are the indications that shed light on the role of, on the one hand, genotoxicity and, on the other hand, inflammation, ensuing cytotoxicity and regenerative cell proliferation (hyperplasia).

The wood dusts cannot be and consequently have not been tested directly for genotoxic properties. Workable surrogates are extracts and condensates. These types of preparation have been tested in various genotoxicity assays and have demonstrated that the genotoxicity of the two dusts is similar, with regard to its nature and its potency. Two aspects determine the strength of the genotoxic properties: the magnitude of the effect and the concentration at which it is observed. The magnitude of the effect in the various genotoxicity tests was small. Furthermore, the outcomes do not refer to neat concentrations, as in the case of pure chemicals, but to dilutions of the extract or condensate with unknown concentration and composition. Therefore the outcome is hard

to relate to the original material wood dust. Moreover, there are several explanations for the genotoxicity observed under the circumstances of the tests. It may reside in endogenous components or preservatives, that may be present even when assumed absent (Wol98b). Alternatively, genotoxic molecules may have been formed during preparation of the dust surrogates. At least in the case of isolation of condensates, that requires heating of the wood, this is plausible. The bulk of the original material, however, has escaped testing, because it does not dissolve or evaporate under the circumstances needed for preparation of the surrogates. But this untested fraction probably is the material that is likely to play an important role in the inflammation- and cytotoxicity-inducing properties of the dust. Thus, whether the genotoxicity of the surrogates bears any relevance to the carcinogenicity of inhaled wood dust in humans is enigmatic.

There are two more relevant lines of evidence regarding the contribution of the genotoxicity to tumour formation. The first is the genotoxicity in the peripheral blood of wood dust-exposed humans, the proof of which is scarce. Findings of this nature are difficult to interpret, for any chemical. Therefore they do not play a crucial role in the Committee's decision.

Furthermore, the specificity of the mutations found in the DNA of adenocarcinomas may provide a clue to the role of the genotoxicity in carcinogenesis. A difference in specificity between adenocarcinomas from spontaneous and wood dust-exposed individuals would suggest that the genotoxicity is central to the genesis of adenocarcinoma. This, however, has not been investigated properly. The publications on mutations in sinonasal adenocarcinomas concern small numbers of biopsies and the exposure history of most of the patients involved is not documented. Thus, the mutation specificity hypothesis has not been sufficiently verified to allow any conclusions.

The conclusion the Committee draws from the overall genotoxicity observations is that it is enigmatic whether the genotoxicity observed bears any relevance to the (proven or suspected) carcinogenicity of inhaled hardwood and softwood dust in humans.

The other relevant matter is that of the contribution of inflammation, cytotoxicity and regenerative tissue response to carcinogenesis. These phenomena have almost exclusively been detected in connection with mixed exposure. Therefore attribution to one of the dusts or both, is not possible. These local tissue reactions have not been investigated upon exposures shorter than semi-chronic, neither in humans, nor in animals. This means that an argument in favour of these being the primary effects responsible for carcinogenesis is lacking. If the cytotoxicity and regenerative hyperplasia would have been overt after short exposures of humans or animals, this would have been a strong argument to overrule the hypothesis that the genotoxicity test outcomes are indicative of the pathway the development of cancer follows. As they have been noted

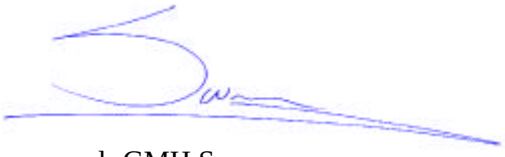
after chronic or semi-chronic exposure, in humans as well as in animals, they may have been the result of genotoxicity.

Which methods are suitable for deriving toxicology-based recommended exposure limits for hardwood and softwood dust? Should the two dusts be treated with the same method? To be able to answer these questions several characteristics need to be taken into account. The similarity of the genotoxicity evidence is in favour of one method for both. The data on local tissue responses are neither in favour of, nor against, a one-method approach, as it is undecided whether both dusts can induce them. Differences in chemical or physical properties, or in the presence of preservatives and moulds would lend plausibility to an approach using different methods. However, differences of these kinds are assumed to exist, not sufficiently demonstrated to support an approach with different methods. Thus, as far as investigated similarity predominates. The Committee therefore recommends to treat them identically when deriving toxicology-based recommended exposure limits.

The circumstances under which the genotoxicity has been found do not allow any conclusions as to its contribution to carcinogenesis. Additional findings, from for instance mutation specificity of tumours, are insufficient to resolve the matter. Furthermore, the doubt as to the contribution to carcinogenesis also applies to the inflammation- and cytotoxicity-inducing properties. How much these contribute to tumour formation is uncertain, as their presence has not been investigated after exposures of short duration, which would make a strong case for a threshold. Therefore it remains elusive whether carcinogenesis in the airways can be avoided by levels sufficiently low to prevent local cytotoxicity. The Committee cannot propose a method to derive figures, because the clues available are insufficient to distinguish among (a) a direct genotoxic carcinogen with a major role for its genotoxicity, (b) an indirect genotoxic carcinogen with a major, if not an essential role for inflammatory or regenerative hyperplastic changes, or (c) a non- genotoxic carcinogen with an essential role for regenerative hyperplasia following recurrent tissue damage, the first option leading to the proposal to apply the linear model, the second and third to the proposal to apply the threshold model. Previously the Minister of Social Affairs accepted the recommendation of linear extrapolation in similarly elusive situations. If linear extrapolation would be applied, the results would be 5.8 mg of inhalable wood dust per m^3 for a reference additional lifetime risk of nasal cancer — representing adenocarcinoma — of 1 in 250, and 0.06 mg per m^3 for that of 1 in 25 000, both for workplace exposure during forty years (see Appendix C).

According to the Committee, the assessment of the health hazards of hardwood and softwood dust would benefit from the following research: carcinogenicity testing of softwood dust, analysis of sinonasal histology and function in animals and humans upon sub-acute exposure to each type of dust — all with established preservative- and mould-free preparations — and identification of the responsible constituent(s). In addition, exposure measurements under various working conditions and longer follow-up in the softwood cohort studies would be helpful.

The Hague, 18 July 2000,
for the committee



dr PW van Vliet,
secretary

dr GMH Swaen,
chairman

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Annexes

Annex **A**

The request for advice

On 12 November 1998 the President of the Health Council of the Netherlands received the following letter from the State Secretary of Social Affairs and Employment (reference: ARBO/AMIL/9834631):

Your evaluation report 1998/13 WGD on the subject of wood dust was completed in September. In the report, your Dutch Expert Committee on Occupational Standards comes to the conclusion that the dust from hardwood is genotoxically carcinogenic.

In 1991, in its report RA8/91, the committee recommended a health-based exposure limit for all types of wood dust, based on a threshold approach. Based on this advisory opinion, a statutory exposure limit was established for wood dust, which came into effect on 1 January 1998.

My question is: how do the two advisory opinions relate to each other? In order to clarify this point, I would request that you produce an additional advisory report explaining what implications the genotoxicity of hardwood has for the health-based exposure limit that was recommended in 1991. Essentially, I would like to know whether the threshold approach that was adopted at that time is still valid, or whether it needs to be replaced with a risk-based approach. The latter option could result in different threshold values being applied for hardwood and softwood. I would very much like to hear your view on this point. I look forward to receiving your advisory report within two months.

Director, Working Conditions
(signed R Laterveer), on behalf of
the State Secretary of Social Affairs and Employment
JF Hoogervorst

Annex **B**

The committee

- GMH Swaen, *chairman*
  epidemiologist, Maastricht University, Maastricht
- PJ Boogaard (from Februari 1, 2000 on)
  toxicologist, Shell Int. Chemicals BV, Amsterdam
- HC Dreef - van der Meulen
  animal pathologist, NV Organon, Oss
- VJ Feron
  professor of toxicology, Utrecht University, Utrecht; TNO Nutrition and Food Research Institute, Zeist
- GR Mohn
  professor of cellular mutation genetics, Leiden University, Leiden
- GJ Mulder
  professor of toxicology, Leiden University, Leiden
- MJM Nivard
  genetic toxicologist, Leiden University, Leiden
- PC Noordam, *consultant*
  Ministry of Social Affairs and Employment, The Hague
- H te Riele
  molecular biologist, Netherlands Cancer Institute, Amsterdam
- H Roelfzema, *consultant*
  Ministry of Health, Welfare and Sport, The Hague

- D Roos (until February 1, 2000)
  professor of immunology, University of Amsterdam, Amsterdam; Central Laboratory for Bloodtransfusion, Amsterdam
- W Slob
  biologist, National Institute of Public Health and the Environment, Bilthoven
- ALM Verbeek
  professor of epidemiology, Catholic University of Nijmegen, Nijmegen
- EJJ van Zoelen
  professor of cell biology, Catholic University of Nijmegen, Nijmegen
- JA van Zorge, *consultant*
  Ministry of Housing, Spatial Planning and the Environment, The Hague
- PW van Vliet, *secretary*
  Health Council of the Netherlands, The Hague

The Committee consulted PJ Slootweg, professor of pathology, Utrecht University.

Secretarial assistance: M Javanmardi.
Lay-out: J van Kan.

Annex **C**

Linear extrapolation

A group of British furniture makers is the only cohort of which the relative risk *and* the exposure have been quantified (Ach84). Therefore this cohort's data are suited best for calculations. The calculations will be based on the risk of nasal cancer, because histological specifications were not reported and the background data from the Dutch population concern nasal cancer as a whole, *i.e.*, code 160 of the 'International Classification of Diseases'. Alternatively, the percentage of adenocarcinomas in the nasal cancers would have to be estimated, but that would introduce other uncertainty. The nasal tumours all occurred in the group with the longest exposure, dating back to the forties and fifties. The SMR of this subcohort was 23.3; its members had been exposed for forty years or longer.

The furniture makers had been exposed to hardwood dust exclusively, or almost exclusively, but as outlined in chapter 4 a distinction between hardwood and softwood does not have to be made for setting toxicology-based recommended exposure levels; the calculations are applicable to both types of dust. The actual exposure measurements were performed, gravimetrically, in the seventies and eighties (Jon86); the concentrations of (inhalable) wood dust appeared to be 7.8 and 4.2 mg per m^3 on average, respectively (Jon86, IAR95). The decrease probably reflects exposure-reducing measures taken as soon as the health hazards of wood dust inhalation became known. It is reasonable to assume an even higher exposure in earlier days. For the calculations this average concentration is assumed to have been 10 mg per m^3, slightly higher than the highest of the means measured. If, in reality, the average exposure would have been higher, the calculated reference concentrations would be underestimations. Levels higher by one or

more orders of magnitude are unlikely to have occurred, however; such concentrations are exceptional for aerosols. A tenfold higher concentration would create an environment that is exceptionally difficult to work in, for it would reduce the sight to 2-3m, increasing considerably the risk of accidents. Peak exposure to such a concentration, though, could have occurred, but still be compatible with 8-hour-average exposure to 10 mg/m^3.

Reference concentrations can be calculated with the following formula, representing the linear relationship of exposure and effect:

$$y = ax + 1$$

In this formula y is the SMR, *a* the slope and x the concentration. As y is 23.3 and x is 10 mg per m^3 the slope is 2.2.

In the Netherlands 31 per 100.000 (or 0.0775 per 250) men die of nasal cancer annually (CBS93). This is the reference figure appropriate for the (male) furniture workers. The upper and lower reference additional risk levels for occupational exposure situations in the Netherlands are 1 in 250 and 1 in 25 000 for 40 years of exposure. Thus, the reference SMRs for nasal cancer are 1.0775/ 0.0775 = 13.9 and 0.0875/0.0775 = 1.13. They correspond to wood dust concentrations of 5.8 and 0.06 mg per m^3, respectively.

Annex **D**

Comments on the public draft

A draft of the present report was released for public review earlier in 2000. The following organisations and persons have commented on that draft:

- Th van Amersfoort, Bouw- en Houtbond FNV, Woerden, the Netherlands
- O Axelson, University of Linköping, Sweden
- FA de Boer, Vereniging Van Nederlandse Houtondernemingen, Almere, the Netherlands
- AJM Ceelaert, Nederlandse Emballage- en Palletindustrie Vereniging EPV, Vereniging HAS en Vereniging van Nederlandse Borstelfabrikanten, Tilburg, the Netherlands
- P Demers, University of British Columbia, Vancouver, Canada
- H Savolainen, Institute of Occupational Health Sciences, Lausanne, Switzerland
- T Scheffers, DSM, Geleen, the Netherlands
- SF Vuijk, Centrale Bond van Meubelfabrikanten, Heemstede, the Netherlands