Bitumen (vapour and aerosol)

Health-based recommended occupational exposure limit

Gezondheidsraad **Voorzitter**
Health Council of the Netherlands

Aan de Staatssecretaris van Sociale Zaken en Werkgelegenheid

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Mijnheer de staatssecretaris,

Graag bied ik u hierbij het advies aan over de beroepsmatige blootstelling aan bitumen (damp en aerosol). Het maakt deel uit van een uitgebreide reeks, waarin gezondheidskundige advieswaarden worden afgeleid voor concentraties van stoffen op de werkplek. Dit advies over bitumen (damp en aerosol) is opgesteld door de Commissie WGD van de Gezondheidsraad en beoordeeld door de Beraadsgroep Gezondheid en Omgeving.

Ik breng u hierbij onder de aandacht dat bitumen (damp en aerosol) onvoldoende onderzocht is en dat meer onderzoeksgegevens nodig zijn voordat een definitieve conclusie over deze stof kan worden genomen. Op dit moment wordt de kankerverwekkendheid van bitumenrook geëvalueerd door het internationale onderzoekscentrum IARC. Afhankelijk van de voortgang van enkele lopende epidemiologische onderzoeken wordt deze evaluatie naar verwachting binnen twee of drie jaar afgerond. De raad verwacht dat deze activiteiten een waardevolle aanvulling zijn voor de risico-evaluatie van bitumen (damp en aerosol). De Gezondheidsraad stelt daarom voor zodra de nieuwe gegevens beschikbaar zijn, de stof opnieuw op het werkprogramma van SZW te plaatsen.

Ik heb dit advies vandaag ter kennisname toegezonden aan de minister van Volksgezondheid, Welzijn en Sport, de minister van Sociale Zaken en Werkgelegenheid en de staatssecretaris van Volkshuisvesting, Ruimtelijke Ordening en Milieubeheer.

Hoogachtend,

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Dutch Experst Committee on Occupational Standards
a committee of the Health Council of the Netherlands

to:

the State Secretary of Social Affairs and Employment

No. 2007/01OSH (R), The Hague, January 30, 2008

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Vraagstelling

Op verzoek van de minister van Sociale Zaken en Werkgelegenheid leidt de Commissie WGD van de Gezondheidsraad gezondheidskundige advieswaarden af voor stoffen in de lucht op de werkplek waaraan beroepsmatige blootstelling kan plaatsvinden. In het voorliggende rapport bespreekt de commissie de gevolgen van blootstelling aan bitumen (damp en aerosol). De conclusies van de commissie zijn gebaseerd op wetenschappelijke publicaties die vóór januari 2007 zijn verschenen.

Fysische en chemische eigenschappen

Bitumen is bij kamertemperatuur een donkerbruine tot zwarte vaste of stroperige substantie, die verkregen wordt door vacuümdistillatie van ruwe petroleumolie. Het is een complex mengsel van een groot aantal stoffen, waaronder niet-aromatische koolwaterstoffen, asfaltenen en maltenen, cyclische alkanen, aromatische koolwaterstoffen en heterocyclische verbindingen met stikstof, zuurstof en zwavel. De exacte samenstelling, en daarmee de fysische eigenschappen, hangt af van de oliebron waaruit de ruwe petroleumolie wordt gehaald en van het raffinageproces. Dit laatste is weer afgestemd op het gewenste gebruik.

Bitumen is duurzaam, onoplosbaar in water en heeft sterke hechteigenschappen met mineraalaggregaten. De belangrijkste toepassing is als bindmiddel in

asfalt voor weg- en dakbedekkingen. Ook wordt het gebruikt in sommige verfsoorten als waterdicht beschermmiddel. Asfalt en dus ook bitumen wordt bij de meeste toepassingen verhit (tot 160°C bij asfaltering van wegen; tot 230°C bij dakbedekkingen). Daardoor ontstaan dampen en aerosolen van bitumen (bitumenrook), die onder andere polycyclische aromatische koolwaterstoffen (PAK) en andere verbindingen kunnen bevatten.

Monitoring

Er worden verschillende methoden gebruikt om bitumendampen en -aerosolen in de lucht te meten. Het meest conventionele is meting van het totale gehalte aan deeltjes in aerosolen, zoals ‘total particulate matter’ (TPM) en ‘benzene-soluble matter’ (BSM). Steeds vaker wordt ook ‘total organic matter’ (TOM) gemeten in zowel dampen als aerosolen. Er bestaan geen methoden die dampen en aerosolen kunnen specificeren die alleen afkomstig zijn van bitumen.

Er zijn geen biomonitormethoden die specifiek zijn voor blootstelling aan bitumenrook.

Grenswaarden

Tot eind 2006 gold in Nederland een bestuurlijke grenswaarde voor asfaltrook (bitumineus) van 5 mg per m^3 (tijdgewogen gemiddelde (tgg) van 8 uur). In het Verenigd Koninkrijk gelden advieswaarden van 5 mg TPM per m^3 (tgg 8 uur) en van 10 mg TPM per m^3 (tgg 15 minuten). De Amerikaanse organisaties NIOSH en ACGIH hebben advieswaarden aanbevolen van respectievelijk 5 mg TPM per m^3 (ceiling, tgg 15 minuten) en 0,5 mg BSM per m^3 (tgg 8 uur). Zowel NIOSH als ACGIH hebben bitumenrook aangemerkt als verdacht kankerverwekkend voor de mens (respectievelijk notatie ‘Ca’ en klasse A4).

In Duitsland is, volgens het Duitse kankerverwekkende classificatiesysteem, bitumen (damp en aerosol) geclassificeerd in categorie 2. Ook geldt in Duitsland een huidnotatie.

Opname, verdeling en uitscheiding

De opname, verdeling en uitscheiding van stoffen die in bitumenrook aanwezig zijn, zijn afhankelijk van de eigenschappen van die stoffen en van de reacties tussen deze stoffen. Polycyclische aromatische koolwaterstoffen (PAK) en niet-aromatische koolwaterstoffen worden bij inademing door de longen opgenomen in het lichaam en via het bloed naar alle organen getransporteerd, met name naar

organen met een hoog vetgehalte. PAK worden door verschillende enzymen in het lichaam afgebroken, terwijl lange ketens van de niet-aromatische koolwaterstoffen nauwelijks worden afgebroken. Uitscheiding vindt plaats in de urine en feces.

Verschillende onderzoeken met mensen en dieren hebben aangetoond dat bepaalde PAK in condensaten van bitumenrook ook door de huid kunnen worden opgenomen.

Gezondheidseffecten bij mensen

Langdurig huidcontact met bitumenrook kan mogelijk huidirritatie en huidontsteking veroorzaken. Verhit bitumen kan tevens bij direct contact met de huid brandwonden veroorzaken.

Asfalteerders van wegen en dakdekkers hebben na acute of herhaalde blootstelling aan bitumenrook klachten aan de bovenste en onderste luchtwegen (neus- en keelirritatie, hoesten, droge keel, neusloop en -bloeding, kortademigheid, bronchitis en verminderde longfunctie) gerapporteerd. Deze klachten zijn mild en van voorbijgaande aard. De interpretatie van deze gegevens is echter lastig, omdat in de praktijk mensen die werken met bitumen vaak gelijktijdig zijn blootgesteld aan andere stoffen dan bitumen of omdat zij in het verleden ook blootgesteld zijn geweest aan koolteer. Deze stoffen kunnen ook luchtwegklachten veroorzaken, waardoor het moeilijk is de klachten toe te wijzen aan blootstelling van enkel bitumenrook. Een ander probleem is dat vaak alleen naar symptomen is gekeken en geen nader onderzoek is uitgevoerd naar de achterliggende oorzaken van deze symptomen.

In een paar epidemiologische onderzoeken is geprobeerd een relatie te leggen tussen de hoogte van de blootstelling en het optreden van effecten, maar de gegevens bleken onvoldoende om een duidelijke blootstellingsresponsrelatie te kunnen vaststellen. Ongeacht de mogelijke interpretatieproblemen blijkt uit een Amerikaans onderzoek dat asfalteerders van wegen vaker luchtwegklachten rapporteerden dan niet-blootgestelde wegonderhoudswerkers. Deze asfalteerders waren blootgesteld aan gemiddeld 1 mg TPM per m^3 en 0,4 mg BSM per m^3 (tgg van 8 uur, geometrisch gemiddelde) of minder.

Naast luchtwegklachten zijn ook misselijkheid, hoofdpijn, maagpijn en vermoeidheid beschreven, maar de hoeveelheid gegevens daarover zijn zo beperkt dat het moeilijk is die toe te schrijven aan blootstelling aan bitumenrook. Er is geen onderzoek gedaan naar de nadelige effecten van bitumenrook op het zenuwstelsel en op de vruchtbaarheid en nageslacht.

In verschillende epidemiologische onderzoeken is onderzocht of bitumenrook kankerverwekkend is. Dit heeft inconsistente uitkomsten opgeleverd, wat voor een deel verklaarbaar zou kunnen zijn doordat niet altijd goed rekening is gehouden met andere factoren dan bitumenblootstelling, maar die wel uitkomsten kunnen hebben beïnvloed. In een recent uitgevoerd internationaal cohortonderzoek, georganiseerd door het internationale kankeronderzoekscentrum IARC, bleek de sterfte aan longkanker bij asfaltwerkers verhoogd. De verhoging was klein, maar wel statistisch significant. Verder onderzoek binnen dit cohortonderzoek moet nog uitwijzen of mogelijke andere factoren dan bitumenblootstelling de resultaten hebben beïnvloed. Naar het oordeel van de commissie is het bewijs dat bitumenrook longkanker kan veroorzaken bij de mens zwak. Het is verder op dit moment onduidelijk of bitumenrook verantwoordelijk was voor de waargenomen kankergevallen of dat andere stoffen, bij gelijktijdige blootstelling, daarvoor verantwoordelijk waren. De zwakke associatie is voor de commissie echter voldoende reden tot zorg dat bitumenrook kankerverwekkend voor de mens kan zijn.

Gezondheidseffecten bij dieren

Een aanzienlijk deel van het onderzoek met proefdieren betrof blootstelling van de huid. Korte en langdurige blootstelling aan condensaten van bitumenrook leidde tot lokale huideffecten zoals huidirritatie. Bij langdurige blootstelling werden ook zweren en kleine abcessen gevonden.

Eenmalige blootstelling of blootstelling van enkele dagen aan bitumenrook leidde niet tot acute longontsteking bij ratten (15 tot 70 mg TPM per m^3). In een ander onderzoek veroorzaakte inademing van 16 mg/m^3 gedurende vijf opeenvolgende dagen echter wel neusirritatie. Ratten die gedurende langere tijd bitumenrook moesten inademen (5 dagen per week gedurende 14 weken), vertoonden irritatie in de neus en neusholten bij 100 mg/m^3 (totaal koolwaterstof in de vorm van aerosol en damp), maar niet bij 4 of 20 mg/m^3. Muizen en cavia's die gedurende lange tijd aan bitumenrook werden blootgesteld, kregen bronchitis, longontsteking, longemfyseem en bronchiëctasieën. Het is echter niet duidelijk bij welke blootstellingsconcentraties deze effecten optraden.

Tot nu toe is niet bewezen dat chronische inademing van bitumenrook bij dieren longtumoren kan veroorzaken. In enkele onderzoeken veroorzaakten condensaten van bitumenrook wel huidtumoren bij direct contact, maar in andere onderzoek kon dit niet worden bevestigd.

Bitumenproducten en condensaten van bitumenrook zijn ook onderzocht op genotoxiciteit en mutageniteit. De resultaten waren echter inconsistent en moei-

lijk te interpreteren vanwege de grote variatie in de opzet van de testen en in blootstellingscondities, zoals de temperaturen waarbij dampen werden gegenereerd. Omdat bij verhitting van bitumendampen en aerosolen vrijkomen waarin kankerverwekkende stoffen als PAK en PAC kunnen voorkomen, mag worden verwacht dat bitumenrook genotoxische eigenschappen bezit en dus schade kan toebrengen aan het DNA, ook al komen deze kankerverwekkende stoffen in lage concentraties in deze dampen en aerosolen voor.

Evaluatie

De evaluatie van de nadelige gezondheidseffecten van bitumenrook wordt bemoeilijkt door de onbekende invloed van verstorende factoren op de uitkomsten van het epidemiologisch onderzoek en andere onzekerheden. Zo is de samenstelling van bitumenrook niet altijd hetzelfde, omdat deze onder andere afhangt van het beoogde gebruik van bitumen. Verder is het op dit moment onzeker of de vaak gebruikte blootstellingsparameters voor bitumenrook, zoals TPM en BSM, de juiste parameters zijn om een relatie tussen blootstelling en de geobserveerde nadelige gezondheidseffecten te kunnen vaststellen. In de derde plaats vindt naast bitumenrookblootstelling tegelijkertijd vaak ook blootstelling aan andere stoffen plaats, zoals koolteer en dieseluitlaatgassen, die vergelijkbare effecten (longkanker, irritatie luchtwegen) kunnen veroorzaken als bitumenrook. In hoeverre gelijktijdige blootstelling aan deze stoffen de resultaten van de epidemiologische onderzoeken heeft beïnvloed, is op dit moment nog niet duidelijk. Ten vierde wordt de interpretatie van een aantal epidemiologische onderzoeken naar het ontstaan van longkanker door bitumenrook bemoeilijkt doordat er geen rekening is gehouden met rookgewoonten. Zoals bekend is roken sterk geassocieerd met het ontstaan van longkanker. Ten slotte zijn veel gegevens uit proefdieronderzoeken niet bruikbaar doordat de blootstellingsconcentratie niet werden gerapporteerd of omdat de bitumenrook in het laboratorium niet altijd representatief was voor de werksituatie.

De commissie is van mening dat er meer onderzoek nodig is om duidelijkheid te krijgen over de invloed van de verstorende factoren op de resultaten van de epidemiologische onderzoeken. Zij is ervan op de hoogte dat in dit kader op dit moment goed opgezet onderzoek bij mensen en dieren wordt uitgevoerd, en dat het internationale kankeronderzoekscentrum IARC hoge prioriteit geeft aan een evaluatie van het kankerrisico van bitumenrook. De commissie verwacht dat de gegevens van de lopende onderzoeken een waardevolle aanvulling zullen zijn voor de risico-evaluatie van bitumenrook.

Aanbeveling

Op grond van de beschikbare gegevens over de carcinogeniteit en genotoxiciteit, en het gegeven dat in dampen van verhit bitumen kankerverwekkende PAK en PAC kunnen voorkomen, is de commissie van mening dat er reden tot zorg is dat bitumen (damp en aerosol) kankerverwekkend is. De bewijslast daarvoor is echter zwak en meer onderzoek is nodig voordat een definitieve conclusie kan worden gegeven. De commissie beveelt daarom aan om bitumen (damp en aerosol) te classificeren als verdacht kankerverwekkend voor de mens en geeft verder aan dat bitumenrook onvoldoende is onderzocht. Dit komt overeen met een categorie 3 classificatie volgens de criteria van de Europese Unie. Binnen deze categorie komt de situatie voor bitumenrook het meest overeen met subcategorie b.

Het aanbevelen van een gezondheidskundige advieswaarde is op dit moment niet mogelijk vanwege de onzekerheden in interpretatie van de beschikbare gegevens. De commissie onthoudt zich daarom van een advies daarover.

Executive Summary

Scope

At 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 in the workplace. These recommendations are made by the Council's Dutch Expert Committee on Occupational Standards (DECOS). In this report, the committee discusses the consequences of occupational exposure to bitumen (vapour and aerosol). The committee's conclusions are based on scientific publications before January 2007.

Physical and chemical properties

Bitumen is a black or brown solid or viscous liquid that is obtained from non-destructive vacuum distillation of crude petroleum oil. It is a complex mixture of naphtenic, aliphatic and/or aromatic hydrocarbons and heterocyclic compounds containing sulphur, nitrogen and oxygen. The exact chemical composition, and thus the physical properties, depends on: the crude source; the refinery processes; and, application practices. The refinery process is geared to the desired application.

Bitumen is durable, insoluble in water, and forms strong cohesive mixtures with mineral aggregates. Most of the bitumen is used as a binder in asphalt for road paving and roofing. It is also used in paint to protect surfaces against water.

Bitumen is in most cases heated (112-162°C, paving bitumen; 166-229°C, roofing bitumen) during which bitumen vapours and aerosols are released that may contain carcinogenic polycyclic aromatic hydrocarbons (PAH) and compounds (PAC).

Environmental and biological monitoring

Various methods are used to monitor bitumen-derived vapours and aerosols. The more conventional methods are total particulate matter (TPM) or solvent soluble/organic particulate matter (*e.g.*, benzene-soluble matter (BSM)). Recently more often the amount of total organic matter (TOM) in both aerosol and vapour is determined. No methods exist that specifically characterise the vapours and aerosols released from hot bitumens.

Internal exposure to polycyclic hydrocarbons from bitumens is frequently monitored by determination of urinary 1-hydroxypyrene. However, this biomarker is not specific for bitumen exposure and may easily be confounded by other sources of polycyclic aromatic hydrocarbons in the working place.

Limit values

Up to the end of 2006, in the Netherlands, there was an administrative occupational exposure limit for asphalt smoke (bituminous) of 5 mg/m^3 (8-h TWA). In the United Kingdom, occupational exposure standards were established of 5 mg TPM/m^3 (8-h TWA) and 10 mg TPM/m^3 (15-min STEL). The National Institute for Occupational Safety and Health (NIOSH, the USA) has recommended an exposure limit of 5 mg TPM/m^3 (ceiling, 15-min TWA). The American Conference of Governmental Industrial Hygiene (ACGIH) recommended a Threshold Limit Value of 0.5 mg BSM/m^3 of the inhalable aerosol.

In Germany, bitumen (vapour and aerosol) is classified as a category 2 carcinogen. Both ACGIH and NIOSH indicated that there is a cause of concern that bitumen fumes may be carcinogenic (Class A4, ACGIH; ‘Ca’ notation, NIOSH).

Germany has assigned for bitumen (vapour and aerosol) a skin notation.

Toxicokinetics

The absorption, distribution and excretion of constituents present in bitumen vapours and aerosols depend on their properties and mutual interactions. Constituents such as polycyclic aromatic hydrocarbons and aliphatic hydrocarbons may be absorbed through the epithelia of the respiratory tract and are distributed

throughout all internal organs, particularly in those with high fat contents. PAH are metabolised, whereas long-chain aliphatic hydrocarbons are not expected to undergo extensive metabolism. PAH and aliphatic hydrocarbons are released from the body in the urine and faeces; the release of aliphatic hydrocarbons is slow.

Several human, animal and *in vitro* studies showed that certain PAH, which were present in condensates of bitumen fume, were taken up by the skin.

Effects

Effects in humans

Prolonged skin contact with bitumen fumes may cause skin irritation and dermatitis. Furthermore, direct skin contact with heated bitumen may cause skin burns.

The main health complaints after acute and repeated bitumen fume exposure under road pavers and roofers are respiratory tract effects, such as nose and throat irritation, coughing, dry throat, nasal discharge, nose bleeding, shortness of breath, and asthma. These effects appear to be of mild severity and transient in nature. However, the interpretation of these findings proved not to be easy. A main problem is namely that in practice workers, who use bitumen products, are at the same time also exposed to other substances, or have a past exposure to coal tar pitch fumes. These substances may also produce respiratory effects, making it difficult to ascribe effects to bitumen fume exposure only. Another problem is that in most epidemiological studies health assessment included symptomatology only. For the right interpretation of the observed effects additional information, for instance on physiology and immunology, is needed.

A few attempts have been made to associate the level of bitumen fume exposure to respiratory effects, but in none of these studies a clear exposure-response relationship could be established. However, it should be kept in mind that among road paving workers respiratory health symptoms were more frequently reported at concentrations (geometric mean) at or below 1.0 mg TPM/m^3 and 0.4 mg BSM/m^3 compared to unexposed maintenance workers (irrespective the causal agent and other possible interpretation errors).

Data on effects other than those on the respiratory tract are very limited and, therefore, should be interpreted with caution. These include symptoms of nausea, headaches, stomach pain and fatigue. Human data on neurological effects and effects on reproduction and development have not been reported.

The carcinogenicity of bitumen fume from various sources and processes has been investigated in several studies. However, the results on lung cancer risk in

epidemiological studies are inconsistent. This could partly be ascribed to (confounding) factors that were present in part of these studies, such as: co-exposure to other substances; differences in use of various bitumen sources; and, absence of information on past exposure, for instance to coal tar and asbestos. In a recently well-performed large and powerful multicenter cohort study, assembled by IARC, a small but statistically significant association was found between lung cancer mortality and average bitumen fume exposure among bitumen workers. Further research is now going on to control for possible confounders in this multicenter cohort study. Overall, the evidence that bitumen fume exposure may cause lung cancer is weak. It is still unclear whether bitumen fumes or other substances, that were also present in the workplace, were responsible for the observed effects. Also evidence for an association between bitumen fume exposure and cancer at other sites than the lung is weak and inconsistent. For the committee, the weak association is a cause for concern that bitumen (vapour and aerosol) may be carcinogenic to humans.

Effects in animals

Interpretation of animal data for assessing human risk is hampered by several factors. One is that investigators used laboratory-generated bitumen fumes or condensates that did not always represent the field-generated fumes. Another is that a variety of bitumen sources, exposure routes and end-points have been used. Furthermore, only a minority of the animal studies reported on the exact exposure concentration.

A substantial number of animal studies are available on dermal exposure with laboratory derived fume condensates or solutions of bitumen in solvent. These studies revealed local skin effects, such as dermatitis after short- and long-term exposure, and ulcers and small abscesses after long-term exposure.

Concerning acute and sub-acute exposure, inhalation of paving bitumen fumes of 15 or approximately 70 mg TPM/m^3 did not cause acute pulmonary inflammation in rats. In one study, nasal irritation was observed at approximately 16 mg/m^3 (bitumen fume, not specified) after five days of exposure.

Rats inhaling laboratory-generated fumes of bitumen condensates for 14 weeks (6 hours/day, 5 days/week) did show irritation in the nasal and paranasal cavities at 100 mg/m^3 (total hydrocarbon (aerosol and gas phase)), but no such signs of irritation were found in groups exposed to 4 or 20 mg/m^3. In mice and guinea pigs exposed to bitumen fume for a prolonged time symptoms of pneu-

monitis, bronchitis, emphysema and bronchiectasis were reported, but no actual bitumen fume concentrations in the air were determined.

So far no evidence was found in animals supporting the hypothesis that chronic inhalation of bitumen fume induces lung tumours. However, when condensates of bitumen fume were applied to the skin, papillomas and epidermal carcinomas were found in some studies, but not in all.

Both bitumen products and condensates of bitumen fume have been tested for mutagenicity and genotoxicity *in vivo* and *in vitro*. The results of these tests were inconsistent and difficult to interpret due to the many variations in study design and exposure conditions, like the temperature at which the fumes were generated.

However, because during heating of bitumen products fumes are released that may contain carcinogenic PAH and/or PAC, it is expected that the fumes have some level of genotoxic potential, although the amount of these carcinogens in those fumes may be low.

Evaluation

The evaluation of adverse health effects associated with occupational bitumen (vapour and aerosol) exposure is complicated by the presence of confounding factors and other limitations. First, bitumen fume and its condensate may vary from one source to the other and may also differ amongst various applications. Second, at the moment it is still uncertain how well available exposure parameters correlate with the observed adverse health effects, and thus what can be measured to monitor workplace exposure. Third, most workers using bitumen are also exposed to other agents (*e.g.*, coal tar (mainly in the past), silica dust, diesel exhaust). These may cause similar adverse health effects as bitumen fume and thus it is reasonable to believe that they can interfere with the adverse health effects observed upon bitumen fume exposure. To what extent these agents affect the outcome of the epidemiological studies on bitumen fume exposure is not clarified yet. Fourth, data from the literature suggest that exposure to bitumen fumes may lead to lung cancer. But lung cancer is also strongly associated with tobacco smoking. This confounding factor should be taken into account when interpreting epidemiological data, which was not always done.

Data from animal experiments are too limited to conclude on an exposure-response relationship and critical adverse health effects.

More research is needed to shed more light on the confounding and limiting factors so that more understanding in the adverse health effects of bitumen exposure can be obtained. In relation to this, the committee is aware of ongoing well-

designed research in humans and animals on these subjects, and that IARC has put bitumen on a list to be evaluated within a few years. The committee expects that the newly generated data will be a valuable contribution to the risk assessment of bitumen.

Recommendation

Taking all the available carcinogenic and genotoxic data into account, including the expectation that fumes of heated bitumen may contain carcinogenic PAH and or PAC, the committee is of the opinion that there is a cause for concern that bitumen (vapour and aerosol) is carcinogenic. However, the evidence for carcinogenicity is weak, and further experiments are necessary before a final conclusion can be drawn. Therefore, the committee recommends classifying bitumen (vapour and aerosol) as a suspected human carcinogen that has been insufficiently investigated. This recommendation corresponds to EU classification in category 3. The situation is furthermore comparable with subcategory b of this category.

At the moment the committee considers the reliability of the available data too limited to recommend a health-based occupational exposure limit. Therefore, it abstains from making such a recommendation.

Chapter 1

Scope

1.1 Background

At request of the Minister of Social Affairs and Employment (annex A), the Dutch Expert Committee on Occupational Standards (DECOS), a committee of the Health Council of the Netherlands, performs scientific evaluations on the toxicity of existing substances that are used in the workplace. The purpose of the evaluations is to recommend a health-based occupational exposure limit for concentrations in the air, provided the database allows derivation of such a value. In the Netherlands, these recommendations serve as basis in setting legal occupational exposure limits by the minister.

1.2 Committee and procedure

This document contains the assessment of DECOS, hereafter called the committee, of the health hazard of bitumen (vapour and aerosol). The members of DECOS are listed in annex B. MI Willems, RA Bausch-Goldbohm and ED Kroese of TNO Chemistry, Toxicological Risk Assessment, in the Netherlands prepared the first draft of this report.

In 2005, the president of the Health Council released a draft of the report for public review. The individuals and organisations that commented on this draft

are listed in annex C. The committee has taken these comments into account in deciding on the final version of the report.

1.3 Data

The recommendation of the committee on the health-based occupational exposure limit of bitumen (vapour and aerosol) is based on scientific data, which are publicly available.

Numerous studies have been published on the monitoring techniques, exposure, and adverse health effects of bitumen fumes. Also other international authorities and reviewers published evaluations and reviews. It was beyond the scope of this document to evaluate the complete database. Therefore, the committee restricted its search to the more recently published studies and mainly based this document on the hazard review document by NIOSH (2000):

- National Institute for Occupational Safety and Health (NIOSH). Hazard Review: Health effects of occupational exposure to asphalt. December 2000, Centers for Disease Control and Prevention[1].

In addition, the committee consulted other evaluations and reviews, such as:

- Deutsche Forschungsgemeinschaft (DFG). Bitumen (vapour and aerosol). In Occupational toxicants: Critical data evaluation for MAK values and classification of carcinogens, Volume 17; H Greim, ed., Wiley-VCH Verlag GmbH, Weinheim, Germany, 2002[2];
- International Programme on Chemical Safety (WHO, IPCS). Concise international chemical assessment document 59: Asphalt (bitumen). World Health Organization, Geneva, Switzerland, 2004[3].

Other literature has been retrieved from the online databases Medline, Toxline, and Chemical Abstracts. The main search topics were toxicity, carcinogenicity, genotoxicity, and metabolism in animals and man. The last updated online search was in January 2007.

A list of abbreviations and symbols used in this document is given in annex Q.

Chapter 2

Identity, properties and monitoring

2.1 Identity

Bitumen is defined as a product obtained during processing of certain types of petroleum. Asphalt refers to a mixture of bitumen (as a binder) and mineral aggregates. In North American usage, the term asphalt describes bitumen only. To prevent confusion of the terminologies, a glossary of terms is given in annex D.

Bitumen may be divided in three different types to meet the technical requirements of different applications (Concawe 1992).[4] These are penetration grades, hard bitumens, and oxidized bitumens (air blown) (see also IARC Monograph from 1985).[5] As a result, the European Inventory of Existing Commercial Substances (EINECS) listed 9 entries to cover bitumen (see annex E for more details). Below is given some information of the most basic form of bitumen:

CAS number	8052-42-4
EINECS number	232-490-9
RTECS number	C199000
Substance name	bitumen
Synonyms	asphalt (the USA); asphaltum; asphalt cement; asphalt cutbacks; asphalt emulsion;; high or low penetration asphalt; petroleum asphalt; petroleum bitumen

2.2 Physical properties and chemical composition

The basic form of bitumen (CAS no. 8052-42-4) is a black or brown solid or viscous liquid. It is obtained as residuals from non-destructive atmospheric or vacuum distillation of crude petroleum oil. Bitumens are complex mixtures and contain predominantly naphthenic, aliphatic and/or aromatic hydrocarbons and heterocyclic compounds containing sulphur, nitrogen, and oxygen. Depending on the specifications for application, they may be straight-run, air-blown, thermally converted, solvent precipitated, or blended. As a result, no two bitumens are chemically identical, the exact chemical composition of bitumen being dependent on: the chemical complexity of the original crude petroleum; the refinery processes involved in manufacturing bitumen; and, application practices.[1,6]

Although the exact chemical composition of bitumens is quite variable, attempts have been made to analyse the presence of polycyclic aromatic hydrocarbons (PAH) and other polycyclic aromatic compounds (PAC) in the fumes[1]. Both the presence of PAH and PAC (including those containing oxygen atoms (O-PAC) and sulphur atoms (S-PAC) in their aromatic rings) are of interest because some of them may cause mutations and cancer.[1,3,7] In general, PAH and PAC are found in fumes of bitumen from various sources, although the amounts varied and are considered low compared to the concentrations found in for instance coal tar pitch fumes.[4,8] Not only the concentrations differed, but also the PAH and PAC profiles, which is explained by source differences and by differences in generation conditions (*i.e.*, heating temperature and concentrations of the raw material).[8,9]

A summary of the physical properties of the basic form of bitumen (CAS no. 8052-42-4) is given below (ECB 2000)[10]:

Melting point	:	30-130 °C (softening point, 57 °C)
Boiling point	:	> 400 °C at 1,013 hPa
Flash point	:	> 230 °C
Density	:	1,000-1,050 kg/m^3 at 15 °C
Vapour pressure	:	Below 0.1 kPa at 20°C. Bitumen comprises components with molecular weights in the range of 500 to 15,000 or more, and so has negligible volatility at ambient temperatures.
Partition coefficient	:	> 6 (log P_{ow})
Water solubility	:	Negligible.
Solubility in organic solvents	:	Partially soluble in aliphatic solvents; soluble in carbon disulfide

Most bitumen is processed hot. During these heating processes vapours are released. When these vapours cool down and condense (aerosols), they are enriched in the more volatile components, also present in bitumen.[3] Because bitumen vapours do not condense all at once workers are at the same time exposed to bitumen vapours and aerosols. In this report and for practical reasons bitumen vapours and aerosols are sometimes subsumed under the term ‘bitumen fumes’. The physical state of bitumen fume cooled down at room temperature varies from light straw- or amber-coloured low viscosity liquid to black or dark-brown solid or viscous liquid.[1]

Of special interest are the laboratory-generated or storage-tank bitumen fumes. In particular when a large quantity of bitumen fume is needed, collecting laboratory-generated or storage-tank fumes is more practical than collecting fumes at worksites. However, overall it is difficult to produce bitumen fumes in the laboratory that have a similar chemical composition as the field-generated ones. This is not only due to the variation in composition of the field-generated fumes, as described previously, but also because the composition of laboratory-generated fumes is easily affected by generation temperature, heating time, rate of stirring, changes in pressure, and storage conditions.[1,3]

2.3 EU classification and labeling

The EU did not classify or label bitumen (vapour and aerosol).

2.4 Environmental monitoring

2.4.1 Validated analytical methods

An extensive evaluation on analytical sampling and analysis methods of bitumen fumes can be found in the hazard review of NIOSH.[1] Various methods have been used for characterizing bitumen vapour and fume exposures. However, most of the methods are non-specific, and none can be used to characterize total bitumen fumes exposure.

Total (and respirable) particulates (TPM). Some authorities in the EU and the USA (ACGIH) now use the terms 'inhalable' or 'total inhalable' instead of 'total'. TPM contains both organic and inorganic solid or liquid particles. NIOSH recommends the gravimetric Methods 0500 or 0600. Both methods use a membrane filter as the sampling medium (glass fibre or PTFE filter). Therefore, these methods are not useful for collecting vapours. Furthermore, they are non-specific, because whatever is deposited on the membranes, it is included in the determination. Moreover, when bitumen fumes are sampled, air stripping can cause volatile fume components to be lost from the sampling medium.

Solvent-soluble or organic particulate matter. This matter is obtained by organic solvent extraction of TPM. NIOSH recommends using Method 5042 to determine total particulates and the benzene-soluble fraction of total particulates (BSM) employing a single sampler. Also this method is non-specific, because most organic compounds are soluble in benzene. Furthermore, air stripping can cause loss of volatile bitumen fume components, and since a membrane filter is used, it is not useful for collecting vapours. Also Concawe published a practical guidance for monitoring benzene-soluble inhalable particulate matter (Concawe report no. 7/02, 2002).[11] An equivalent method results in a cyclohexane-soluble fraction of total particulates. Also other solvents may be used, such as carbon disulfide and carbon tetrachloride (Burstyn *et al*. 2000).[12] However, the results obtained using different solvents may not be identical, because they are not equivalent.

Total organic matter (TOM). Samples of TOM are obtained by extraction of organic matter from XAD-2 tubes plus membrane filters (polytetrafluorethylene, PTFE), which are put in series. XAD-2 captures the more volatile components in

the bitumen-derived aerosol and vapour. Since recently, the method is more often used to quantify the amount of total organic material in both aerosol and vapour (Binet *et al*. 2002[13]; Burstyn *et al*. 2000[12]; Ekström *et al*. 2001[14]; Kriech *et al*. 2002[15]).

Selected solvent methods. Selected volatile organic solvents that may be present in bitumen fumes or vapour can be determined by various NIOSH methods. These include: Method 1550 for naphthas; Method 1300 and 1301 for ketones.

Polycyclic aromatic hydrocarbons (PAH). A selection of (non-alkylated) PAH (*i.e*., benzo[a]pyrene) can be determined by NIOSH Method 5506, 5515 and 1501. Method 5506 involves liquid chromatography with ultraviolet and fluorescence detection, whereas Method 5515 uses gas chromatography with a flame ionization detector. These methods are mainly used for samples that contain low amounts of alkylated PAH and PAC. However, bitumen fumes are composed of many alkylated isomers of PAH, along with PAC, whereas it contains low amounts of non-alkylated PAH. The problem is that these alkylated PAH and PAC are difficult to separate from non-alkylated PAH. For this reason, quantification of PAH in bitumen fumes is unreliable when these or comparable methods are used. Method 1501 is used to determine naphtalene.

2.4.2 *Exposure assessment and choice of sampling and analytical method*

For risk assessment, historical occupational exposure and other exposure data from human and animal studies need to be compared. This is complicated by the complex and variable composition of bitumen and by the different sampling and analytical methods that have been used in the past. The more conventional methods to estimate worker's exposure are total particulate matter (TPM) and benzene soluble matter (BSM). Consequently, so far most occupational exposure limits for bitumen fumes are expressed in TPM or BSM. In recent years more and more often bitumen fume exposure (aerosol and vapour) is assessed by determining total organic matter (TOM), which is the sum of the aerosolised particles and the vapours. International round robin testing revealed significant variations between laboratories performing these tests (Ekström *et al.* 2001).[14]

In some cases also individual components of bitumen fumes are determined, such as individual unsubstituted PAH (*i.e*., acenaphthalene, anthracene, naphthalene, benzo[a]pyrene), total PAC (O-PAC, N-PAC, S-PAC), or sulphur-containing compounds.[1]

A point of concern is that it is uncertain how well these exposure parameters correlate with the observed adverse health effects, and thus which is the best met-

ric for monitoring workplace exposure to fumes and vapour of bitumen. Future research is needed to give a more reliable answer on this question.

2.5 Biological monitoring

Various investigators have sampled readily accessible body fluids for biomarkers of bitumen fume exposure.[1,3] However, biomarkers specific for bitumen fume exposure have not been identified so far. Yet various biomarkers are used to estimate the internal exposure to bitumen fumes. These comprise: urinary excretion of 1-hydropyrene and other hydroxylated PAH, thioether or glucaric acid metabolites; detection of DNA and protein damage, such as DNA strand breaks in lymphocytes, DNA and protein adducts; and, detection of oxidative damage in peripheral blood cells (see also section 4.3 in this document).

Chapter 3

Sources

3.1 Natural sources

Natural bitumen may be formed geologically from petroleum.[2,4]

3.2 Man-made sources

3.2.1 Production[1]

Bitumen is a residuum produced by the nondestructive distillation of crude petroleum at atmospheric and under reduced pressures in the presence or absence of steam. It differs from coal tar in that tar is produced by the destructive distillation of coal. Depending on its use, bitumen undergoes various refining processes to achieve the desired performance specifications. There are three major types of bitumen: penetration grade bitumens, hard bitumens, and oxidized (air-blown) bitumens. These types of bitumen are manufactured to meet performance specifications that are based on the physical properties of the bitumen product and not on chemical properties. Processing of bitumen for specific uses includes emulsifying (bitumen emulsion), or adding light hydrocarbons (cutback bitumen), polymers (polymer modified bitumen), or other materials.

3.2.2 Use[1]

Bitumen is used as a binder in asphalt. Its value is high, because of its adhesive properties, durability, flexibility, water resistance and its ability to form strong cohesive mixtures with mineral aggregates.

Most of the bitumen is used for paving and roofing. For these operations penetration grade and oxidized bitumens are used, while for painting and waterproofing hard bitumens are used. The use of bitumen in the workplace in Europe varies from country to country, but overall about 80% is used for road paving and maintenance (about 85% are penetration grades, 10% are bitumen emulsions, and 5% are cutback bitumens), and about 10% in roofing (about 50% are polymer modified bitumens, and the other 50% oxidized bitumens).[4] The remaining use concerns various other activities, such as painting for waterproofing operations.

Most bitumen products need to be heated before use. In general roofing bitumens are applied at higher temperatures than paving bitumens.[1,3] The recommended application temperatures are: 112-162 °C for road paving (bitumen cements, cutback bitumens); and, 166-229 °C for roofing (in the USA, oxidized bitumen (type I to IV)).

Some of the products do not require heating during installation, such as bitumen shingles, roll goods, underlayment felts, roof coatings, and mastics.

Chapter 4

Exposure

4.1 General population

No data available.

4.2 Working population

It is estimated that about 100,000 to 200,000 workers in Western Europe are exposed to bitumen fume (Boffetta *et al*. 2003).[16] In the USA, approximately 300,000 workers are employed in hot-mix bitumen facilities and paving sites; 50,000 workers in roofing operations; and 1,500-2,000 in roofing manufacturing plants.[1]

NIOSH[1] and the DFG[2] have evaluated worker exposure levels of bitumen fume in detail. A summary of these evaluations is given below, supplemented with recent publications. In addition, this section is subdivided into three subsections (road paving and maintenance; roofing operations; and, other applications), because the composition of bitumen fume can differ by use (see section 2.2). To be complete, in a separate subsection some data on exposure to individual constituents of bitumen fume is given.

4.2.1 Road paving and maintenance

Between 1994 and 1997 seven surveys were performed in a large NIOSH/FHWA (Federal Highway Administration) evaluation among bitumen paving workers.[1] One of the goals was to characterize bitumen fume exposure. In general, most personal-breathing zone air concentrations for both TPM and BSM were on average below 0.5 mg/m^3 (8-h TWA). Furthermore, NIOSH reported on exposure levels during paving operations in a tunnel in Boston. Personal exposure to TPM and BSM ranged from 1.09 to 2.17 mg/m^3 and 0.30 to 1.26 mg/m^3, respectively (full-shift; Sylvian and Miller 1996, source NIOSH 2000).[1] In a cross-sectional exposure assessment, the geometric mean of TPM was 0.37 mg/m^3 (maximum 0.85 mg/m^3) and of BSM 0.24 mg/m^3 (maximum 4.4 mg/m^3) during paving operations (37 full-shift personal-breathing zone samples; Hicks 1995.[17]

In Germany, maximum concentrations of bitumen (vapour and aerosol) were measured during road construction of: 2.9 mg/m^3 (unspecified) for drivers and road rollers; 10.1 mg/m^3 for asphalting foremen; and, 12.2 mg/m^3 for drivers of finishing machines (Bau-Berufsgenossenschaft 2001, source DFG 2002).[2]

For a multi-center international cohort study (assembled by IARC), a database of exposure measurements was created, called the Asphalt Worker Exposure (AWE) database (Boffetta *et al*. 2001[18]; Burstyn *et al*. 2000 and 2003[19,20]). The cohort-study consisted of seven surveys (see section 6.1.2 for more details on these surveys). The AWE-database was developed to standardize the compilation of exposure data from seven surveys that were included in the cohort. The earliest samples collected for this database were obtained in the 1960s, but most samples were collected in the late 1970s and between 1985 and 1997. Bitumen fume exposure was expressed as occupational exposure to solid-phase total organic matter of bitumen origin. Concerning road paving and construction work, a specific Road Construction Workers' Exposure Matrix (ROCEM) was created. This exposure matrix is developed on the basis of company questionnaires, analysis of the AWE database, and expert evaluations.

A semi-quantitative estimate of exposure to bitumen fume during paving was 0.15 mg/m^3 (geometric mean; 557 samples; geometric standard deviation, 8.94; 95% geometric confidence interval 0.13-1.18).[20] For bitumen mixing it was 0.12 mg/m^3 (geometric mean; 64 samples; geometric confidence interval 0.07-0.20). Time trend analysis showed that exposure to bitumen fume steadily decreased from the 1970s up to now; in the Netherlands on average from approximately 1.5 mg/m^3 to less than 0.5 mg/m^3.

Using statistical modeling and the data of the surveys, also the correlation patterns between various exposure measures (*e.g.*, bitumen fume, bitumen vapour, inhalable dust, benzo[a]pyrene, PAH) were examined.[21] There was a strong correlation between bitumen fume and inhalable dust levels, indicating that inhalable dust mainly contained organic particulate matter from bitumen fume. This meant that inhalable dust data were representative for bitumen fume exposure. Among the seven surveys, no such consistent correlation was found between bitumen fume and bitumen vapour levels. Also, no or a weak correlation was found between benzo[a]pyrene or total PAH and bitumen fume or vapour. This means that other factors than bitumen fume or vapour have an important bearing on benzo[a]pyrene and total PAH levels.

4.2.2 *Roofing operations*

In a cross-sectional exposure study, Hicks (1995)[17] collected personal-breathing zone air samples from 34 roofing manufacturers and 38 roofing contractors. The geometric means for TPM were 1.4 (max. 12) mg/m^3, and 0.55 (max. 2.5) mg/m^3, respectively. Levels of BSM were 0.27 (max. 3.7) mg/m^3 and 0.25 (max. 2.4) mg/m^3, respectively.

A cross-sectional evaluation performed by Gamble *et al*. (1999)[22] revealed geometric means of TPM of 0.60 (max. 6.2) mg/m^3, and of BSM of 0.08 (max. 1.3) mg/m^3 (77 personal exposure samples from roofing manufacturing). For roofing application, the geometric means were 0.34 (max. 2.7) mg/m^3 for TPM, and 0.12 (max. 1.2) mg/m^3 for BSM (60 samples).

The German Bau-Berufsgenossenschaft (2001, source DFG 2002)[2] reported on maximum bitumen fume (vapour and aerosol) concentrations of 8.8 mg/m^3 (unspecified) for heat welding and bitumen sheeting, and of 27.7 mg/m^3 for hot casting of bitumen.

Kriech *et al*. (2004)[15] conducted a field-study on 42 bitumen-roofing workers working at seven different sites across the United States. Personal monitoring systems were attached to the most highly exposed workers, with an average sampling time of 5.1 hours (break periods were excluded). A total of 26 samples were analysed. The average concentration of TPM was 1.67 mg/m^3 (SD 2.08), with a geometric mean of 1.15 mg/m^3 (GSD 2.17), and a median of 1.01 mg/m^3. The average concentration of BSM was 0.98 mg/m^3 (SD 2.11), with a geometric mean of 0.36 mg/m^3 (GSD 3.73, n = 26). The authors also determined TOM: 2.31 mg/m^3 (average; SD 2.61), and 1.60 mg/m^3 (GM; GSD 2.22).

4.2.3 *Other applications*

A few exposure data were collected at hot-mix plants, refineries and terminals or other facilities. For instance, at hot-mix plants, Hicks (1995)[17] reported geometric mean concentrations of TPM and BSM of 0.78 (max. 15) mg/m^3 and 0.15 (max. 1.7) mg/m^3, respectively (a total of 33 samples). In addition in other hot-mix manufacturing plants, Gamble et al. (1999)[22] found geometric mean concentrations of 0.45 (max. 1.3) mg TPM/m^3, and 0.06 (max. 0.14) mg BSM/m^3 (20 samples).

Furthermore, Hicks (1995)[17] measured geometric means of 0.18 (max. 14) mg/m^3 and 0.16 (max. 13) mg/m^3, respectively, at refineries and terminals (44 samples). The German Bau-Berufsgenossenschaft (2001, source DFG 2002)[2] reported of maximum concentrations of bitumen (vapour and aerosol) of 4.3 mg/m^3 (unspecified) for production of bitumen sheeting, and 19.3 mg/m^3 for foam glass installation.

4.2.4 *Individual constituents of bitumen fume*

Some investigators analysed individual constituents of bitumen fumes, such as polycyclic aromatic hydrocarbons and derivates, and several (semi-)volatile organic compounds (VOC). A brief summary of the results is given below.

Polycyclic aromatic compounds

Analysis of polycyclic aromatic compounds, in particular polycyclic aromatic hydrocarbons (PAH), are of interest because the potential genotoxicity and carcinogenicity of bitumen and its fumes is partly due to the presence of these compounds, even though the content of PAH and PAC in bitumen is low compared to their concentration in coal tar (Väänänen *et al*. 2003).[23] For this reason, in many countries the use of coal tar in road construction and roofing is limited. Concerning PAH, it is known that some four- to six-ring PAH are carcinogenic. In relation to this, the higher the temperature of the bitumen, the higher the proportion of these carcinogenic PAH in bitumen fumes (Concawe 1992).[4] In addition, the vapour phase of heated bitumen consists mainly of low molecular weight (Mw) PAH (below Mw 228), whereas the particulate phase constitutes the higher molecular weight PAH.[24]

In general, to assess inhalation exposure to a complex mixture of PAH, the concentrations of 10 to 20 individual PAH are measured. Measuring individual

PAH and PAC is not easy, because some of them cannot be easily separated or quantified. However, in the evaluations of NIOSH[1] and DFG[2] exposure data on a series of individual compounds can be found. Below is given only a brief summary, with a particular interest in total PAC or PAH.

In the large NIOSH/FHWA survey[1] among bitumen paving workers total PAC levels ranged from 0.3 to 22 g/m^3 (geometric mean, PAC_{370}), and from 0.05 to 2.9 μg/m^3 (geometric mean, PAC_{400}). PAC_{370} and PAC_{400} refer to the emission wavelength (in nm) at which the concentration was spectrofluorometrically measured. At 370 nm in particular two- and three-ring PAC are measured, whereas at 400 nm mainly four-ring and larger compounds are measured.

Knecht (2000, source DFG 2002)[2] reported on PAH in bitumen fumes during production and transport of rolled bitumen (B65) in a German bitumen mixing plant. The results on the 19 individual PAH measured can be found in the evaluation of the DFG. Concerning total PAH (sum of the 19 individual compounds), concentrations of total PAH were presented as follows:

- mixed platform (165°C): in aerosol 4.50; in vapour 79.10; total 83.60 (μg/m^3)
- transport (165°C): in aerosol 1.50; in vapour 4.10; total 5.60 (μg/m^3)
- mixer platform outlet (170°C): in aerosol 1.01; in vapour 80.45; total 81.46 (μg/m^3)
- transport (170°C): in aerosol -; in vapour 11.30; total 11.30 (μg/m^3).

During stone mastic bitumen paving and remixing in 1999 and 2000, Finnish bitumen workers from nine paving sites were on average exposed to 5.7 μg/m^3 total PAH (geometric mean; sum of 15 PAH; range 0.87-46 μg/m^3)[23]. Exposure to 2-3 ring PAH was 5.4 (range 0.82-43) μg/m^3, and of 4-6 ring PAH 0.22 (range 0.05-2.5) μg/m^3. Furthermore, the vapour phase compounds accounted for more than 90% of the measured PAH during work. Samples were taken in the breathing zone.

Among highway construction workers, working in the Greater Boston area, air concentrations of PAC, pyrene and benzo[a]pyrene were measured (McClean *et al*. 2004).[25] Exposure was highest among pavers. They (n=59) were on average exposed to: 4.1 μg/m^3 PAC (geometric mean; GSD 3.1 μg/m^3; range 0.3-40 μg/m^3); and, 0.18 μg/m^3 pyrene (GSD 3.5 μg/m^3; range 0.01-1.7 μg/m^3). Concentrations of benzo[a]pyrene were below detection limit (0.01 μg/m^3).

Volatile organic compounds

Across the seven paving sites in the NIOSH/FHWA study[1], area concentrations of VOC ranged from 0.5 to 30 mg/m^3. Gamble *et al*. (1999)[22] reported that geometric mean concentrations of total VOC were in increasing order: 0.3 mg/m^3, roofing application; 0.7 mg/m^3, roofing manufacturing; 1.1 mg/m^3, hot-mix manufacturing; and, 1.6 mg/m^3, bitumen distribution.

4.2.5 Dermal exposure

There is a lack of information regarding skin exposure to bitumen fume (condensates). However, in some studies dermal exposure to bitumen fume (condensates) has been examined in more detail by using pre- and postshift skin wipe samples and monitoring the presence of PAH. Yet, though dermal exposure due to bitumen fume exposure is demonstrated, the results are of limited value, because of the presence of potential bias, such as co-exposure to coal tar pitch in roofers (Wolff et al. 1989)[26], and limitations in analysis techniques (Hicks 1995; various occupations).[17] Others could not show the presence of any PAH during paving operations (Zey 1992, source NIOSH 2000).[1]

4.2.6 Summary on exposure

Despite the many potential problems encountered by measuring bitumen fume exposure in the air, analysis of the data indicated the highest personal exposure (TPM, BSM) during flooring and waterproofing activities, followed by roofing products manufacturing, bitumen refining, roofing application, activities in hot-mix bitumen plants and road paving.[1]

4.3 Biomarkers

Urinary 1-hydroxypyrene, a metabolite of pyrene, is often used as biological marker for exposure to polycyclic aromatic hydrocarbons. Since these compounds (including pyrene) may be present in bitumen fumes, several investigators reported on urinary 1-hydroxypyrene excretion. For instance, in a Swedish study by Levin *et al*. (1995,1999)[27,28] road pavers had significantly higher urinary 1-hydroxypyrene levels than unexposed controls, although the exposure to PAH and the levels of 1-hydroxypyrene were low compared to workers who are exposed to coal tar products, which contain high concentrations of PAH. Similar

results were reported by Hatjian *et al*. (1995, after a re-classification based on external exposure data on pavers and roofers)[29], Järvholm *et al*. (1999, road pavers)[30], Burgaz *et al*. (1998, road pavers)[31] and Toraasen *et al*. (2001, road pavers).[32]

Another way to measure internal exposure to electrophilic compounds, such as can be generated from PAH, is measuring the levels of urinary thioethers. Pasquini *et al*. (1989)[184] found that exposed smoking road pavers, who used bitumens, had statistically significantly increased levels of urinary thioethers compared to unexposed non-smokers, but the levels did not differ between these unexposed controls and exposed non-smoking workers. Overall, the findings on urinary thioether excretion are contradictory. For instance, Burgaz *et al*. (1988)[34] and Hatjian *et al*. (1995)[29] also did not find increased levels in bitumen fume exposed workers when compared to unexposed workers. However, Lafuente and Mallol (1987)[35] and Burgaz *et al*. (1992; in another study)[36] did find significantly higher levels in exposed workers. Both Burgaz *et al*.[34,36] and Hatjian *et al*.[29] observed that smoking had a higher contribution to thioether excretion than bitumen fume exposure.

Overall, 1-hydroxypyrene and thioethers as biomarkers may be useful when workers are exposed to high concentrations of PAH. However, in general PAH concentrations in bitumen fumes are low compared to coal tar fumes, which increases the chance that internal levels are influenced by external factors, such as ambient air pollution, tobacco smoking, consumption of fried food, and individual variations in metabolism. This limits the use of these biomarkers in assessing internal exposure to bitumen fumes. A detailed description of the individual studies on these biomarkers and bitumen fume exposure can be found in the evaluations of NIOSH[1], DFG[2] and IPCS[3]. NIOSH concluded in its evaluation that the use of urinary-1-hydroxypyrene as a biomarker for bitumen fume is limited, and is only useful to assess relatively high exposure to bitumen or asphalt, or to demonstrate reduction of exposure by using preventive measures. The committee subscribes this viewpoint.

Chapter 5

Kinetics

5.1 Pharmacokinetics

As IPCS[3] stated ‘mixtures do not lend themselves to kinetic analyses. Because bitumen is a complex mixture, its pharmaco-kinetic pattern will vary depending upon the properties and interactions of the individual constituents’. The committee agrees with this statement.

However, the kinetics of some of the individual components has been studied in considerable detail. These include PAH. PAH are, dependent on size and viscosity of the matrix, absorbed through the epithelia of the respiratory tract and the skin, which are the major routes of uptake from occupational exposure. They are also metabolised. Most of these metabolites are inactive and cause no harm, but some do and are able to initiate cancer. After absorption and distribution through all body parts, in particular those high in fat tissue, the metabolites are released from the body in the urine and faeces.[37]

Short- and long-chain aliphatic hydrocarbons are absorbed and distributed through the body in a comparable way as PAH (ATSDR 1999).[38] The shorter the chain length, the easier they are absorbed. They can accumulate in fat tissue. Depending on the length of the chains, they may be metabolised into fatty acids, and into several alcohol, ketone and carboxylic acid derivates. Chains longer than 16 carbon atoms are not expected to undergo extensive metabolism in ani-

mals and humans. In general, aliphatic hydrocarbons are slowly eliminated in the urine and faeces.

5.2 Dermal uptake

Overall, studies on dermal absorption of bitumen fumes, emissions or solutions were mainly focussed on dermal uptake of PAH, such as benzo[a]pyrene, which is a known carcinogen (see sections below).

5.2.1 Human data

Knecht et al. (2001)[39] studied dermal absorption of bitumen components in a human volunteer study under controlled conditions. Ten non-smoking and non-occupationally exposed males were exposed to emissions of commercial bitumen B65 (20 mg/m^3 of which 2.5 $\pm$ 1.6 mg/m^3 concerned particulates and 17.9 $\pm$ 3.7 mg/m^3 vapour phase; generation temperature 200°C) in an exposure chamber for 8 hours, with a 45-min break after 4 hours of exposure. During exposure the volunteers only wore shorts. Also they had to put on a breathing mask through which clean air was blown to prevent inhalation of the emitted bitumen. To allow inhalatory exposure, two persons did not wear a mask. Internal exposure was monitored by measuring the PAH metabolites of pyrene, chrysene and phenanthrene from urine that was collected for 24 hours after the start of the exposure. Urine collected before exposure served as own control. The total amounts of PAH metabolites in those who were exposed dermally as well as inhalatory was about 370 ng/g creatin for 1-hydroxypyrene, about 690 ng/g creatine for 6-hydroxychrysene, and about 85 ng/g creatine for hydroxyphenanthrene metabolites (extrapolated from graph). The percentage PAH metabolites due to dermal exposure alone was 57.9% for pyrene, 55.6% for chrysene and 52,7% for phenanthrene.

Potter *et al*. (1999)[40] examined the dermal and systemic bioavailability of PAH in low and high viscosity oil products using human skin explants. To the oil products, including bitumen (Cas no. 8052-42-4), trace amounts of radiolabelled benzo[a]pyrene were added. Oil solutions were brought on the surface of the explanted skins for 6 hours at 37°C. Following exposure, bioavailability was assessed by monitoring the amount of radiolabelled benzo[a]pyrene and radiolabelled DNA (DNA adducts) in the skin samples. Bioavailability of benzo[a]pyrene and the presence of DNA adducts was lowest for bitumen solutions. Bitumen had the highest viscosity of all the oils used.

McClean *et al*. (2004)[41] measured exposure to PAH among bitumen paving workers. Personal air and dermal patch samples were analysed on the presence of pyrene using high-pressure liquid chromatography. Furthermore, the total absorbed dose was determined by measuring urinary 1-hydroxypyrene. The workers had an inhalatory and dermal exposure of 0.3 $\mu g/m^3$ and 5.7 ng/cm^2, respectively. The authors used distributed lag models to evaluate the possibility that measurements are not only influenced by this exposure, but also by exposure that occurred in the near past. They calculated that 'the impact of dermal exposure was approximately eight times the impact of inhalation exposure'. Furthermore, the authors concluded that 'dermal exposure that occurred during the preceding 32 hours has a statistically significant effect on urinary 1-hydroxypyrene, while the effect of inhalation exposure was not significant'. Other investigators noted the large portion of data near or under detection limit. In addition, quantification of the impact of dermal exposure compared to inhalation exposure is disputed due to the low 1-hydroxypyrene levels after inhalation[42].

5.2.2 *Animal data*

Potter et al. (1999)[40] not only examined bioavailability of benzo[a]pyrene in various viscous oil products in human skin explants (see previous section), but also in mice *in vivo*. This time bioavailability of benzo[a]pyrene and the presence of DNA adducts were measured in the skin and in whole blood. Solutions of oils were applied on the shaved, dorsal skin of mice (5 animals per group; animal species not defined) for 6 hours. The results indicated that the amount of adducts in the skin and in the blood increased when viscosity was lower. Again, bitumen showed the lowest bioavailability and had the highest viscosity.

The same research group (Brandt *et al*. 1999)[43] reported on the carcinogenic potency for dermal exposure to viscous oil products. The same experimental setup was used as in the previous study, with radiolabelled benzo[a]pyrene as tracer for dermal uptake. The degree of DNA adduct formation in the skin and blood samples was shown to be a function of the viscosity of the oil product and of the aromaticity. The authors concluded that for the tested bitumen solutions, the amount of DNA adduct formation was too low to express carcinogenicity. According to them this was not only due to the high viscosity, but also to their low PAC content.

Genevois *et al.* (1996)[13,44] used laboratory-generated bitumen fume condensates for skin painting studies in mice. These condensates were very oily in appearance and therefore rapidly penetrated the skin. DNA adducts were found

in the skin, lungs and lymphocytes. This demonstrated that after dermal application systemic uptake had occurred. The authors also reported that the pattern of DNA adducts differed from that found after dermal application of coal-tar fume condensates. In this study, no specific adducts were identified. Analysis of PAH revealed larger amounts of unsubstituted PAH in coal-tar fume condensates than in bitumen fume condensates.

5.3 Mechanism of action

There are no data available on the mechanism of action of bitumen vapour and fume.

5.4 Summary and evaluation

Bitumens and bitumen fumes do not lend themselves to kinetic analysis, because kinetics will vary depending upon the characteristics of the individual constituents.

Regarding dermal uptake, investigators were mainly focussed on certain PAH constituents in the bitumen (fume) condensates. In general, PAH are absorbed through the skin, although dermal uptake highly depends on the viscosity of the applied solution. Since the concentration and the composition of PAH may differ by bitumen type and use, it is very difficult to assess the health consequences of dermal exposure to bitumen.

Chapter 6

Effects

Numerous human and animal studies have been published on the non-carcinogenic and carcinogenic effects of bitumen and bitumen containing products. Most of these studies have recently been evaluated by various international authorities, such as the NIOSH[1,3], DFG[2] and the IPCS[3]. In the text of this chapter only those studies are described in more detail, which are relevant for risk assessment.

6.1 Observations in humans

The available epidemiological studies include cohort and case-control studies with occupational bitumen fume exposure of various sources (*i.e.*, (hot mix) bitumen, bitumen-containing paintings, other bitumen-containing products) and industries (*i.e.*, road paving and construction work, roofing and slating, painting, insulation operations). It is evident that in none of these sources and industry operations bitumen is the only substance to which workers are exposed. Some of these substances are suspected or known carcinogens and may induce non-carcinogenic adverse health effects by their own (*i.e.*, coal tar pitch, man-made mineral fibres, formaldehyde, silica dust, gasoline or diesel fuels, herbicides).[45,46] This limits the interpretation of the results and usefulness of epidemiological data for risk assessment.

6.1.1 *Non-carcinogenic effects*

Local effects on skin

Direct contact with hot bitumen or asphalt may cause skin burns, as is described in various case reports and evaluations (Baruchin *et al*. 1997[47]; DFG 2002[2], IPCS 2004[3]). Also, prolonged skin contact with bitumen fumes causes skin irritation and dermatitis, pruritus (itchy skin), and occasionally rashes (Davies 1996[48]; Riala *et al.* 1998[49]; Schaffer *et al*. 1985[50]). Detailed data on skin effects can be found in annex F and G. Overall, given the presence of confounding co-exposure (*i.e.*, diesel fuel exhaust, coal tar, fibreglass) and environmental conditions (wind, heat and humidity, ultraviolet radiation), the extent to which bitumen fumes may be associated with these skin effects is unclear.

No data are available on bitumen-related dermal photosensitisation.

Respiratory effects

Several investigators examined adverse respiratory health effects among road pavers, road maintenance workers, roofers and other jobs involving exposure to bitumen fumes (see annex G for individual study details). These surveys revealed both upper and lower respiratory tract effects, such as irritation in the nose and throat, coughing, dry throat, nasal discharge, nose bleeding, bronchitis, shortness of breath, asthma, and lung functions changes. However, to what extent these symptoms can be attributed to bitumen fume exposure alone is unclear, because in many studies the numbers of cases were too small, and co-exposure with for instance coal tar pitch fumes (especially roofers), diesel exhaust or asbestos was likely. Furthermore, in most of these studies no quantitative or qualitative bitumen fume exposure data were presented. Moreover, the observed respiratory symptoms in some of these studies are difficult to interpret, because these were based on questionnaires only. Although questionnaires are standardised and useful in health assessment, the method is prone for subjective information. Additional information by clinical examination (*e.g.*, physical examination, lung function testing, immunological tests), is needed to confirm the diagnosis.

A limited number of studies reported on the level of bitumen fume exposure in relations to acute (respiratory) health effects. In none of them exposure to other substance than those present in bitumen fume could be ruled out. An example is the Norwegian cross-sectional study by Norseth *et al*. (1991).[51] They examined the exposure to volatile organic compounds and to bitumen fume in

relation to subjective symptoms in 333 road repair and construction workers (79 with personal exposure measurement data). These data were compared to 247 non-exposed maintenance workers. The mean weekly exposure to bitumen fume for the exposed workers was 0.36 mg/m^3 (median, 0.21 mg/m^3; minimum-maximum, 0.20–1.29 mg/m^3). The authors reported that exposed workers had more symptoms (abnormal fatigue, reduced appetite, laryngeal/pharyngeal irritation, and eye irritation) than non-exposed workers ($p<0.05$). Also they noted that more symptoms were reported not only when exposure to bitumen fume was higher (mean symptom sum for exposures <0.40 mg/m^3 was 1.3; for exposures >0.40 mg/m^3 it was 3.0 ($p<0.05$)), but also when the temperature of bitumen was higher (r=0.22; $p<0.01$). Although low concentrations of volatile compounds were measured, no correlation was found between exposure and symptoms, except for 1,2,4-trimethyl benzene. Later the authors re-analysed their data by using a new statistical model.[52] With this new model they came to the conclusion that there was no correlation between the sum of symptoms and exposure to bitumen fumes. The committee observed some limitations in this study, such as that the sum of symptoms was based on the number of days with symptoms, and that symptoms were not confirmed by clinical examination. Furthermore, the reporting on the re-analyses was in an abstract only, in which no details on the models used were given.

In another field study, Gamble *et al*. (1999)[22] examine d the association between bitumen fume exposure and changes in lung function and symptoms among 170 Americans, who worked in five different industries (hot mix bitumen manufacturing, hot mix bitumen paving operations, bitumen distribution terminals, roofing manufacturing, and roofing application). Exposure was estimated by taking personal air samples, which were analysed for the presence of several substances, including total and respirable particulate, benzene-soluble fraction of total particulate, and volatile compounds. Exposure was monitored daily for two days. The geometric mean exposure levels monitored were for: total particulate, 0.60 mg/m^3 (GSD, 2.18 mg/m^3; maximum, 6.16 mg/m^3; in roofing manufacturing); respirable particulate, 0.14 mg/m^3 (GSD, 2.52 mg/m^3; maximum, 1.38 mg/m^3; in roofing application); benzene-soluble fraction, 0.12 mg/m^3 (GSD, 2.71 mg/m^3; maximum, 1.23 mg/m^3; in roofing application); and, volatile hydrocarbons, 1.58 mg/m^3 (GSD, 3.41 mg/m^3; maximum, 19.80 mg/m^3; in bitumen distribution terminals).

At the two measurement days, lung function tests were performed at the beginning and at the end of the shift; symptom recording was also done during the day. Overall, no reductions in lung functions over the shift period were found.

The main respiratory symptoms recorded were nose and throat irritation, coughing, and difficulty in breathing. Most of these symptoms were mild in severity. However, statistical analysis revealed no significant relationship between the extent of bitumen fume exposure and the incidence of symptoms. The committee noted that in the study no group of un-exposed workers was included. Furthermore, at the roofing manufacture sites only a maximum of 12 to 13 participants with the highest exposure were allowed to participate in the study.

Between 1994 and 1997, NIOSH performed health hazard evaluations on the acute health effects among road pavers, who worked with crumb-rubber modified bitumen (CRM) and unmodified bitumen in open-air highway paving operations. With the help of the American Federal Highway Administration (FHWA), a total of seven evaluations were performed in seven different locations. A composite report on the level of exposure in relation to respiratory health effects was made by Burr *et al.* (2001)[53]. Exposure was monitored by taking personal full-shift air samples at each site. Concerning unmodified bitumen fume exposure, the concentration of total particulate ranged between 0.07 and 0.81 mg/m^3 (geometric mean), and of benzene soluble particulate between 0.02 and 0.44 mg/m^3 (geometric mean).

Response data were analyzed from a total of 52 exposed workers, with different job titles but all with bitumen fume exposure, and 42 workers with no known bitumen fume exposure. Data were obtained by questionnaires and lung function testing. The most frequently reported symptoms were eye, nose and throat symptoms; the frequency of complaints being higher in the unmodified bitumen fume exposed group than in the non-exposed group. However, only for throat irritation this was statistically significant (odds ratio, 3.6; $p<0.03$). Also chest tightness and wheezing were reported, but the authors considered the incidence too low to calculate odds ratios. Also they observed that the concentration of total particulate and benzene soluble particulate from unmodified bitumen was significantly higher when eye, nose and throat irritation was present ($p<0.02$ for all comparisons). In three of the exposed workers work-related bronchoreactivity was observed. Overall, workers exposed to CRM fumes had higher odds ratios than those exposed to unmodified bitumen fumes.

The authors remarked that workers were aware of the type of bitumen being used and some of them were known to be concerned about possible health effects. The committee noted the low number of participants at each site.

Overall, in none of these three studies, a clear exposure-response relationship could be established between the level of bitumen fume exposure and the reported adverse respiratory tract effects.

Other non-carcinogenic effects

Among workers exposed to bitumen fumes (*i.e.*, road paving operations, insulation of cables, manufacture of fluorescent light fixtures) symptoms of nausea, stomach pain, decreased appetite, headaches, and fatigue have been reported (see annex G). However, data from the available studies are insufficient to determine the relationship between bitumen fume exposure and these types of symptoms. This is mainly due to restrictions in study design and confounding co-exposure.

Burstyn *et al*. (2005) reported on a large historical cohort of European male road paving workers.[54] In that study a strong association was found between cumulative and average exposure to benzo[a]pyrene and mortality from ischemic heart disease (cumulative exposure (>2,013 ng/m^3-years), relative risk (RR) of 1.58 (95% CI, 0.98-2.55); average exposure (>273 ng/m^3), RR of 1.64 (95% CI, 1.13-2.38)). The authors also discussed the interference with possible sources of confounding and bias, but still their data suggest a higher risk for ischemic heart disease resulting from exposure to bitumen fumes.

So far, no human data are available which address bitumen fume exposure to neurological effects and effects on reproduction and progeny. Concerning immunological effects, Karakaya *et al*. (1999)[55] found changes in various immunological blood parameters in road paving workers. However, the study is of limited value because: exposure to coal tar could not be excluded; only a small number of workers participated in the study; and, no specific data were presented for controls.

6.1.2 *Carcinogenic effects*

A lot of effort has been invested in finding an association between occupational bitumen fume exposure and cancer risk, in particular lung cancer. A reason for this is that the fumes may contain carcinogen PAH and/or PAC. The epidemiological studies were mainly performed on road pavers and construction workers, roofers and slaters, and to a lesser extent on workers from other professions or operations.

Annex H shows the results of the individual cohort studies by occupation or type of operation. The studies included retrospective and proportional mortality studies performed in the USA and in West-European countries. In addition, annex K summarises the results of the case-control studies.

Lung cancer

Concerning lung cancer, an effort has been made to correlate lung cancer mortality and incidence to bitumen fume exposure in rood pavers and roofers. This has resulted in variable outcomes (see annex H and K for individual study results). The variability may be explained by the possible weak carcinogenic effects of bitumen fume exposure, in combination with the many confounders that were present in the field studies, such as: limitations in design (low number of cases or participants, short latency period); confounding from co-exposure to coal tar; differences in exposure conditions; and, failure to correct for smoking habits.

Partanen and Boffetta (1994)[6] combined the results of twenty epidemiological studies conducted on road pavers and roofers, and examined three broad job categories: 1) roofers (exposed to bitumen fumes and previously often to coal-tar fumes), 2) highway maintenance workers and road pavers (exposed to bitumen fumes as well as possibly coal-tar fumes previously), and 3) miscellaneous and unspecified bitumen workers. In roofers, the aggregated relative risk for lung cancer was statistically significantly increased (RR 1.8; 95% CI, 1.5-2.1) compared to highway maintenance workers and road pavers (RR, 0.9; 95% CI, 0.8-1.0). The third unspecified group had an excess aggregated relative risk of 1.5 (95% CI, 1.2-1.8). Although roofers seemed to be at higher risk, the authors could not make a definite conclusion, one of the reasons being the possible co-exposure with coal tar fumes.

To shed more light on the controversial findings, recently, a large and powerful multicenter cohort study was assembled by the International Agency for Research on Cancer (IARC). The study is performed in seven European countries (Denmark, Finland, France, Germany, Norway, Sweden, the Netherlands) and Israel (Boffetta *et al*. 2001, Boffetta *et al*. 2003).[16,56,57] The cohort includes 29,820 workers (911,209 person-years) engaged in road paving, bitumen mixing, roofing, waterproofing, or other specified jobs where exposure to bitumen fumes was possible. A detailed description on the number of companies involved, employment duration, follow-up period, number of workers in study, and reference groups is given in annex I. Overall, workers were employed for at least one season; the follow-up period was between 1953 and 2000; and, standardised mortality ratios (SMRs), relative risks (RRs), and their 95 confidence intervals (95% CI) were calculated as ratios of observed and expected number of deaths. Exposure to bitumen fume, coal tar, 4-6 ring polycyclic aromatic hydrocarbons, organic vapour, diesel exhaust, asbestos, and silica dust were assessed by the Road Construction Workers Exposure Matrix (ROCEM, see section 4.2.1 in this

document). Not only were data analysed using ROCEM-based exposures, but data were also analysed based on internal comparison between subsets of the cohort with different job and exposure categories.

Concerning exposure levels, Burstyn *et al*. (2003)[20] reported on bitumen fume exposure levels (benzene soluble matter) in paving and bitumen mixing in seven surveys that monitored exposures in both job classes (extracted from Asphalt Worker Exposure (AWE) database). The geometric mean exposure level for paving jobs was 0.15 mg/m^3 (95% CI, 0.13-0.18 mg/m^3; sample size, n=557), and for bitumen mixing 0.12 mg/m^3 (95% CI, 0.07-0.20 mg/m^3; sample size, n=64). For other job classes, the AWE database did not contain sufficient information.

Annex J shows the findings of the individual countries. The overall mortality of the bitumen workers was below the expected number of deaths based of the general population (Table J1 in annex J).

Across all participating countries, small but statistically significant excess for lung cancer mortality was found among bitumen workers (SMR 1.17; 95% CI, 1.04-1.30) compared to building and ground construction workers (SMR 1.01; 95% CI, 0.89-1.15). The relative risk for lung cancer was only slightly increased among bitumen workers as a whole (RR 1.09; 95% CI, 1.07-6.35). The investigators observed that these finding was not consistent among countries, which could point towards confounding by country. The excess of lung cancer mortality was furthermore only associated with average exposure, but not with cumulative exposure nor with duration of exposure when a 15-year lag time was taken into account. Closer examination of the data revealed that it is difficult to attribute the excess lung cancer mortality to bitumen fume exposure for several reasons. One is that confounding by other exposures within the industry may have occurred. For instance, when the possible effect of coal tar was taken into account the excess lung cancer mortality was further reduced (Boffetta *et al*. 2003)[56,57]; also the statistical power weakened). No reduction of the excess of lung cancer mortality was observed when co-exposures of 4-6 ring PAH, organic vapour, silica dust, diesel exhaust or asbestos were taken into account. Another factor is that smoking habits were not taken into account. Cigarette smoking is strongly associated with specifically lung cancer. In addition, apart form the multicenter study, in the Dutch cohort adjustments for smoking habits were made (Hooiveld *et al*. 2003).[58] After adjustment for these habits the association between bitumen fume exposure and lung cancer risk weakened. Watkins *et al*. (2002)[59], who used data from an American case-control study on roofers, suggested that smoking habits contributed more strongly to lung cancer than bitumen fume exposure.

Overall, the investigators concluded that the results of the analysis showed a small but significant excess of lung cancer in bitumen workers. However, they also pointed out that since confounding from co-exposure with other substances in the investigated industries, smoking habits and other lifestyle factors cannot be ruled out, the results of this multicenter study do not allow a final conclusion on the presence or absence of an association between lung cancer risk and occupational exposure to bitumen fumes (Boffetta *et al*. 2003).[56,57]

The committee is aware that in 2004 a case-control study of lung cancer, nested within this multicenter cohort, has been started to control for confounders of the multicenter study. The outcome of this study is not available yet.

Cancers at other sites

A few epidemiological studies reported on associations between bitumen fume exposure and cancers at other sites than the lungs. Most of these studies concerned population-based case-control studies.

In several case-control studies associations were found between bitumen fume or bitumen exposure and the occurrence of bladder and renal cancer (Jensen *et al*. 1988[60]; Risch *et al*. 1988[61]; Mommsen *et al*. 1983[62]; Bonassi *et al*. 1989[63]). Other isolated studies have reported elevated risks for cancer of the brain (Hansen 1989[64]), mouth and pharynx (Bender *et al*. 1989[45]; Hansen 1989[65]), stomach (Engholm *et al*. 1991)[66], liver (Austin *et al*. 1987)[67], and leukaemia (Bender *et al*. 1989[45]; Engholm *et al*. 1991[66]) (see also annex H and K). In the meta-analysis study by Partanen and Boffetta (1994)[6] increases of bladder cancer (RR 1.22; 95% CI, 0.95-1.53), stomach cancer (RR 1.28; 95% CI, 1.03-1.59), and leukaemia (RR 1.41; 95% CI, 1.05-1.85) were reported for bitumen workers; roofers showed increased risk in cancers of the stomach (RR 1.7, 95%CI, 1.1–2.5), nonmelanoma skin cancer (RR 4.0, 95% CI 0.8-12.0), and leukaemia (RR 1.7, 95% CI 0.9-2.9). In addition, in the multicenter cohort study of IARC, Boffetta *et al*. (2003)[56,57] reported that the results of cancer of the head and neck (buccal cavity and pharynx) were similar to those of lung cancer (based on a smaller number of deaths: SMR (bitumen worker), 1.27; 95% CI, 1.02-1.56; 92 observed cases), but that no association was found between employment (job title) or bitumen fume exposure and any other cancers.

Overall, interpretation of the findings of the studies is limited by lack of consistency among studies and the potential of confounding by co-exposure with other substances; concerning head and neck cancer in the multicenter cohort study, alcohol drinking and the use of smokeless tobacco products may have been potential confounders. Furthermore, many of the studies organized broad

job classifications that are prone to errors in defining bitumen exposure. For these reasons, evidence for an association between bitumen fume exposure and cancers at other sites than the lung is weak, if at all present.

Genotoxic endpoints

Various studies have been reported on genotoxic endpoints in workers exposed to bitumen fumes. Below a short summary is given.

Pasquini *et al.* (1989)[184] reported that the urine of road pavers who used bitumens was more frequently mutagenic, as measured by the Ames test using TA-98 strains, than that of non-exposed controls (positive score, 82% and 28%, respectively).

A limited number of studies reported on the presence of DNA-adducts in white blood cells of roofers as a measure of exposure to PAH (Fuchs *et al.*, 1996[68]; Herbert *et al.*, 1990[69,70]). However, due to the combined exposure with coal tar products the meaning of these findings for bitumen fume exposure is unclear. Fuchs *et al*.[68] also detected DNA-adducts, although at low levels, in blood cells of road pavers and bitumen painters.

In a cross-sectional study by Toraasen *et al*. (2001)[32,71], roofers using bitumen products but not coal-tar products showed small but significant higher levels of DNA strand breaks (Comet assay) in peripheral blood cells than unexposed construction workers, while for roofers also using coal-tar products the increase was significant. These observations were most pronounced in the end of the working week. Small increases in DNA strand breaks (Comet assay) in blood cells of roofers, who were exposed to bitumen fumes but not to coal tar pitch fumes, were also observed by Reid *et al*. (2000)[72], and by Fuchs *et al*. (1996).[68]

A few investigators reported on cytogenetic effects in road pavers and to a lesser extent roofers. For instance, Major *et al*. (2001)[73] reported that 22 Hungarian road pavers, who worked with coal-tar free bitumen products, showed significant increases in chromosome aberrations in their peripheral blood cells, and to a lesser extent sister chromatid exchanges, compared to unexposed controls. Higher levels of sister chromatid exchanges in blood cells of road pavers were also found by Burgaz *et al*. (1998; also micronuclei were increased)[31], and by Hatjian *et al*. (1995).[29] None of these workers were co-exposed to coal tar pitch fumes. However, Järvholm *et al*. (1999)[30] reported no differences in sister chromatid exchanges or micronuclei between a group of Swedish road pavers and unexposed controls.

Overall, different exposure situations in the workplace, the use of non-specific biomarkers, and a series of confounders (*i.e*., report bias, smoking bias,

environmental bias, occupational classification bias, co-exposure) hamper the interpretation of the study results. Therefore, an association between occupational exposure to bitumen fume and these genotoxic endpoints is still uncertain.

6.2 Observations in animals

It is difficult to obtain a sufficient quantity of paving and roofing bitumen fumes at the worksites. For this reason, in many of the animal studies laboratory-generated bitumen fume condensates were used. Although currently the heating process in the workplace may be reproduced in the laboratory and thus may be considered qualitatively comparable in composition (*i.e.*, Bonnet *et al*. 2000[74] and Brandt *et al*. 2000)[8], this was and is not always the case. In particular fumes generated in the laboratory above 230°C are not representative, as their composition may differ significantly from the fumes produced in the field, which are normally produced at lower temperatures. Detailed data on compositional differences between laboratory and field generated bitumen fumes have been published by Kriech *et al*. (1999)[75], Kurek *et al*. (1999)[76], and McCarthy *et al*. (1999).[77]

6.2.1 Irritation and sensitisation

Draize scores for skin irritation reactions were performed on nine New Zealand white rabbits by the American Petroleum Industry (API, 1982)[78,79]. A single dermal application (occlusion) of two residues from a vacuum distillation of the residuum from atmospheric distillation of crude oil (CAS 64741-56-6; sample 81-13 and 81-14) resulted in a score of 0.5-0.8 (minimally irritating) after a 14-day observation period. This was 0.2 and 0.4 after 24 and 72 hours, respectively. The dose applied was 0.5 mL (not specified). In addition, when these distillate residues were administered into the conjunctival sac of the right eye (0.1 mL, dose not specified) the Draize score was 4.0-4.7 (minimally irritating) after 24 hours. No visible effects were observed 72 hours and 7 days after administration.

The DFG evaluated a study performed by API (1984) concerning the possible allergic effects of two distillates (the same distillates as in the previous paragraph).[2] For this study, male Hartley guinea pigs were used for the occlusive patch test. Undiluted test material (0.4 mL) was applied once weekly for 6 hours for a total of three weeks. A provocation test performed 14 days later showed that the distillates were not active. The study included a positive control.

6.2.2 *Acute and sub-acute toxicity*

The number of animal studies on the acute toxicity of bitumen fume is very limited, and concerned various exposure routes and end-points (see annex L). In summary, inhalation of paving bitumen fumes did not cause acute pulmonary inflammation in rats exposed to 15 or to approximately 70 mg TPM/m^3 for 5 days (Ma *et al.* 2003[80], Antonini *et al.* 2003[81]), whereas intratracheal instillation of a solution of road bitumen fume condensate did (Ma *et al.* 2000).[82] Sikora *et al.* (2003)[83] described signs of nasal neurogenic inflammation and nasal irritation in rats, which were exposed to 16 $\pm$ 8 mg/m^3 bitumen fume (not specified) for 5 days. This finding is in contrast with the findings of Fuhst *et al.* (2001, 2003)[84,85], who did not find any symptoms in the nose of rats exposed by inhalation to 20 mg/m^3 bitumen fume for 14 weeks (see next section). No notable toxicity was observed in rabbits and rats after a single dermal (2 g/kg bw) or single oral (5 g/kg bw) application, respectively, of vacuum residuum distillation products of bitumen.[78,7978,79]

6.2.3 *Sub-chronic toxicity*

The number of short-term toxicity studies is also very limited (see annex L). One study involved inhalation exposure (Fuhst *et al.* 2001, 2003[84,85]; Pohlmann *et al.* 2001[86]). In that study, Wistar rats (n=16/sex/group) were nose only exposed to bitumen fumes regenerated in the laboratory from a sample of bitumen tank condensate at 180°C of 4, 20 or 100 mg THC/m^3 (total hydrocarbon from bitumen aerosol and vapour; actual exposures were: 5.5, 28,2 and 149,2 mg THC/m^3, respectively) for 6 hours/day, 5 days/week for 14 weeks. Exposure did not increase the mortality. Nor were there any effects observed in the animals exposed to 4 and 20 mg/m^3. However, at 100 mg/m^3 a statistically significantly dose-related increase in histopathological changes in the nasal and paranasal cavities was observed.

In addition, three weekly dermal applications of bitumen vacuum residuum distillation products (200-2,000 mg/kg bw) for 4 weeks to the skin of rabbits resulted in reduced food consumption (1,000 mg/kg bw) and minimal to moderate dermatitis and keratinosis (1,000-2,000 mg/kg bw) (DFG 2002).[2]

6.2.4 *Chronic (non-carcinogenic) toxicity*

Concerning inhalation exposure, in none of the studies published on this matter actual bitumen fume concentrations in the air were measured (see annex L). This hampers the usefulness of these studies in quantitative risk assessment. Mice that were exposed to bitumen-water aerosols (bitumen heated at 121°C) for 16.5 (30 min/day, 5 days/week) to 21 months (6-7.5 hours/day, 5 days/week), developed symptoms of pneumonitis, bronchitis and emphysema (Simmers 1964).[87] In addition, Hueper and Payne (1960)[88] reported on chronic fibrotic pneumonitis, bronchial epithelial metaplasia and bronchiectasis in rats and guinea pigs that were exposed to air-blown roofing bitumen that was evaporated at 121-135°C for 5 hours/day, 4 days/week for 2 years.

A few reports were published on long-term dermal exposure (see annex L). Mice exposed to various bitumen condensate solutions for 19 to 22 months showed chronic dermatitis (Simmers 1965[89]; Kireeva 1968[90]), and formation of ulcers and small abscesses (Wallcave *et al*. 1971)[91]. The committee noted that for these studies various sources of bitumen condensates were used and that the exact doses applied to the skin were difficult to assess from the original publications. Furthermore, in a study performed by the American Petroleum Institute, male and female mice were dermally exposed by topical application of 50 μL of liquids or semisolids bitumen vacuum residuum, twice a week for one year.[92] The results revealed local dermatotoxic effects (desquamation, alopecia or irritation).

6.2.5 *Carcinogenicity*

Several studies have been performed on the carcinogenicity of bitumen in animals (see annex M for a complete outline).

Concerning inhalation exposure, Hueper and Payne (1960)[88] were not able to demonstrate lung tumour development in rats and guinea pigs, which were exposed to unknown concentrations of air-blown roofing bitumen fumes for 2 years. Also Simmers (1964)[87] could not demonstrate a clear induction of lung tumours in mice exposed to bitumen-water aerosols for at least 16 months.

Fuhst *et al*. (2007) performed an inhalation study using Wistar rats.[93] The animals were nose-only exposed to clean air, or to 6.8, 34.4 or 172 mg/m^3 of bitumen fume (total hydrocarbon of bitumen fume) for 6 hours a day, 5 days a week for 2 years. The number of animals per group per sex was 50 (clean air and highest dosed group) or 86 (other exposure groups). Bitumen fumes (particulate

and vapour) were regenerated in the laboratory from bitumen fume condensate samples, which were collected from the headspace of hot bitumen storage tanks at road paving worksites. At sacrifice hematological analyses, gross pathology and histopathology were performed on animals. Twelve animals of each control and highest-dosed group and of each sex were sacrificed at 7 days, 3 and 12 months in experiment for interim analyses, that included bronchoalveolar lavage, gross pathology, and histopathology. Mortality did not differ among the groups. However, a significant reduction in mean body weight was observed in the mid and highest-dosed groups (males and females), which corresponded with reduced food consumption. Concerning non-carcinogenic effects, only minor effects were observed on heamatology and bronchoalveolar lavage analyses. Dose-related degenerative, inflammatory, and proliferative lesions (basal cell hyperplasia) were observed in the nasal cavity and the lung. No increases in the number of tumour-bearing animals were observed among the groups, nor were statistically significant increases in organ-related tumour incidences found when exposed animals were compared to control animals. In one single male of the highest dose group a poorly differentiated adenocarcinoma was observed in the nasal cavity. Based on the results, the authors consider bitumen fume not to be tumorigenic to rats.

In two dermal carcinogenicity studies bitumen fume condensates were topically applied to the skin of mice, twice a week for 78 (Niemeier *et al.* 1988)[94] or 104 (Sivak *et al*. 1997)[95] weeks. The fumes were generated up to a temperature of 316°C. Niemeier *et al*. found a statistically significant increase in skin tumours compared to unexposed animals. Sivak *et al*. also observed increased incidence and number of skin tumours, but only with raw roofing and neat bitumen fume condensates, while the residuum of these condensates did not produce skin tumours. The latter types of condensates were low in PAH content.

Other dermal carcinogenicity studies concerned raw bitumen products from various sources (road paving, roofing, and bitumen-based paints), and dissolved in different organic solvents (toluene, benzene, acetone). In summary, contradictory outcomes were reported. For instance, positive outcomes were reported by Robinson *et al*. (1984; bitumen-based paints)[96], Simmers *et al*. (1959, 1965; mixture of steam-refined bitumens)[89,97,98], API (1986, 1989; various (vacuum) residuum from liquids or semisolids petroleum refinery streams; tumours only observed at the treatment site)[92,99], and McKee and Lewis (1987; raw bitumen)[100]. No skin tumours were found by for instance Emmett *et al*. (1981; roofing bitumen, not specified)[101], McKee *et al*. (1986; raw bitumen)[102], and McGowan *et al*. (1992; naphtenic bitumen, and bitumen residuum).[103]

The committee noted that large variations of bitumen sources were used. Also the production processes differed. Both the source and process may have influenced the final composition and content of the carcinogenic substances present in bitumen fume, fume condensates and solvent-solubilized bitumen, the main influencing factors most likely being the heating temperature and the presence of PAH.

6.2.6 *Genotoxicity*

Bitumen products and fumes were tested for genotoxic properties in various systems. As test materials, bitumen solutions, extracts and condensates from various sources and processes have been used. A summary is given below, while more details of the individual studies are given in annex N.

Non-heated bitumen products. Extracts and solutions of various bitumen products were tested on mutagenicity by the (modified) Ames *Salmonella* assay, using various TA-strains with or without a metabolic activation system[33,96,103-107]. In none of these studies bitumen products showed significant mutagenic activity. In addition, some authors reported that the content of PAH was very low or even undetectable[33,96,106]. Furthermore, no notable increases in DNA strand breaks in *in vivo* and *in vitro* test systems were found[33,105], nor DNA-adducts in mice[108], and chromosome aberrations and micronuclei in bone marrow cells of rats[109].

Bitumen fume and fume condensates (re)generated at a maximum of 230°C. Variable outcomes were reported using the (modified) Ames mutagenicity assay. In two studies, storage tank bitumen fume condensates (147-157°C) did not show mutagenic activity.[9,53] Laboratory-regenerated bitumen fume condensates from various sources and heated up to 200°C showed no[110], weak to moderate[110,111], or significant mutagenicity.[112] In five nose-only exposed Big Blue mice, bitumen fumes regenerated at 170°C (100 mg TPM/m^3) did not induce mutagenic activity in the lungs after 4 weeks of exposure.[113] Non-specific DNA-adducts were detected *in vitro* (with metabolic activation system) for laboratory-regenerated bitumen fumes[112,114], but only very low levels were found for field-generated fumes.[115] Whole-body or nose-only exposure to laboratory-regenerated bitumen fumes for 5 to 10 days revealed DNA-adducts in the lungs of mice (152-198 mg TPM/m^3)[116] and rats (25-58 mg/m^3)[117], and in the liver of rats (50 mg TPM/m^3; not at 5 mgTPM/m^3).[118] Whole-body exposure, however, did not induce more micronuclei in bone marrow cells of rats than in controls after exposure to 58 mg/m^3 for five days[117], but intratracheal installation of 9 mg/kg bw did.[119]

Bitumen fumes and fume condensates regenerated at a minimum of 230°C. Using modified Ames mutagenicity test, condensates of bitumen fume, regenerated in the laboratory up to 316°C, showed weak to moderate mutagenic activity[9,111,120]. In all these studies, it was reported that coal-tar pitch fume condensates were up to a 100 times more mutagenic than the tested bitumen fume condensates. Furthermore, condensates of laboratory-regenerated bitumen fume (316°C) caused micronuclei formation *in vitro*[121,122] and DNA-adducts in the lungs of rats *in vivo* by intratracheal installation[123], but no chromosomal aberrations *in vitro*.[9]

Overall, mutagenicity and genotoxicity *in vitro* were minimal for whole bitumens, whereas for bitumen fume condensates it correlated with generation temperature and collection method. No mutagenicity was found *in vivo*. Low levels of DNA adducts were found following exposure *in vivo* but these did not result in clastogenicity. Overall interpretation of the results and their validity is hampered by several factors. One factor is the source. Fumes have been generated from different bitumen products, in the field or in the laboratory. Consequently, the amount and type of genotoxic constituents in the fumes may have varied considerably and that may have influenced the results. Also it makes a difference whether volatile or non-volatile fractions or condensates are tested. Another factor is temperature. At the worksites, bitumen fumes are generated at about 160°C for road paving operations, and up to 230°C for roofing operations. Results indicate that higher temperatures and longer heating time affect the chemical composition and PAH profile. Also the total and benzene-soluble particles in the air are higher at higher temperatures than at lower temperatures, leading to more frequent findings of genotoxicity.[1] In addition, the amount of genotoxic PAH in bitumen fume is much lower than in, for instance, coal tar pitch fumes.

Overall, because during heating of bitumen products fumes are released that may contain carcinogenic PAH and/or PAC, it is expected that these fumes have some level of genotoxic potential, although the amount of these carcinogens in those fumes may be low. However, the results of the tests are inconsistent and difficult to interpret because of the presence of confounding factors.

6.2.7 *Reproduction toxicity*

No data are available on the reproduction toxicity and development toxicity of bitumen vapour and aerosols in animals.

6.3 Summary and evaluation

6.3.1 Human data

Prolonged skin contact with bitumen fumes may cause skin irritation and dermatitis. Furthermore, direct skin contact with heated bitumen may cause skin burns.

The main health complaints of workers using bitumen products are respiratory tract effects, such as nose and throat irritation, coughing, dry throat, nasal discharge, nose bleeding, shortness of breath, and asthma. These effects have been described in various occupations, such as in bitumen paving and road construction workers, roofers and in cable insulation operations. The interpretation of these data proved, however, not to be easy. A main problem is namely that in practice workers who use bitumen products are at the same time also exposed to other substances, or have a past exposure to coal tar pitch fumes. These substances may also produce respiratory effects, making it difficult to ascribe effects to bitumen fume exposure only. Another problem is that in most epidemiological studies health assessment included symptomatology only. For the right interpretation of the observed effects additional information, for instance on physiology and immunology, is needed.

A few attempts have been made to associate the level of bitumen fume exposure to respiratory effects, but in none of these studies a clear exposure-response relationship could be established. However, it should be kept in mind that among road paving workers respiratory health symptoms were more frequently reported at concentrations (geometric mean) at or below 1.0 mg TPM/m^3 and 0.4 mg BSM/m^3 compared to unexposed maintenance workers (irrespective the causal agent and other possible interpretation errors).

Data on effects other than those on the respiratory tract are very limited and, therefore, should be interpreted with caution. These include symptoms of nausea, headaches, stomach pain and fatigue. Human data on neurological effects and effects on reproduction and development have not been reported.

The carcinogenicity of bitumen fume from various sources and processes has been investigated in several cohort and case-control studies. However, the results on lung cancer risk in epidemiological studies are inconsistent, which could partly ascribed to (confounding) factors that were present in part of these studies, such as: co-exposure to other carcinogens and non-carcinogens; differences in use of various bitumen sources (*e.g*., road paving, bitumen roofing, use of bitumen-based paints); design limitations (*e.g*. limited statistical power); absence of information on smoking habits and other lifestyle factors; and, absence of infor-

mation on past exposure, for instance to coal tar (roofers) and asbestos. In a recently well-performed large and powerful multicenter cohort study, assembled by IARC, a small but statistically significant association was found between lung cancer mortality and average bitumen fume exposure among bitumen workers. Further research is now going on to control for possible confounders in this multicenter cohort study. Overall, the evidence that bitumen fume exposure may cause lung cancer is weak. It is still unclear whether bitumen fumes or other substances, that were also present in the workplace, were responsible for the observed effects. Also evidence for an association between bitumen fume exposure and cancer at other sites than the lung is weak and inconsistent. For the committee, the weak association is a cause for concern that bitumen (vapour and aerosol) may be carcinogenic to humans.

6.3.2 *Animal data*

For the animal experiments both field- and laboratory-generated bitumen fume or bitumen fume condensates were used. It should be kept in mind that these laboratory-generated fumes and condensates may differ in composition from those obtained from the field, though they are considered qualitatively but not quantitatively comparable.

Direct skin and eye contact caused slight to mild skin and eye irritation in rabbits.

Several animal studies have been performed on the acute, short-term and long-term toxicity. These studies comprised a variety of bitumen sources, exposure routes, and end-points, resulting in data on specific toxicity being limited. Also, only a minority of the animal studies reported on the exact exposure concentration, which further limits the use of these studies for quantitative risk assessment.

Inhalation of paving bitumen fumes of 15 or approximately 70 mg/m^3 (TPM) did not cause acute pulmonary inflammation in rats. In one study, nasal irritation was observed at approximately 16 mg/m^3 (bitumen fume not specified) after five days of exposure. Rats inhaling field-generated fumes of bitumen condensates for 14 weeks (6 hours/day, 5 days/week) did show irritation in the nasal and paranasal cavities at 100 mg/m^3 (total hydrocarbon (aerosol and gas phase)), but no such signs of irritation were found in groups exposed to 4 or 20 mg/m^3. In mice and guinea pigs exposed to bitumen fume for a prolonged time symptoms of pneumonitis, bronchitis, emphysema and bronchiectasis were reported, but no actual bitumen fume concentrations in the air were determined.

A substantial number of animal studies concerned dermal exposure. These studies revealed local skin effects, such as dermatitis after short- and long-term exposure, and ulcers and small abscesses after long-term exposure.

So far, no evidence was found that chronic bitumen fume exposure induces lung tumours after inhalation. However, bitumen fume condensates induced papillomas and epidermal carcinomas when applied to the skin.

Both raw bitumen products and condensates of bitumen fume have been tested for mutagenicity and genotoxicity. No mutagenic activity was found *in vivo*, while *in vitro* the activity appeared to depend on the generation and collection method. Overall, because during heating of bitumen products fumes are released that may contain carcinogenic PAH and/or PAC, it is expected that these fumes have some level of genotoxic potential, although the amount of these carcinogens in those fumes may be low.

Chapter 7

Existing guidelines, standards and evaluations

7.1 General population

No guidelines for the general population were found.

7.2 Working population

7.2.1 Occupational exposure limits

A few countries or organisations have set an occupational exposure limit for bitumen fumes, based on non-carcinogenic effects. These include, the United Kingdom, Denmark, and from the USA, NIOSH and ACGIH (see Table 7.1 for values). The latter two organisations based their exposure limits on mild acute effects in exposed workers (*i.e.* eye irritation, nasal and throat irritation, and lower respiratory tract symptoms). Up to the end of 2006, in the Netherlands an administrative OEL was valid of 5.0 mg/m^3 (8-8 TWA).[124]

Table 7.1 Occupational exposure limits of bitumen fumes (CAS no. 8052-42-4) in a number of countries.

country	concentration mg/m^3	reference period	additional information	reference
The Netherlands	-	-	-	-
Germany	-	-	-	DFG[125];AGS[126]
The UK	5.0	8-h TWA	OES: as TPM	HSE[127]
	10.0	15-min TWA	OES: as TPM	
Sweden	-	-	-	SNB[128]
Denmark	1.0	8-h TWA	As cyclohexane soluble fraction of total dust	Arbejdstilsynet[129]
Norway	5.0	8-h TWA	As TPM	Arbeidstilsynet[130]
The USA				
- ACGIH	0.5	8-h TWA	TLV: as benzene-soluble inhalable aerosol	ACGIH[131]
- IOSH	5.0	15-min (ceiling)	REL: as TPM	ACGIH[131]

7.2.2 Skin Notation

In 2001, DFG assigned for bitumen (vapour and aerosol) a skin notation in view of its skin permeability.[125]

7.2.3 Classification as a carcinogen

In 1987, an IARC Working Group concluded in its overall evaluation that bitumens are not classifiable as to their carcinogenicity to humans (Group 3).[132] Extracts of steam-refined and air-refined bitumens were classified as possibly carcinogenic to humans (Group 2B).

Germany classified bitumen (vapour and aerosol) as a Category 2 Carcinogen*, based on the presence of genotoxic PAH.[125] Germany is the only European country that classified bitumen (vapour and aerosol).

* Category 2 carcinogens (definition used by DFG): Substances that are considered to be carcinogenic for man because sufficient data from long-term animals studies or limited evidence from animal studies substantiated by evidence from epidemiological studies indicate that they can make a significant contribution to cancer risk. Limited data from animal studies can be supported by evidence that the substance causes cancer by a mode of action that is relevant to man and by results of in vitro tests and short-term animal studies.

In addition, ACGIH[131] classified bitumen fume (coal tar free) in Class A4[*]. Furthermore, NIOSH[1] concluded from the epidemiological and experimental data that 'it was not possible to definitively classify bitumen fumes generated either during paving or roofing activities *per se* as cancer causing substances. The main problem with the epidemiological data was the high correlation with co-exposures to other established carcinogenic mixtures, such as smoking, polycyclic aromatic hydrocarbons, coal tar and diesel exhaust'. NIOSH classified bitumen fumes as a potential occupational carcinogen (notation "Ca").

* Class A4 (definition used by ACGIH): Not classifiable as a human carcinogen. Agents which cause concern that they could be carcinogenic for humans but which cannot be assessed conclusively because of a lack of data. *In vitro* or animal studies do not provide indications of carcinogenicity which are sufficient to classify the agent into one of the other categories.

Chapter 8

Hazard assessment

8.1 General comment

Bitumen is a complex mixture of naphthenic, aliphatic and/or aromatic hydrocarbons, and heterocyclic compounds containing sulphur, nitrogen, and oxygen. The exact chemical composition depends on the original crude petroleum, the manufacturing processes and its intended use. Its major use is in bitumen paving and road construction, roofing and waterproofing. All this means that there is not only a great variability in composition, but also in exposure of workers to the individual constituents. As a result, there is no single unequivocally characterized bitumen fume or bitumen fume condensate. This should be taken into consideration when evaluating the hazards of bitumen (vapour and aerosol) exposure in the workplace. Also the application process causes further variability in the composition of bitumen fumes.

The evaluation of adverse health effects associated with bitumen fume exposure is further complicated by the presence of bias and other uncertainties. These apply to all applications with bitumen. A short summary of the main bias is given below.

Co-exposure. Pavers and roofers are almost always exposed to various agents at the same time. This may include in addition to bitumen fume, coal tar, polycyclic aromatic hydrocarbons, organic vapours, asbestos, silica dust and diesel exhaust. Coal tar, a recognized carcinogen, was previously included in paving

and roofing bitumen. Its use has now been limited to special applications, such as airport and special industrial areas. Exposure to coal tar in the past may have contributed to the mixed effects of bitumen fume exposure in human studies. At present, road pavers may still be exposed to coal tar products when old asphalt is recycled. In addition, on reconstruction jobs, roofers may also still be exposed to old, tar containing, roofing material. To what extent these agents influence the outcome of bitumen fume exposure is not clear yet.

Field- versus laboratory-generated bitumen fumes. Although currently the heating process in the field may be reproduced in the laboratory, this was and is not always the case. In particular fumes generated or regenerated in the laboratory above 230°C are not representative, as their composition may differ significantly from the fumes produced at lower temperatures. In practice, paving and roofing bitumen is heated to a maximum of 230°C.

Smoking habits. Of main interest is whether inhalation of bitumen fumes may cause lung cancer. Tobacco smoking is strongly associated with lung cancer. Therefore, smoking habits should be taken into account when interpreting epidemiological data. This was not always the case. As is shown in the Dutch cohort of the IARC multicenter study, correcting for smoking weakened the association between bitumen fume exposure and lung cancer risk.

Correlation between exposure and adverse health effects. At the moment, it is uncertain how well available exposure parameters correlate with the observed adverse health effects, and thus what can be measured to monitor workplace exposure. Several reasons account for that, including: a limited dataset; lack of clarity on the bitumen constituent or constituents that are responsible for the adverse health effects; and, unknown co-exposure in the past. These factors are in particular a problem for long-term health effects.

Most likely none of these bias and uncertainties dominate the final outcome. It is the overall uncertainty that complicates quantitative risk assessment of bitumen fume exposure. However, the committee is of the opinion that the presence of these uncertainties should not preclude a judgement regarding human health in an occupational environment.

8.2 Hazard identification

8.2.1 Carcinogenicity

A main concern to the committee is whether exposure to bitumen (vapour and aerosol) may induce or promote cancer. This is important to know because certain constituents in the particulate matter of bitumen fumes are known carcino-

gens, such as the high molecular polycyclic aromatic hydrocarbons and certain heterocyclic aromatic compounds. In addition, bitumen fumes may contain yet unknown carcinogenic constituents.

A lot of effort has been directed at finding an association between occupational exposure and cancer risk, in particular lung cancer risk. However, the results on lung cancer risk in epidemiological studies are inconsistent, which could partly ascribed to (confounding) factors that were present in part of these studies. In a recently well-performed large and powerful multicenter cohort study, assembled by IARC, a small but statistically significant association was found between lung cancer mortality and average bitumen fume exposure among bitumen workers. Further research is now going on to control for possible confounders in this multicenter cohort study. Overall, the evidence that bitumen fume exposure may cause lung cancer is weak. It is still unclear whether bitumen fumes or other substances, that were also present in the workplace, were responsible for the observed effects. Also evidence for an association between bitumen fume exposure and cancer at other sites than the lung is weak and inconsistent. However, as long as it is not excluded that bitumen fumes are carcinogenic, epidemiological data show that there is a cause for concern.

So far, no evidence was found in animals that chronic inhalation of laboratory-generated or -regenerated bitumen fume induces lung tumours. Some investigators, but not all, found benign and malignant skin tumours in several strains of mice when they were dermally exposed to laboratory-generated roofing bitumen fume condensates or formulations from bitumen-based paints. Overall, animal data are too limited to conclude whether bitumen fume exposure will result in lung and skin cancer.

Bitumen products and condensates of bitumen fume have been tested for genotoxicity. No mutagenic activity was found *in vivo*, while *in vitro* the activity appeared to depend on the generation and collection method. Overall, because during heating of bitumen products fumes are released that may contain carcinogenic PAH and/or PAC, it is expected that these fumes have some level of genotoxic potential, although the amount of these carcinogens in those fumes may be low.

8.2.2 *Non-carcinogenic adverse health effects*

Overall, most complaints from workers who are exposed to bitumen fumes concern irritation of the upper respiratory tract (i.e., coughing, dry throat, nasal discharge and nose bleeding). Also shortness of breath and asthma have been reported in some but not all studies. Up to now, investigators were, however, not

able to correlate the extent of bitumen fume exposure to these respiratory health effects or to establish clear exposure-response relationships. Several reasons may account for this, as stated earlier in this report, one being simultaneous exposure to other substances, which is in practice a common situation, and another being lack of clarity whether vapours are responsible for the observed effects. However, irrespective the causal agent and possible interpretation errors, it should be kept in mind that among road paving workers respiratory health symptoms were more frequently reported at concentrations (geometric mean) at or below 1.0 mg TPM/m^3 and 0.4 mg BSM/m^3 compared to unexposed maintenance workers. Furthermore, in some studies general symptoms have been reported, such as nausea, stomach pain, and headache, but the data are too limited to correlate these effects to bitumen fume exposure only.

The limited data from short- and long-term animal studies show comparable respiratory tract effects after inhalatory exposure as in humans; in one subchronic study, upper respiratory tract effects were only observed in rats at 100 mg/m^3 (total hydrocarbon from bitumen aerosol and vapour) (NOAEL, 20 mg/m^3). In most studies animals were dermally exposed to bitumen fume condensates or solutions. The results from these studies indicate irritating skin effects, such as dermatitis, and on chronic exposure ulcers and abscesses. Irritation to the skin was also observed in humans.

Since the set of human and animal data is limited, combined with the presence of bias and other uncertainties, quantitative risk assessment based on non-carcinogenic effects is not justified.

No human data are available which addresses bitumen fume exposure to effects on reproduction and progeny. Nor are there any animal data published on this subject. Therefore, the committee is not able to classify the substance as toxic to the reproduction and progeny.

8.3 Conclusion and recommendation

The quantitative risk assessment is hampered by insufficient information and the presence of confounding factors. Of main concern is the absence of a clear dose-response relationship, the uncertainty how well available exposure parameters correlate with the observed adverse health effects, and the influence of confounding factors in the epidemiological studies.

More research is needed to shed more light on these problems, and to get more evidence that the critical effect of bitumen fume exposure is upper respiratory tract irritation or lung cancer. Regarding this, the committee is aware of ongoing research in humans and animals. These include a large nested-case con-

trol study from the data obtained from the IARC multicenter study and a human study among paving workers. All these studies are performed under the currently accepted standards. Furthermore, IARC has put bitumen on a list to be evaluated within a few years. The committee expects that these studies and evaluations will be a valuable contribution to the risk assessment of bitumen.

Taking all the available carcinogenic and genotoxic data into account, including the expectation that fumes of heated bitumen may contain carcinogenic PAH and or PAC, the committee is of the opinion that there is a cause for concern that bitumen (vapour and aerosol) is carcinogenic. However, the evidence for carcinogenicity is weak, and further experiments are necessary before a final conclusion can be drawn. Therefore, the committee recommends classifying bitumen (vapour and aerosol) as a suspected human carcinogen that has been insufficiently investigated. This recommendation corresponds to EU classification in category 3. The situation is furthermore comparable with subcategory b of this category, as is explained in annex O and P in this report.

At the moment the committee considers the reliability of the available data too limited to provide a health-based recommended occupational exposure limit. Therefore, it abstains from making such a recommendation.

8.4 Additional consideration

Bearing in mind the considerations and conclusions in the previous section, and irrespective of the confounding co-exposure and tobacco smoking practices, human data indicate irritation of the upper respiratory tract. It should be noticed that among road paving workers respiratory health symptoms were more frequently reported at concentrations (geometric mean) at or below 1.0 mg TPM/m^3 and 0.4 mg BSM/m^3 compared to unexposed maintenance workers. These exposure concentrations concern particles or aerosols. The committee emphasises that it might be that symptoms of irritation are caused by bitumen vapour.

Some animal skin painting studies indicate that exposure to bitumen fume condensates or solutions cause skin cancer, though other animal skin painting studies could not confirm this. Skin absorption studies showed also that carcinogenic components (polycyclic aromatic hydrocarbons) present in bitumen fume condensates are absorbed by the skin. Although data on skin carcinogenesis are weak, the committee cannot rule out that chronic exposure to bitumen fume causes skin cancer. This may warrant a skin notation.

Finally, the committee desires to re-evaluate the adverse health effects of exposure to bitumen (vapour and aerosol), including the carcinogenic classifica-

tion, as soon as the outcome of the above mentioned on-going epidemiological and animal studies have been presented.

8.5 Groups at extra risk

According to the committee, it is possible that personal health factors, such as pre-existing asthma, may increase workers risk for lower respiratory tract symptoms (coughing, wheezing, shortness of breath) or changes in pulmonary function, although the current data are insufficient to determine the relationship with bitumen fume exposures.

Chapter 9

Research needs

More information is needed to assess completely the health risks associated with exposure to bitumen (vapours and aerosols). As NIOSH (2000)[1] stated, the main question to be answered are:

1 What health effects are associated with exposure to bitumen fumes?
2 What bitumen constituent(s) is/are responsible for the acute and chronic adverse health effects?
3 What bitumen constituent(s) should be used as the metric for monitoring workplace exposure?
4 What is an appropriate health-based occupational exposure limit for bitumen fume that will prevent any adverse health effect?

To answer these questions various studies need to be performed. These include: studies on exposure parameters; epidemiological studies on exposure and adverse health effects; dose-response studies; short- and long-term animal studies; and, carcinogenicity and genotoxicity studies.

Research is ongoing to partly elucidate these questions.

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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 committee

- G.J. Mulder, *chairman*
  professor of toxicology; Leiden University, Leiden
- R.B. Beems
  toxicologic pathologist; National Institute of Public Health and the Environment, Bilthoven
- L.J.N.G.M. Bloemen
  epidemiologist, Environ, The Netherlands
- P.J. Boogaard, *advisor*[*]
  toxicologist; Shell International, The Hague
- P.J. Borm
  professor of inhalation toxicology; Centre of Expertise in Life Sciences, Hogeschool Zuyd, Heerlen
- J.J.A.M. Brokamp, *advisor*
  Social and Economic Council, The Hague
- D.J.J. Heederik
  professor of risk assessment in occupational epidemiology; IRAS, Utrecht University, Utrecht
- TM Pal
  occupational physician; Netherlands Center for Occupational Diseases, Amsterdam

* Due to conflict of interest P Boogaard is acting as advisor for this report, and not as a member.

- I.M.C.M. Rietjens
  professor of toxicology; Wageningen University, Wageningen.
- T. Smid
  occupational hygienist epidemiologist; KLM Health Safety & Environment, Schiphol; and, professor of working conditions; Free University, Amsterdam
- G.M.H. Swaen
  epidemiologist; Dow Benelux NV, Terneuzen
- R.A. Woutersen
  toxicologic pathologist; TNO Nutrition and Food Research, Zeist
- P. Wulp
  occupational physician; Labour Inspectorate, Groningen
- J.M. Rijnkels, *scientific secretary*
  Health Council of the Netherlands, The Hague

The first draft of the present report was prepared by MI Willems, RA Bausch-Goldbohm and ED Kroes of TNO Chemistry, Toxicological Risk Assessment, Zeist, the Netherlands, by contract with the Ministry of Social Affairs and Employment.

P. Gooskens, Ms. M. Javanmardi and Ms. F. Smith provided secretarial assistance. Lay-out: Ms. M. Javanmardi and Ms. J. van Kan.

The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the President and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the establishment meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.

Annex **C**

Comments on the public review draft

A draft of the present report was released 2005 for public review. The following organisations and persons have commented on the draft document:

- H. Roos, VBW Asfalt, the Netherlands
- J. Sturm, European Asphalt Pavement Association, Belgium
- K. Soraas, European Bitumen Association, Belgium
- P.T. Grass, Asphalt Institute, the USA
- R.D. Zumwalde, National Institute for Occupational Safety and Health, the USA.

Annex **D**

Glossary of terms

Terms are obtained from Concawe[4], NIOSH[1], Partanen *et al*.[6] and IPCS[3].

Asphalt: Paving material that contains mineral aggregate (usually sized stone fractions, sands, and a filler, such as limestone) coated and cemented together with a binder (bitumen; previously also tar and coal tar pitch). In North America the term is commonly used to refer to bitumen only.

Asphalt hot mix: The term commonly used in North America to refer to asphalt as a paving material.

Bitumen: The product of non-destructive distillation of crude oil in petroleum refining. It is a dark solid or semisolid material that is predominantly composed of asphaltenes, straight and branched aliphatic hydrocarbons, naphthene aromatics, and resins. The vacuum distillation removes most of PAH with three to seven benzenoid rings.

- ***Penetration grade bitumens:*** Bitumens that are usually produced from crude petroleum oil atmospheric distillation residues by using further processing, such as vacuum distillation, thermal conversion, partial oxidation (air-rectification/semi-blowing) or solvent precipitation. They are principally used for road surfacing and roofing.

- ***Hard bitumens:*** These bitumens are produced using similar processes to penetration grades but have lower penetration values and softening points. They are mainly used to manufacture bitumen paints and enamels.
- ***Oxidized bitumens (air blown):*** Bitumens that have been treated by blowing air through it at elevated temperatures to produce physical properties required for the industrial use of the final products. Applications include use in roofing materials, and waterproof papers.

Bitumen fumes: The cloud of small particles created by condensation from the gaseous state after volatilization of bitumen.

Processed bitumens: bitumens that are processed to meet specific properties. Examples are:

- ***Bitumen emulsion***: Emulsified bitumen.
- ***Cutback bitumen:*** A derivate of bitumen that is liquefied by the addition of diluents (typically petroleum solvents). It is used in both paving and roofing operations.
- ***Bitumen cement:*** Bitumen that is refined to meet specifications for paving, roofing, industrial, and special purposes.
- ***Mastic bitumen:*** A mixture of bitumen and fine mineral material in proportions such that it may be poured hot into place and compacted by hand-troweling to a smooth surface.

Coal tar: A tar that contains polycyclic aromatic compounds and is produced by the destructive distillation of bituminous coal.

Coal tar pitch (CTP): A black or dark brown cementitious solid that is obtained as a residue in the partial evaporation or fractional distillation of coal tar.

Coal tar pitch volatiles (CTPV): Volatile matter emitted into air when coal tar, coal tar pitch, or their products are heated.

Annex **E**

Identity of bitumens and bitumen vacuum residues

Source: Concawe 1992.[11]

Bitumen (asphalt) Cas no. 8052-42-4 EINECS 232-490-9	A very complex combination of high molecular weight organic compounds containing a relatively high proportion of hydrocarbons having carbon numbers predominantly greater than C_{25} with high carbon-to-hydrogen ratios. It also contains small amounts of various metals such as nickel, iron or vanadium. It is obtained as the non-volatile residue from distillation of crude oil or by separation as the raffinate from a residual oil in a deasphalting or decarbonisation process.
Vacuum residues (petroleum) CAS no. 64741-56-6 EINECS 265-057-8	A complex residuum from the vacuum distillation of the residuum from atmospheric distillation of crude oil. It consists of hydrocarbons having carbon numbers predominantly greater than C_{34} and boiling above approximately 495 °C (923 °F).
Hydrosulphurized vacuum residues (petroleum) CAS no. 64742-85-4 EINECS 265-188-0	A complex combination of hydrocarbons obtained by treating a vacuum residuum with hydrogen in the presence of a catalyst under conditions primarily to remove organic sulphur compounds. It consists of hydrocarbons have carbon numbers predominantly greater tan C_{34} and boiling approximately above 495 °C (923 °F).
Oxidized asphalt CAS no. 64742-93-4 EINECS 265-196-4	A complex black solid obtained by blowing air through a heated residuum, or raffinate from a deasphalting process with or without a catalyst. The process is principally one of oxidative condensation, which increases the molecular weight.

Asphaltenes (petroleum) CAS no. 91995-23-2 EINECS 295-284-8	A complex combination of hydrocarbons obtained as a complex solid black product by the separation of petroleum residues by means of a special treatment of a light hydrocarbon cut. The carbon/hydrogen ratio is especially high. This product contains a low quantity of vanadium and nickel.
Thermal cracked vacuum residues (petroleum) CAS no. 92062-05-0 EINECS 295-518-9	A complex combination of hydrocarbons obtained from the vacuum distillation of the products from a thermal cracking process. It consists predominantly of hydrocarbons having carbon numbers predominantly greater than C_{34} and boiling above approximately 495 °C (923 °F).
Dewaxed heavy paraffinic vacuum residues (petroleum) CAS no. 94114-22-4 EINECS 302-656-6	A complex combination of hydrocarbons obtained as a residue from the molecular distillation of a dewaxed heavy paraffinic distillate. It consists of hydrocarbons having carbon numbers predominantly greater than C_{80} and boiling above approximately 450 °C (842 °F).
Distillation. Residue hydrogenation residues (petroleum) CAS no. 100684-39-7 EINECS 309-712-9	A complex combination of hydrocarbons obtained as a residue from the distillation of crude oil under vacuum. It consists predominantly of hydrocarbons having carbon number predominantly in the range above C_{50} and boiling in the range above approximately 360°C (680 °F).
Vacuum distillation. Residue hydrogenation residues (petroleum) CAS no. 100684-40-0 EINECS 309-713-4	A complex combination of hydrocarbons obtained as a residue from the distillation of crude oil under vacuum. It consists predominantly of hydrocarbons having carbon number predominantly in the range above C_{50} and boiling in the range above approximately 500°C (932 °F).

Annex **F**

Epidemiological data on skin effects of bitumen (fume) exposure

study design and population information	exposure and health assessment information	skin effects	notes
Non-carcinogenic effects			
Data evaluated from: Tavris *et al.* 1984; Schaffer *et al*. 1985 Waage and Nielson 1986; Chase *et al.* 1994; and Miller and Burr 1996a,b, 1998. (ref. IPCS 2004[3])		Skin irritation, pruritus, or rashes.	WHO commented that the presence of confounding co-exposure and environmental conditions might have influenced the results.
Retrospective review covering a period of 10 year (1985-995); 92 patients treated for bitumen burns. (ref. Baruchin *et al*. 1997[47])	Exposure to hot bitumen by direct contact.	Skin burns due to hot bitumen.	Does not concern fume exposure.
Not available. (ref. Schwartz *et al*. 1957 (source DFG)[2]	Prolonged skin contact.	Dermatitis, acne-like changes and keratosis. Effects were less severe than those caused by coal tar.	

Israel; retrospective-study; 50 workers exposed to bitumen-asphalt vapour during production or during road or roof construction work. (ref. Schaffer *et al*. 1985[50])	Exposure was for 8 hours per day for at least 6 months without a break. Minor airborne concentrations of PAH were measured.	Sequelae of burns (9.7%), hyperkeratosis on the hand (14.6%), xeroderma (12.6%), contact dermatitis (7.8%), nail damage (4.8%), infections and mycoses (21.5%), basocellular mainly premalignant epitheliomas (solar keratosis) (14.5%); including two cases of epithelioma basalis, and dermatitis resulting from photosensitisation (14.5%).	
Finland retrospective study; 50 roofers and 101 road pavers. (ref. Riala *et al*. 1998[49])	Health assessment by questionnaire. 48% of the road pavers and 58% of the roofers responded on the questionnaire.	Skin irritation: 44% of the studied roofing workers, 31% of the studied road construction workers. Dermatitis (often or sometimes): 15% of the roofers and 22% of the road construction workers.	Co-exposure with man-made mineral fibres and amine-containing products likely.
Case report (ref. Lübbe *et al*. 1996[133])		One case of facial discoid lupus erythematosus one month after accidental skin contact with cold liquid bitumen (cutback, solvents: toluene and benzene).	
The United Kingdom; case report; 28 Dockyard workers (ref. Davies 1996[4])	Health assessment performed during 2 to 3 days after outbreak of bitumen containing fine dust, from 'hotblack' paint, after a shot blasting operation. The workers were involved in dismantling and/or cleaning up.	Symptoms varied from erythrema, through oedema, to vesiculation and exudation in 3 cases. Examination of the skin 3 to 4 months later showed no permanent sequelae.	
Carcinogenic effects			
Case report. (ref. Peila *et al*. 1999[134])	Accidental bitumen exposure by dermal contact.	One case of malignant acral melanomas was found after skin burn caused by bitumen.	Does not concern fume exposure.
Retrospective register-based study, Denmark; data obtained from the Danish registry agencies; period data collection 1984-1994. (ref. Lei *et al*. 2001[135])	Only data on non-melanoma skin cancer (NMSC) were analysed. Associations were made between certain professions.	74 cases of NMSC were identified. Eleven of them were occupationally exposed to "bitumen, tar and such-like".	Cases could have been exposed to both bitumen fumes and coal tar fumes.

Denmark; historical cohort study; 679 mastic bitumen workers; follow-up period 1959-1984 (ref. Hansen 1989[64])	Mastic asphalt was a mixture of sand, stone powder, and finely divided limestone with a high content (12-17%) of hard bitumen. Mastic asphalt was heated before use (storage temperature 250 °C). Concentration of bitumen fume condensate (personal samples): mean 41 mg/m^3 (median, 19,7 mg/m^3; range, 0.5-260 mg/m^3). Concentration of total PAH (workplace air): mean, 0.20 mg/m^3; median, 0.18 mg/m^3.	Non-melanoma skin cancer: Standardized morbidity ratio (SMR): 67 (95% CI, 0.14-1.96). Observed no. of cases 3, expected 4.9.
Mortality surveillance among highway maintenance employees of the Californian Department of Transportation; 1,570 deaths cases between 1970-1983. (ref. Maizlish *et al*. 1988[46])	Highway workers were exposed to various compounds, such as hot bitumen and bitumen fumes, asbestos, solvents, pesticides, hydrogen sulphide and diesel exhaust.	Standardized proportional mortality ratio for skin cancer was 2.18 (observed, 14 cases, expected, 6.4 cases; 95% CI, 1.19-3.66).
Mortality surveillance among roofers and waterproofers aged 20 years or more; 1,798 death cases between 1960 and 1971.Male population of the USA served as control group. (ref. Hammond *et al*. 1976[136])	Most of the workers were exposed to both hot coal tar pitch and bitumen fumes.	Standardized mortality ratio for skin cancer (except melanomas) was 4.00 (observed, 3 cases; expected, 0.75 cases; 95% CI, 0.83-11.7).

Annex **G**

Epidemiological studies on the *non-carcinogenic* effects of bitumen fume exposure

study design and population information	exposure and health assessment information	health effects	limitations and potential biases
Road paving and maintenance operations			
European historical cohort study; 12,367 male asphalt paving workers from Denmark, Finland, France, Germany, Israel, the Netherlands and Norway; earliest follow-up in 1953, latest ended in 2000, average 17 years of follow-up. (ref. Burstyn *et al*. 2005[54])	Exposure data: benzo[a]pyrene (BaP) was assessed quantitatively using measurement-driven exposure models. Study focussed on fatal ischemic heart disease (IHD).	Cumulative BaP exposure of >2,013 ng/m^3-yrs: 85 deaths, relative risk for IHD was 1.58 (95%CI, 0.98-2.55). Average BaP exposure of >273 ng/m^3: 83 deaths, relative risk for IHD was 1.64 (95%CI, 1.13-2.38).	Although authors were not able to control for all possible sources of confounding and bias, their results support the hypothesis that occupational exposure to BaP (PAH) causes fatal ischemic heart disease.

Cross-sectional study, Norway; 333 exposed pavers (79 pavers with personal exposure monitoring (group I), 254 pavers no personal exposure monitoring (group II)); and 247 controls (maintenance workers, group III). (ref. Norseth *et al.* 1991[51], 2000[52])	Exposure data: bitumen fume concentration (total organic compounds), average 0.36 mg/m^3. Concentration of bitumen vapour was mostly below 5 mg/m^3. Health assessment included standardised self-administered questionnaires; smokers and non-smokers separated. Response rate: group I: 100%, group II: 57%, group III: 70%.	Symptoms reported more in pavers than in controls: fatigue, reduced appetite, eye irritation, laryngeal-pharyngeal irritation; no differences between pavers and controls for symptoms of: headache, dizziness, nausea, abdominal pain, disturbed sleep, skin reactions, or a 'smell of sweetness'. Symptom sum scores: increased with increasing bitumen fume concentration (total organic compounds) ($p<0.05$); increased with increasing bitumen temperatures ($p<0.01$).	Comments of NIOSH: use of self-administered questionnaires; variations in response rate among different groups; lack of control for smoking in all analyses. Comments of DFG: a dependence effect on health and bitumen emissions could not be demonstrated. After a re-analysis, authors claimed that there was no relationship anymore between bitumen fume exposure and symptom scores.
Analysis of seven cross-sectional studies, performed by NIOSH and FHWA on exposure during open-air highway paving operations; 52 workers exposed to bitumen during paving with hot-mix bitumen; 42 non-exposed controls. (ref. Burr 2001[53], Tepper *et al.* (2006)[137])	Exposure to crumb-rubber modified (CRM) and unmodified bitumen. Personal breathing-zone sampling: all samples below 1.4 mg/m^3 total particulates (8-h TWA); geometric mean, range 0.06-0.81 mg/m^3); Geometric means benzene-soluble particulates, range 0.02-0.44 mg/m^3; on average below 0.5 mg/m^3 bitumen fume (8-h TWA). Medical evaluations conducted over 4 days, included questionnaire about acute health effects, smoking and work history, and lung function tests.	Odds ratios (95% CI) are based on person-days with symptoms. Data concern unmodified bitumen fume exposure only: - burning, itchy, stuffy, or irritated nose: 2.4 (0.8-7.2); - burning, itchy, painful, or irritated eyes: 1.4 (0.4-4.7); - sore, dry, scratchy, or irritated throat: 3.6 (1.1-11.8); - cough: 2.7 (0.6-11.9). Airborne concentrations of TP, BSP and PAC were significantly higher on days when symptoms of the eye, nose or throat were present. In general, workers exposed to CRM bitumen fumes had higher odds ratios than workers exposed to unmodified bitumen fumes.	Authors noted the possibility of reporting bias because workers were aware of type of exposure and possible acute health effects. DECOS noted the small population under study. A comparable analysis on the same data with comparable results was performed by Tepper *et al*.
Survey, Denmark; 166 pavers. (ref. Hasle *et al.* 1977 (cited from Fries and Knudson, 1990)[138])	No exposure values or dose-response information was provided.	Chronic bronchitis was reported in 25% of the workers. Difficulty in breathing in 40% of the workers.	Study results were not published.
Norway; pavers (ref. Waage and Nielson 1986 (cited from Fries and Knudson, 1990)[138])	No exposure values or dose-response information was provided.	Among workers significantly higher prevalences of smarting eyes, stomach pains, and skin irritation. Also, increased incidences of headaches, dizziness, sleepiness, nausea, reduced appetite, and markedly reduced lung function.	Study results were not published.

Former East Germany; 34 road construction workers; graveyard workers served as control group. (ref. Bittighofer *et al.* 1983[139])		No increase in incidence of bronchial or pulmonary disorders compared to control group.	Comments of DFG: poorly documented study.
Retrospective cohort study, the USA; 4,849 highway maintenance workers, who worked more than one year during the period 1945-1984. (ref. Parker *et al.* 1989[140])	No exposure data. Information obtained from 1,530 death certificates. Subjects were classified as either rural or urban workers.	Standardised mortality ratio (SMR) for all diseases, 0.91 ($p<0.01$), which was lower than expected; SMR for chronic renal failure among (long-term) rural workers was significantly elevated (SMR 6.76, 3 cases, $p<0.05$). However, these results appear unlikely to be related to maintenance work.	
Cross-sectional study, Australia; 92 road workers regularly exposed to bitumen fumes; 38 hard rock quarry workers and 43 office workers served as control groups. (ref. Douglas and Carney 1998[141])	No actual exposure measurements. Health assessment included questionnaires, blood and urine biochemistry.	Study focused on renal disorders. Authors concluded that road workers were far more likely to have evidence of early stage renal disease than controls. Renal dysfunction was non-specific.	Comments: study presented as a summary only.
Cross-sectional study, Australia; 41 road construction workers; 35 quarry workers served as controls. (ref. Carney and Ferguson 1998[142])	No information.	Study focused on renal disorders and cardiovascular risk. No significant differences found between the two groups.	
Case-control study; 16 male road construction workers; 12 unexposed male controls. (ref. Karakaya *et al.* 1999[55])	Exposure was assessed by determining levels of urinary 1-hydroxypyrene excretion (indicator for PAH exposure).	Study focused on immunological functions (analyses on T-cell subsets, B-cells, serum immunoglobulin levels and white blood cell percentages). According to the authors, data suggest that chronic exposure to PAH may affect some immune functions in humans.	
Roofing operations			
Survey, the USA; 34 roofers; also exposure to coal-tar pitch and fibreglass. (ref. Hervin en Emmett 1976[143])	All air samples were below 5 mg/m^3 for bitumen fumes, and 10 mg/m^3 for fibreglass; exposure to coal-tar pitch volatiles and bitumen fumes not evaluated separately. Medical interview and limited physical exams.	Skin problems (burning, irritation and blistering): 68% of the roofers; eye irritation: 56% of the roofers; 18% had conjunctivitis. Symptoms are correlated to coal tar pitch exposure and not to bitumen fume exposure.	Comments of NIOSH[1]: small sample size; lack of control group; presence of possible confounding factors, such as co-exposure with coal tar or fibreglass.

Survey, the USA; 50 roofers. Also exposure to coal-tar pitch and fibreglass. (ref. Emmet 1986[144])	Exposure to coal-tar pitch volatiles and bitumen fumes not evaluated separately. Health assessment by questionnaires.	Skin and eye complaints were correlated to coal tar pitch exposure and not to bitumen fume exposure. No information given to complaints other than skin and eye irritation.	Comments of NIOSH[1]: small sample size; lack of control group; presence of possible confounding factors, such as co-exposure with coal tar or fibreglass.
Survey, former East Germany; 6 roofers with more than 20 years of working experience. Five of them were smokers. (ref. Maintz *et al.* 1987[145])		Four of the workers were diagnosed with chronic bronchitis (recognised as an occupational disease) and five of them had a history of obstructive pulmonary function.	Comments of NIOSH[1]: small sample size; lack of control group; presence of possible confounding factors, such as smoking.
Case-control study, the USA; 25 cases of non-malignant respiratory diseases (NMRD, excluding influenza and pneumonia) and 80 controls. Cases and controls were identified among deaths occurring between 1977-1997. (ref. Watkins *et al.* 2002[59])	Lifetime cumulative exposure before 1977 was estimated. Controls were matched by age, race and gender. History of smoking was only available for approximately 65% of subjects in study.	Results of the analyses were presented as unadjusted odds ratios (unORs). Only the unOR for smoking was statistically significantly elevated. These results suggest that smoking habits contributes more strongly to NMRD than bitumen exposure.	The authors caution that the study is limited by missing data on smoking habits and work history. Also, exposure to bitumen occurred simultaneously with asbestos exposure. IPCS[3] noted that cases and controls were selected from among deaths of active and retired employees, and not from among any workers ever employ-ed at these facilities.
Registry-based nationwide follow-up study, Finland; 2,548 construction workers; reference Finnish population; follow-up 1986-1998. (ref. Karjalainen *et al*. 2002[146])	Age adjusted relative risks for asthma were estimated for 24 different construction occupations. The main agent to which bitumen roofing workers were exposed was a bitumen product.	RR for adult-onset asthma for bitumen roofing workers: 2.04 (8 cases, 255 population; 95% CI, 1.02-4.09). Conclusion authors: construction workers have an increased risk of adult-onset persistent asthma.	The study only concerns the presence of asthma. Furthermore, the authors reported of 45 cases that had been recognized as occupational asthma among construction workers, but none of these cases was correlated with bitumen fume exposure (in 4 cases the causative agent could not be found).
Paving and roofing operations			
Cross-sectional study, Sweden; 194 road pavers, 37 roofers, and matched control group. (ref. Nyqvist 1978[147])	No data on actual exposure. Health assessment by self-administered questionnaires, lung function testing. Data on pavers and roofers not separated.	Incidence of complaints of bronchitis symptoms increased with increasing period of exposure. No significant differences in lung function found between matched controls and exposed workers.	Comment of NIOSH[1]: no information on response rate; possible recall-bias; reported years of exposure may not reflect actual exposure.

Israel; retrospective study; 50 workers exposed in bitumen production or during use (road and roofing operations); 15 controls (factory metal-workers). (ref. Schaffer von *et al*. 1985[50]	Exposure was for 8 hours per day for at least 6 months without a break. Minor airborne concentrations of PAH were measured. Health assessment: biochemical and radiological analyses, and lung function tests.	Symptoms reported were irritation of the respiratory passages (feeling of dryness and coughing). Most workers had symptoms of chronic bronchitis. No symptoms reported in controls. Biochemical and lung function tests were normal.	
The USA; 170 bitumen-exposed workers (hot-mix plants, n=11; terminals, n=24; roofing manufacturers, n=43; roofers, n=37; and pavers, n=55) (ref. Gamble *et al.* 1999[22])	Personal exposure data (benzene soluble particulates, 8-h TWAs, geometric mean): open-air paving, 0.09 mg/m^3 (max 0.65 mg/m^3); roofing application, 0.12 mg/m^3 (max 1.2 mg/m^3); roofing manufacturing, 0.08 mg/m^3 (max 1.3 mg/m^3); refineries/ bitumen distribution terminals, 0.05 mg/m^3 (max 1.3 mg/m^3); hot-mix bitumen plants, 0.06 mg/m^3 (max 0.14 mg/m^3). Health assessment included standardised respiratory health questionnaire, serial symptom surveys, and serial lung function tests.	Most symptoms were reported to be mild, and concerned: breathing difficulty, nose irritation, headache, throat irritation, and coughing. No correlation between exposure and symptoms found. No associations found between exposure and lung function tests, smoking frequency, or symptom score.	Comments of NIOSH[1]: small sample sizes from each industry segment; very few data on higher exposure concentrations; possible lack of correlation between 8-hr average exposure measurements and assessed health effects; lack of control group.
Other operations			
Survey, Italy; 22 workers who insulated electrical cables and telegraph and telephone lines. (ref. Zeglio 1950[148] (source NIOSH, DFG, IPCS)[1-3])	Authors raise possibility of residual exposure to coal tar pitch. Health assessment by questionnaires and physical examinations.	Complaints reported: coughing, burning in the throat and chest, hoarseness, headache and nasal discharge. Reported symptoms diminished after leaving work. Workers with longer length of exposure had more instances of chronic nasal, pharyngeal and pulmonary symptoms. Clinical examination revealed rhinitis (n=10), oropharyngitis (n=13), laryngitis (n=4) and bronchitis (n=19).	Comment of NIOSH: small sample size; no control group; possible confounding exposure with coal tar.
Survey, the USA; 462 bitumen workers from 25 American asphalt/ petroleum refineries, who had worked at least 5 years in this industry; 379 controls. (ref. Baylor and Weaver 1968[149])	Questionnaires (obtained from medical personnel) on medical history, occupational history and smoking history. Also physical examination was performed. Average duration of employment, 15.1 years.	No significant differences in cancer, lung disease, and skin disease between workers and controls. The number of miscellaneous lung diseases (bronchitis, asthma, emphysema) was more frequent among workers (8.6% versus 4.3% in controls).	Comment of NIOSH[1] and DFG[2]: study is of limited value because of poor documentation.

Survey, the USA; 15 workers involved in the production of fibrous glass bitumen roofing shingles. (ref. Apol and Okawa 1977 (source NIOSH, IPCS)[1,3])	Also intermittent and variable exposure to mineral dust, felt, and glue. Health assessment by medical interviews and limited physical exams. Average duration of exposure, 7 years.	Most frequently reported health symptoms: nasal irritation (47%), throat irritation (47%), and eye irritation (40%).	Comments of NIOSH[1]: small sample size; lack of control group; lack of evaluation of the relationship between specific work exposures and reported health symptoms.
Survey, the USA; 18 workers in the production of bitumen shingles and rolled roofing materials. (ref. Okawa and Apol 1977[150])	Exposure included not only bitumen fumes, but also dust (limestone) and PAH. Exposure to bitumen fumes could not be adequately determined. Health effects based on interviews.	There were only signs of respiratory irritation.	Study is of limited value because of the small population size and co-exposure with dust and PAH was likely. Only a part of the affected workers (18/50) in the plant were interviewed.
Survey, the USA; 27 symptomatic female workers in a commercial lighting factory exposed to bitumen fumes. Symptoms were reported after introduction of a new bitumen formulation in the plant in the production process. Laboratory workers (n=107) served as reference group. (ref. Chase *et al.* 1994[151])	Health assessment included: interviews, questionnaires, physical examinations, spirometry, blood tests for hepatic, renal functioning, and haematology.	All workers reported symptoms related to central nervous system, ears, nose, and throat. Other symptoms reported were related to: eyes (93%), gastro-intestines (89%), respiratory system (59%), and skin (41%). Physical examinations revealed: conjunctivitis (11%), nose bleeding (52%), throat irritation (59%), and skin rash (15%). No effects on liver, kidneys or lungs (spirometry). Average volume of blood platelets was significantly increased (11/27), but declined after reduction of the exposure.	The study is of limited value because no bitumen fume exposure assessment was performed. It is, furthermore, likely that co-exposure to additives took place.
Survey; 19 individuals employed in an office complex, with an outbreak of physical illness resulting from exposure to volatilised bitumen (overheated fluorescent light ballasts). (ref. Tavris *et al.* 1984[152)])	No data on bitumen fume exposure. Health assessment conducted in 15 of the 19 individuals: interviews, and blood samples.	The most frequently reported symptoms were: headache, eye irritation, sore throat, nasal congestion, nausea, light-headedness, and itchy skin. The symptoms disappeared when the rest of the melted bitumen was removed.	Study did not include a control group. Exposure concerns accidental short-term exposure and is likely not representative for bitumen fume exposure in road paving and roofing.
Case-control study; Fibreglass insulation production facility, the USA; 101 non-malignant respiratory disease cases and 183 matched controls. (ref. Chiazze *et al.* 1993[153])	Quantitative estimates of lifetime exposure to asbestos, talc, bitumen fumes, formaldehyde and silica presented. Bitumen exposure was expressed as "never exposed" or exposed to "$\geq$ 0.01 mg/m^3 days". Data were adjusted for age, smoking and occupational exposure.	Odds ratio for non-malignant respiratory diseases in the bitumen-exposed group, 1.3 (95% CI, 0.82-2.2). No further details given on non-neoplastic diseases.	

Annex **H**

Cohort studies on the *carcinogenic* effects of bitumen fume exposure

study design and population information	exposure and health assessment information	mortality or morbidity rates	notes
Road paving and maintenance operations			
Cohort study in Sweden; 2,572 road pavers; follow-up 1971/1979-1984; average length of follow-up period for mortality was 11.5 years; median age during follow-up was 42 years. (ref. Engholm *et al.* 1991[66])	No quantitative information on exposure.	Standardised incidence ratios: all cancers (47 cases; SIR, 0.86), stomach cancer (6 cases; SIR, 2.07), and lung cancer (8 cases; SIR, 1.24). Standardised mortality ratios: all causes (96 cases; SMR, 0.69), stomach cancer (5 cases; SMR, 2.01), lung cancer (7 cases; SMR, 1.10). No information given on statistical significance or 95% confidence intervals.	Limitations include short latency period and lack of data on exposure. Also the number of cases is small.
Mortality surveillance among highway maintenance employees of the Californian Department of Transportation; 1,570 deaths cases between 1970-1983. (ref. Maizlish *et al.* 1988[46])	Highway workers were exposed to various compounds, such as hot bitumen and bitumen fumes, asbestos, solvents, pesticides, hydrogen sulphide and diesel exhaust. No data on smoking habits available.	Data concerns maintenance workers only. Proportional mortality rates: all cancers 1.2 (95% CI, 0.9-1.5), digestive organs 1.5 (95% CI, 1.0-2.2), lung cancer 1.0 (95% CI, 0.6-1.5).	Authors state that study is inherently limited by lack of independence among causes of death.

Retrospective mortality study, the USA; 4,849 highway maintenance workers employed for at least one year; follow-up 1945-1984; reference group, male population in Minnesota. (ref. Bender *et al.* 1989[45])	Workers are exposed to bitumen, diesel fuels and exhaust, gasoline, polynuclear aromatic hydrocarbons, herbicides, benzene and lead. Highway maintenance work has not employed coal-tar products for 50 years in Minnesota.	During the follow-up 1,530 deaths were recorded. Standardised mortality ratios: leukaemia (30-39 years in the job; 7 cases; SMR, 4.25; 95% CI, 1.71-8.76), urologic cancer (40-49 years latency period; SMR, 2.92; 95% CI, 1.17-6.02). In general cancer rates, including the one for lung cancer, were significantly reduced for maintenance workers (SMR, 0.69; 95% CI, 0.52-0.90) compared to the reference group.	The authors state that the extent to which these findings were directly related to work exposures is unknown.
Proportionate mortality study, the USA; occupational and cause-of-death information on 588,090 males (period 1950-1989) and 88,071 females (period 1974-1989). (ref. Milham 1997[154])	Classification according to job title. This included 7,266 death among 'road graders, pavers, machine operators, and excavators', and 1,437 deaths among 'operating engineers'. These two groups are believed to have had the greatest likelihood of being exposed to bitumen.	Statistically significantly increased proportional mortality ratios (PMR) for road graders, etc.: respiratory system cancer (614 deaths; PMR 1.17), cancer of the bronchus, trachea and lungs (558 deaths; PMR, 1.20). Statistically significantly increased PMRs for operating engineers: respiratory system cancer (136 deaths; PMR 1.21, $p<0.05$), cancer of the bronchus, trachea and lungs (76 deaths; PMR, 1.21, $p<0.05$), all malignancies of the lymphatic and haematopoietic system (42 deaths; PMR, 1.42) and other lymphomas (10 deaths; PMR, 2.00). No confidence intervals given.	Comments of NIOSH[1]: study limitations include interdependence of cause-specific PMRs, inaccuracies resulting from limited data on death certificates, and lack of detailed information on exposure and confounders (*i.e.*, smoking habits).
Mortality study, the USA; 9,585 highway maintenance workers, employed for at least one year; follow-up 1958-1980; general male population of upstate New York served as reference group. (ref. Hwang *et al.* 1995[155])	No information on exposure. Analyses for duration of employment and latency period were performed.	Standardised mortality ratios for labourers: lung cancer, SMR, 1.26 (102 cases observed95% CI, 1.03-1.53); cancer of the rectum, SMR, 1.73(17 cases observed; 95% CI, 1.01-2.78). The SMR of other types of cancer for labourers were not increased.	Authors noted limitations of the study, such as relatively short follow-up period, and censoring of data. Co-exposure to solvents and pesticides is possible.
Roofing operations			
Cohort study in Sweden; 704 roofers; follow-up 1971/1979-1984. (ref. Engholm *et al.* 1991[66])	No quantitative information on exposure.	Standardised incidence ratios: lung cancer (4 cases; SIR, 3.62), stomach cancer (1 case; SIR, 1.98), leukemia (1 case; SIR, 2.26). Standardised mortality ratios: lung cancer (3 cases; SMR, 2.79), stomach cancer (1 case; SMR, 2.30), lymphatic, haematopoietic cancer (2 cases; SMR, 2.68). No details on statistical significance or confidence intervals given.	Limitations include short latency period and lack of data on exposure. Also the number of cases is small.

Proportionate mortality study, the USA; occupational and cause-of-death information on 588,090 males (period 1950-1989) and 88,071 females (period 1974-1989). (ref. Milham 1997[15])	Classification according to job title. Among males, 1,057 were classified as roofers and slaters.	Statistically significantly increased proportional mortality ratios (PMR): respiratory cancer (105 cases; PMR, 1.53; $p<0.01$); larynx cancer (6 cases; PMR, 2.59; $p<0.05$); bronchus, trachea, lung cancer (86 cases; PMR, 1.44; $p<0.01$); bronchus, lung cancer (53 cases; PMR, 1.60; $p<0.01$).	Comments of NIOSH[1]: study limitations include interdependence of cause-specific PMRs, inaccuracies resulting from limited data on death certificates, and lack of detailed information on exposure and confounders (*i.e.*, smoking habits).
Retrospective mortality study, the USA; 5,939 active, probational, and retired roofers and waterproofers (at least 6 years in the union); follow-up 1960-1970; reference total male population. (ref. Hammond *et al.* 1976[136])	No quantitative data on exposure presented.	Standardised mortality ratios (SMR): all cancers (SMR, 1.5; 95% CI, 1.3-1.6); lung cancer (SMR, 1.6; 95% CI, 1.3-1.9); oral cavity, throat, larynx, oesophagus (SMR, 2.00; 95% CI, 1.7-2.8); stomach (SMR, 1.7; 95% CI, 1.1-2.5); bladder (SMR, 1.7; 95% CI, 0.9-2.9).	Potential for confounding because of exposure to coal tar and asbestos. Smoking habits not recorded.
Retrospective mortality study, the USA, Los Angeles; 2,161 deaths and 1,777 lung cancer risks during 1968-1970 (age 20-64 years). (ref. Menck and Henderson 1976[156])	Occupation obtained from death certificates or medical records. No data on exposure presented. Population at risk is estimated to be 2,000 (roofers).	Standardized mortality ratio for lung cancer, 5.0 (95% CI, 2.5-8.9).	Potential for confounding because of exposure to coal tar and asbestos. Also, study is limited, because job title and history may not be accurate.
Retrospective study, the USA; 284,046 respondents to a questionnaire; veterans who served in the army between 1917-1940; follow-up up 1954-1980. (ref. Hrubec *et al*. 1992 (source NIOSH, IPCS)[1,3])	Study included 52 roofers and slaters. Data adjusted for smoking. No quantitative data on exposure presented.	Relative risk for lung cancer among roofers and slaters was 3.0 (4 deaths; 95% CI, 1.30-6.75).	Potential for confounding because of exposure to coal tar and asbestos. Information on work histories was obtained at one time point only.
Nationwide survey from the Finnish Cancer Registry; 109,000 cases of cancer of the entire 1970 population (age 25-64); follow-up 1971-1985. (ref. Pukkala 1995 (source DFG, IPCS)[2,3])	No quantitative data on exposure presented.	Standardised incidence ratio for cancers of the lung, bronchus, and trachea for 'asphalt roofers' was 3.25 (95% CI, 1.92-5.13).	Potential for confounding because of exposure to coal tar and asbestos. Smoking was not considered.
Retrospective mortality study, Switzerland; roofers; period 1979-1982. (ref. Minder and Beer-Porizek 1992[157])	Data obtained from death certificates of all men over the age of 30.	Significantly increased proportional mortality ratio in roofers for cancer of the oral cavity and larynx (6 deaths; PMR, 3.30; 95% CI, 1.21-7.20)	Results were given only for oral cavity. It is not specified whether roofers were exclusively exposed to bitumen fumes.

Paving and roofing operations			
Retrospective cohort in Denmark; 679 mastic bitumen workers; follow-up 1959-1984; reference group, total Danish male population. (ref. Hansen *et al.* 1989[64], 1991[158])	Mastic asphalt is a mixture of fine sand, stone powder, finely derived limestone, and 12-17% bitumen. Exposure assessment involved personal-breathing zone sampling: flooring (n=35), range 0.5-260 mg/m^3 (median, 19.7 mg/m^3); paving (n=2), 3.5-4.3 mg/m^3 of bitumen fume condensate.	Standardised incidence ratio (SIR) for all malignant neoplasms was 1.95 (75 cases; 95% CI, 1.53-2.44). Statistically significant increases of SIR were found for: the lungs (27 cases; SIR 3.44; 95% CI, 2.27-5.01), mouth (2 cases; SIR, 11.11; 95% CI, 1.35-40.14), oesophagus (3 cases; SIR, 6.98; 95% CI, 1.44-20.39), and the rectum (7 cases; SIR, 3.18; 95% CI, 1.28-6.56). Standardised mortality ratios (SMR): all cancers (62 cases; SMR, 2.29; 95% CI, 1.75-2,93), lung cancer (25 cases; SMR, 2.90; 95% CI, 1.88-4.29), non-lung cancer (37 cases; SMR, 2.00; 95% CI, 1.41-2.76).	In this study very high risks were observed. Study have been repeatedly criticised in the literature for potential selection bias and for confounding by alcohol consumption and smoking. Furthermore, subjects in study may have been exposed to coal tar products.
Other operations			
Cancer morbidity, Estonia; 1,486 men in eleven bitumen production factories; follow-up 1974-1984; more than 3 years in job (10,369 person years). (ref. Povarov *et al.* 1988 (source: DFG)[2])	Production of hot-lay bitumen concrete. Benzo[a]pyrene concentration 2-7 ng/m^3.	Standardised mortality ratios: for cancers (SMR, 1.5; 95% CI, 0.9-2.4); lung cancer (SMR, 2.1 in age group 40-64 years; $p<0.05$)).	Study in Russian.

Annex I

IARC multicenter cohort study: study design

Tabel I IARC multicenter cohort study: study design[16,56,57]

Country	No. of companies	Period of employment	Period of follow-up	Duration of follow-up (year)				Number of workers (N) and person years (PY) in the analysis			
				Bitumen workers		Reference group*		Bitumen workers		Reference group*	
				Mean	SD	Mean	SD	PY	N	PY	N
Denmark	6	1953-1996	1968-1996	18.0	8.4	12.6	8.6	158,311	9,652	12,314	1,129
Finland	6	1925-1996	1969-1994	20.3	10.4	23.8	12.9	110,789	5,687	57,173	2,467
France	1	1936-1996	1952-1996	14.9	6.7	18.7	4.8	65,265	4,381	309,730	16,518
Germany	138	1965-1999	1965-2000	17.9	5.4	18.6	5.4	44,510	2,642	46,447	2,652
Israel	1	1913-1997	1968-1998	18.7	7.8	19.3	8.3	9,692	541	12,897	702
The Netherlands	6	1927-1999	1969-2000	11.3	7.0	12.0	7.3	36,433	3,223	29,824	2,486
Norway	58	1914-1999	1953-1999	13.4	5.4	10.3	5.5	33,266	2,513	57,494	5,789
Sweden	**	1925-1992	1971-1995	19.8	10.0	23.0	8.8	22,823	1,181	11,402	1,181
Total				16.9	8.6	16.9	8.8	481,089	29,820	537,281	32,245

* Building and ground construction workers employed by the same companies as the bitumen workers.
** Not applicable.

Annex **J**

IARC multicenter cohort study: data on mortality by country

Source Boffetta *et al.* (2001)[18]

Tabel J.1. Mortality

SMR (95% CI)		All causes	Malignant neoplasms in buccal cavity and pharynx	Malignant neoplasms in trachea, bronchus and lung	Diseases in the circulatory system	Diseases of the respiratory system
All countries[18]		0.96 (0.93-0.99)	1.21 (0.84-1.68)	1.17 (1.04-1.30)	0.93 (0.89-0.98)	1.08 (0.96-1.22)
	Tar free	0.91 (0.86-0.96)	0.91 (0.42-1.73)	1.23 (1.02-1.48)	0.83 (0.76-0.90)	1.01 (0.71-1.23)
Denmark[18]		**1.07 (1.02-1.12)**	1.44 (0.79-2.41)	1.17 (1.00-1.36)	**1.11 (1.03-1.19)**	1.25 (1.05-1.47)
	Tar free	0.88 (0.77-1.00)	1.00 (0.12-3.62)	1.16 (0.73-1.74)	0.83 (0.64-1.05)	0.94 (0.47-1.68)
Norway[159,160]		0.81 (0.75-0.87)	0.87 (0.76-1.00)	1.18 (0.89-1.52)	0.84 (0.76-0.94)	0.91 (0.70-1.17)
	Tar free	0.83 (0.76-0.90)	0.58 (0.07-2.11)	1.27 (0.92-1.71)	0.86 (0.76-0.97)	1.04 (0.76-1.40)
Sweden[161]		0.78 (0.69-0.87)	0.87 (0.69-1.07)	0.91 (0.54-1.43)	0.71 (0.59-0.85)	0.71 (0.38-1.22)
	Tar free	0.89 (0.64-1.22)	0.00 (0.00-15.90)	1.21 (0.15-4.39)	1.36 (0.81-2.15)	0.00 (0.00-2.43)
Finland[162,163]		0.98 (0.86-1.12)	0.98 (0.70-1.33)	1.08 (0.59-1.82)	0.96 (0.77-1.18)	1.26 (0.65-2.21)
	Tar free	1.00 (0.86-1.16)	1.71 (0.04-9.51)	0.98 (0.47-1.80)	1.02 (0.80-1.28)	1.17 (0.54-2.23)
The Netherlands[164]		0.79 (0.59-1.05)	1.07 (0.67-1.62)	1.16 (0.53-2.21)	0.47 (0.24-0.84)	2.11 (0.91-4.16)
	Tar free	0.83 (0.42-1.29)	0.00 (0.00-42.13)	1.80 (0.37-5.26)	0.22 (0.01-1.21)	3.69 (0.45-13.34)
Germany[18]		1.10 (0.95-1.28)	1.29 (0.99-1.66)	**1.09 (1.24-2.79)**	0.90 (0.66-1.19)	1.20 (0.52-2.37)
	Tar free	1.05 (0.85-1.29)	1.75 (0.36-5.11)	1.75 (0.93-3.00)	0.79 (0.50-1.20)	2.01 (0.81-4.14)
France[16]		0.88 (0.76-1.02)	0.92 (0.71-1.17)	0.97 (0.57-1.53)	0.99 (0.71-1.35)	1.11 (0.48-2.18)
	Tar free	0.80 (0.51-1.20)	0.00 (0.00-3.88)	1.67 (0.46-4.29)	0.38 (0.05-1.36)	1.08 (0.03-6.02)
Israel[166]		0.99 (0.90-1.10)	0.65 (0.48-0.84)	1.05 (0.62-1.66)	0.71 (0.59-0.84)	0.79 (0.48-1.22)
	Tar free	0.99 (0.90-1.10)	1.11 (0.03-6.21)	1.05 (0.62-1.66)	0.71 (0.59-0.84)	0.79 (0.48-1.22)

Only subjects with more than one season of employment are included. **Bold**: statistically significant excess compared to general population. Tar free is a tar free subcohort.

Table J.2. Lung cancer mortality by duration of exposure to bitumen fume (years)

SMR (95% CI)		Non-exposed	0-1.7521 L 0-1.4455	1.7522-4.5885 L 1.4456-3.8986	4.5886-9.8699 L 3.8987-8.0547	9.8700 + L 8.0548 +	Test for trend
All countries[18]		1.05 (0.92-1.19)	**1.25 (1.04-1.49)**	1.13 (0.95-1.34)	1.06 (0.88-1.26)	0.95 (0.80-1.12)	0.02
	L	1.05 (0.95-1.16)	1.10 (0.88-1.37)	1.06 (0.85-1.31)	1.08 (0.86-1.34)	1.14 (0.93-1.40	0.79
Denmark[18]		0.46 (0.15-1.07)	**1.40 (1.12-1.73)**	1.08 (0.85-1.35)	1.02 (0.76-1.33)	0.80 (0.50-1.22)	0.01
	L	1.02 (0.82-1.24)	1.28 (0.97-1.66)	0.97 (0.71-1.31)	1.07 (0.73-1.50)	1.52 (0.87-2.47)	0.96
Norway[159,160]		1.49 (1.12-1.95)	0.93 (0.37-1.91)	1.23 (0.61-2.20)	1.62 (0.97-2.53)	0.94 (0.60-1.40)	0.75
	L	1.45 (1.13-1.83)	0.34 (0.04-1.22)	1.53 (0.79-2.67)	1.20 (0.62-2.90)	1.02 (0.59-1.63)	0.56
Sweden[161]		0.90 (0.74-1.09)	0.51 (0.14-1.30)	0.00 (0.00-5.47)	1.82 (0.38-5.33)	1.19 (0.61-2.07)	0.11
	L	0.90 (0.74-1.08)	0.50 (0.10-1.46)	0.98 (0.02-5.44)	1.49 (0.31-4.37)	1.16 (0.53-2.21)	0.19
Finland[162,163]		1.54 (1.06-2.16)	1.45 (0.58-3.00)	0.92 (0.25-2.36)	0.65 (0.08-2.36)	1.50 (0.49-3.50)	0.89
	L	1.32 (0.93-1.81)	1.05 (0.22-3.07)	2.17 (0.71-5.07)	0.00 (0.00-2.06)	**4.07 (1.32-9.50)**	0.21
The Netherlands[164]		0.71 (0.15-2.09)	1.17 (0.59-2.10)	1.37 (0.86-2.070	0.64 (0.29-1.22)	**1.64 (1.05-2.45)**	0.58
	L	0.96 (0.61-1.44)	1.08 (0.43-2.22)	1.59 (0.89-2.63)	1.09 (0.52-2.00)	1.60 (0.90-2.64)	0.61
Germany[18]		**2.23 (1.25-3.68)**	1.77 (0.71-3.64)	1.59 (0.76-2.92)	**2.08 (1.16-3.43)**	0.72 (0.23-1.68)	0.21
	L	**1.79 (1.27-2.44)**	2.56 (0.94-5.57)	1.23 (0.34-3.16)	0.39 (0.01-2.18)	1.65 (0.20-5.97)	0.19
France[165]		0.61 (0.07-2.19)	0.36 (0.01-1.99)	0.42 (0.09-1.22)	0.79 (0.47-1.25)	0.82 (0.59-1.10)	0.23
	L	0.65 (0.39-1.03)	0.54 (0.11-1.57)	0.45 (0.15-1.05)	1.13 (0.70-1.72)	0.78 (0.48-1.19)	0.37
Israel[166]		0.66 (0.34-1.15)	0.00 (0.00-5.27)	2.94 (0.95-6.86)	1.00 (0.21-2.92)	0.86 (0.41-1.58)	0.25
	L	0.64 (0.34-1.10)	1.52 (0.04-8.45)	0.65 (0.02-3.62)	1.40 (0.45-3.27)	1.07 (0.51-1.96)	0.93

L, lagged time (15 years) included. Test for linear trend of SMRs among exposed. **Bold**: statistically significant excess compared to general population.

Table J.3. Lung cancer mortality by cumulative exposure to bitumen fume

SMR (95% CI)		Non-exposed	0-3.8742 L 0-3.6462	3.8743-10.0513 L 3.6463-8.6098	10.0514-26.8325 L8.6099-25.9109	26.8326 + 25.9110 +	Test for trend
All countries[18]		1.05 (0.92-1.19)	1.16 (0.97-1.38)	1.09 (0.91-1.28)	1.07 (0.89-1.28)	1.02 (0.85-1.20)	0.28
	L	1.05 (0.95-1.16)	1.09 (0.88-1.34)	1.21 (0.96-1.50)	0.96 (0.76-1.19)	1.16 (0.94-1.42)	0.96
Denmark[18]		0.46 (0.15-1.07)	**1.36 (1.03-1.76**)	1.11 (0.87-1.40)	1.09 (0.93-1.40)	0.98 (0.73-1.29)	0.10
	L	1.02 (0.82-1.24)	1.15 (0.81-1.59)	1.34 (0.98-1.80)	0.86 (0.60-1.20)	1.33 (0.92-1.87)	0.85
Norway[159,160]		1.49 (1.12-1.95)	0.77 (0.25-1.80)	**1.85 (1.06-3.01)**	1.11 (0.62-1.83)	0.99 (0.64-1.47)	0.54
	L	1.45 (1.13-1.83)	0.37 (0.05-1.35)	1.43 (0.65-2.71)	1.17 (0.65-1.93)	1.06 (0.62-1.70)	0.45
Sweden[161]		0.90 (0.74-1.09)	0.89 (0.02-4.97)	0.42 (0.09-1.24)	0.97 (0.02-5.39)	1.26 (0.69-2.12)	0.11
	L	0.90 (0.74-1.08)	1.56 (0.04-8.69)	0.36 (0.04-1.31)	1.25 (0.15-4.53)	1.22 (0.61-2.18)	0.22
Finland[162,163]		1.54 (1.06-2.16)	1.82 (0.67-3.97)	0.93 (0.25-2.38)	1.40 (0.51-3.04)	0.55 (0.07-1.97)	0.21
	L	1.32 (0.93-1.81)	1.43 (0.30-4.18)	2.85 (1.05-6.20)	0.98 (0.12-3.53)	1.04 (0.13-3.75)	0.45
The Netherlands[164]		0.71 (0.15-2.09)	1.23 (0.76-1.88)	1.35 (0.85-2.05)	0.73 (0.35-1.33)	1.88 (1.00-3.21)	0.80
	L	0.96 (0.61-1.44)	1.59 (0.97-2.46)	0.88 (0.36-1.83)	0.91 (0.42-1.73)	2.70 (1.35-4.84)	0.62
Germany[18]		2.23 (1.25-3.68)	1.58 (0.82-2.76)	1.54 (0.70-2.92)	1.93 (0.94-3.19)	0.91 (0.25-2.32)	0.47
	L	1.79 (1.27-2.44)	1.80 (0.58-4.19)	1.26 (0.26-3.68)	1.71 (0.56-4.00)	0.00 (0.00-2.91)	0.32
France[165]		0.61 (0.07-2.19)	0.74 (0.48-1.10)	0.45 (0.18-0.93)	0.95 (0.54-1.55)	0.87 (0.52-1.38)	0.39
	L	0.65 (0.39-1.03)	0.76 (0.47-1.16)	0.99 (0.40-2.04)	0.77 (0.37-1.42)	0.82 (0.42-1.43)	0.89
Israel[166]		0.66 (0.34-1.15)	2.29 (0.62-5.87)	1.10 (0.13-3.98)	0.79 (0.10-2.96)	0.91 (0.44-1.67)	0.17
	L	0.64 (0.34-1.10)	2.27 (0.62-.831)	0.63 (0.02-3.49)	1.47 (0.40-3.76)	0.88 (0.38-1.74)	0.21

Cumulative exposure expressed as semi-quantitative exposure units x years. **Bold**: statistically significant excess compared to general population.

Table J.4. Lung cancer mortality by average exposure to bitumen fume

SMR (95% CI)		Non-exposed	0-1.2940 L 0-1.3822	1.2941-3.2099 L 1.3823-3.8172	3.2100-4.7572 L 3.8173-4.9677	4.7573 + 4.9678 +	Test for trend
All countries[18]		1.05 (0.92-1.19)	0.91 (0.75-1.09)	1.08 (0.92-1.27)	**1.23 (1.03-1.47)**	1.15 (0.95-1.38)	0.03
	L	1.05 (0.95-1.16)	1.08 (0.86-1.33)	0.92 (0.75-1.13)	**1.30 (1.04-1.60)**	1.21 (0.95-1.51)	0.15
Denmark[18]		0.46 (0.15-1.07)	1.06 (0.77-1.42)	0.98 (0.70-1.34)	**1.32 (1.03-1.67)**	1.10 (0.87-1.35)	0.61
	L	1.02 (0.82-1.24)	1.23 (0.87-1.70)	0.74 (0.41-1.22)	1.33 (0.98-1.78)	1.13 (0.74-1.48)	0.89
Norway[159,160]		**1.49 (1.12-1.95)**	1.27 (0.47-2.77)	1.01 (0.67-1.47)	1.12 (0.70-1.69)	2.20 (0.81-4.79)	0.39
	L	**1.45 (1.13-1.83)**	1.69 (0.46-4.34)	0.69 (0.41-1.09)	1.49 (0.83-2.45)	**3.15 (1.15-6.85)**	0.01
Sweden[161]		0.90 (0.74-1.09)	0.00 (0.00-1000)	0.83 (0.02-4.61)	0.84 (0.42-1.51)	1.15 (0.46-2.37)	0.55
	L	0.90 (0.74-1.08)	-	0.00 (0.00-4.87)	1.04 (0.56-1.78)	0.74 (0.17-2.46)	0.86
Finland[162,163]		1.54 (1.06-2.16)	1.73 (0.47-4.42)	0.75 (0.09-2.70)	0.91 (0.25-2.32)	1.30 (0.69-1.83)	0.88
	L	1.32 (0.93-1.81)	2.73 (0.74-6.99)	2.61 (0.32-9.42)	0.50 (0.01-2.76)	1.53 (0.56-3.33)	0.29
The Netherlands[164]		0.71 (0.15-2.09)	0.92 (0.49-1.57)	1.28 (0.94-1.71)	2.04 (0.75-4.43)	0.00 (0.00-8.48)	0.22
	L	0.96 (0.61-1.44)	0.93 (0.40-1.83)	1.46 (1.02-2.03)	2.60 (0.71-6.66)	0.00 (0.00-1.63)	0.20
Germany[18]		**2.23 (1.25-3.68)**	0.86 (0.37-1.70)	**1.84 (1.14-2.82)**	1.17 (0.24-3.43)	**4.27 (1.38-9.96)**	0.02
	L	**1.79 (1.27-2.44)**	1.23 (0.15-4.43)	0.99 (0.36-2.15)	2.93 (0.60-8.56)	3.28 (0.40-11.84	0.12
France[165]		0.61 (0.07-2.19)	0.70 (0.51-0.95)	0.78 (0.48-1.20)	1.92 (0.62-4.48)	0.76 (0.59-0.97)	0.14
	L	0.65 (0.39-1.03)	0.75 (0.49-1.11)	0.78 (0.48-1.11)	0.78 (0.48-1.19)	0.00 (0.00-95.9)	0.31
Israel[166]		0.66 (0.34-1.15)	1.53 (0.56-3.33)	0.76 (0.09-2.76)	1.25 (0.40-2.91)	0.77 (0.25-1.79)	0.33
	L	0.64 (0.34-1.10)	2.04 (0.82-4.20)	1.07 (0.13-3.87)	0.48 (0.06-1.74)	1.06 (0.39-2.30)	0.17

Average exposure expressed as semi-quantitative exposure units. L, lagged time (15 years) included. Test for linear trend of SMRs among exposed. **Bold**: statistically significant excess compared to general population.

Annex **K**

Case-control studies on the *carcinogenic* effects of bitumen fume exposure

study design and population information	exposure and health assessment information	type of cancer; odds ratios	notes
Road paving and maintenance operations			
4,431 histologically confirmed lung cancer cases; 11,326 cancer controls; diagnosed between 1980-1985;Missouri Cancer Registry, the USA. (ref. Zahm *et al*. 1989[167])	Occupational history obtained from medical records. Sufficient data were obtained for 52% of the cases and 45% of the controls. Data adjusted for age and smoking habits.	Odds ratio for all lung cancers in pavers, surfaces, and material moving equipment operators: 0.9 (32 cases and 64 controls; 95% CI, 0.6-1.5).	Only the job at the time of diagnosis recorded.
Population-based case control study, the USA; 622 male cases of non-Hodgkin's lymphoma; 1,245 age-matched controls; data obtained between 1980 and 1983; cases and controls in urban areas were excluded. (ref. Blair *et al*. 1993[168])	Focus on agricultural occupations. Subjects interviewed by questionnaire. A job exposure matrix was constructed from the data obtained from the questionnaire. Odds ratios were computed for employment in 151 occupations.	Non-Hodgkin's lymphoma: odds ratio for paving occupations 3.4 (3 cases, 2 controls; 95% CI, 0.6-20.8). Odds ratio for exposure to bitumen and creosote 1.0 (53 cases, 105 controls; 95% CI, 0.7-1.5). ORs adjusted for smoking habits and family history of disorder.	

Roofing operations			
The USA; 4,431 histological confirmed lung cancer cases; 11,326 cancer controls; diagnosed between 1980-1985; Cancer Registry, the USA. (ref. Zahm *et al.* 1989[167])	Occupational history obtained from medical records. Sufficient data were obtained for 52% of the cases and 45% of the controls. Data adjusted for age and smoking habits.	Odds ratio for all lung cancers in roofers: 2.1 (6 cases and 7 controls; 95% CI, 0.6-8.2).	Only the job at the time of diagnosis recorded.
Hospital-based study, the USA; 763 lung cancer cases; 900 population controls; white males New Jersey. Period diagnosis new cases 1980-1981. (ref. Schoenberg *et al*. 1987[169])	Occupational history obtained by interviews or patient's next-of-kin. Data adjusted for smoking habits.	13 cases and 8 controls identified as roofers or slaters: odds ratio for lung cancer, 1.7 (95% CI, 0.7-4.4; not statistically significant).	Number of individuals who were exposed to hot bitumen roofing products not identified. Not clear whether roofers and slaters had significant exposure.
Hospital-based multicenter study, the USA; 1,793 cases of lung cancer; 3,228 matched controls; data collected between 1980-1989. (ref. Morabia *et al.* 1992[170])	Data adjusted for age, race, group, region and smoking habits.	7 cases and 6 controls identified as roofers or slaters. Odds ratio for lung cancer, 2.1 (95% CI, 0.7-6.2; not statistically significant).	Number of individual who were exposed to hot bitumen roofing products not identified. Not clear whether roofers and slaters had significant exposure.
Paving and roofing operations			
The USA; 2,973 male cases of lung cancer; 3,210 controls; data obtained from five case-control studies conducted in the USA. (ref. Vineis *et al.* 1988[171])	Study identified 45 cases and 37 controls as roofing and bitumen workers.	Odds ratio, 1.4 (95% CI, 0.9-2.3). Odds ratio is adjusted for age and smoking.	One of the five studies included Schoenberg *et al*. (1987)[168]. Not clear whether workers had significant exposure to bitumen.
Other operations			
Denmark; 212 cases of bladder carcinoma cancer; 259 matched controls; data collected from 1977 to 1979. (ref. Mommsen *et al.*1984[172])	Only 9 cases had worked with kerosene or bitumen. Of these 2 cases were roofers.	Odds ratio for bladder cancer, 3.1 (9 cases, 3 controls; 95% CI, 0.9-11.0).	Study is of limited use, because of the low number of workers likely exposed to bitumen. No data on levels of exposure presented.
Canada; 739 cases of bladder cancer; 781 matched population controls; diagnosed between 1979 and 1982. (ref. Risch *et al.* 1988[61])	Information on occupation, lifestyle factors, etc. obtained from interviews. Data adjusted for smoking habits. Of the cases 46 subjects were exposed to coal tars and bitumen.	Only 67% of the eligible cases and 53% of the eligible controls participated in the study. Odd ratio for bladder cancer among workers exposed to coal tar and bitumen" (> 6 months exposure and employed 8 to 28 years before diagnosis), 3.11 (95% CI, 1.19-9.68).	Study is of limited use, because of rough job category.

Population-based study, Denmark; 96 cases of cancer of the renal pelvis and urethra (benign and malign); 294 hospital controls. (ref. Jensen *et al.* 1988[60])	Cases and controls were matched for several factors. Data adjusted for smoking habits.	9 cases and 6 controls were exposed to bitumen of coal tar. Odds ratio, 5.5 (95% CI, 1.6-19.6).	
Fibreglass insulation production facility, the USA; 144 lung cancer cases and 260 matched controls. Cases and controls were drawn from a historical cohort mortality study of production and maintenance workers, employed between 1940 and 1962, and followed-up to the end of 1982. (ref. Chiazze *et al.* 1993[153])	Quantitative estimates of lifetime exposure to asbestos, talc, bitumen fumes, formaldehyde and silica presented. Bitumen exposure was expressed as "never exposed" or exposed to "≥ 0.01 mg/m^3 days". Data were adjusted for age, smoking and occupational exposure.	Odds ratio for lung cancer in the bitumen-exposed group, 0.96 (95% CI, 0.65-1.4).	
Case-control study, the USA; 39 cases of lung cancer and 133 controls. Cases and controls were identified among deaths occurring between 1977-1997. (ref. Watkins *et al.* 2002[59])	Lifetime cumulative exposure before 1977 was estimated. Controls were matched by age, race and gender. History of smoking was only available for approximately 65% of subjects in study.	Results of the analyses were presented as unadjusted odds ratios (unORs). Only the unOR for smoking was statistically significantly elevated. These results suggest that smoking habits contributes more strongly to lung cancer than bitumen exposure.	The authors caution that the study is limited by missing data on smoking habits and work history. Also, exposure to bitumen occurred simultaneously with asbestos exposure. IPCS[3] noted that cases and controls were selected from among deaths of active and retired employees, and not from among any workers ever employed at these facilities.
Hospital/population-based case control, Canada; 3,730 hospital-based cancer cases; 533 population-based controls. (ref. Siemiatycki 1991 (source NIOSH, DFG, IPCS)[1-3])	Odds ratio calculated for 23 cancer sites, adjusted for confounding variables and smoking habits.	Concerning any exposure to bitumen, only the odds ratio for colon cancer was statistically significantly increased (OR, 1.6; 95% CI, 1.1-2.5). OR for cancer at other sites (*i.e.*, the stomach, prostate, non-Hodgkin's lymphoma, the lungs) was not significantly increased (OR values around 1.0).	
Hospital-based multicenter case-control study, the USA; 80 cases of hepatocellular carcinomas; 146 matched controls. (ref. Austin *et al.* 1987[67])	Occupational or recreational exposures to 26 substances were obtained from these cases and controls.	Seven cases and 5 controls were exposed to bitumen for at least 3 hr/week for at least 6 months. Relative rate was 3.2 (95% CI, 0.9-11.0; $p=0.07$).	

Retrospective case-control study, the USA; 265 cases of primary liver cancer; 530 matched controls. Data were collected for the period 1975-1980. (ref. Stemhagen *et al*. 1983[173])	Focus on agricultural occupations and pesticide exposure. Information obtained by interview and historical survey.	Road building: relative risk for hepatocellular carcinomas 2.60 (95% CI, 0.83-8.19).	It is not clear whether road builders were exposed to bitumen fumes and/or coal tar fumes.
Population-based case control, Canada; 1,279 cases of renal cell carcinoma; 5,370 population controls; data collection 1994-1997. (ref. Hu *et al*. 2002[174])	Mailed questionnaires.	Increased odds ratio in men associated with "coal tar, soot, pitch, creosote, or bitumen" exposure: OR 1.4 (125 cases, 350 controls; 95% CI, 1.1-1.8), adjusted for 10 year age group, province, education, BMI, smoking habits, alcohol use and total consumption of meat.	No data presented on bitumen exposure only.

Annex **L**

Non-carcinogenic acute, short- and long-term animal toxicity

species, strain and number	type of bitumen	observed effects	references (source)
Acute and sub-acute toxicity			
Inhalation exposure			
Female Sprague-Dawley rats (6-8/group).	Bitumen fume generated at paving temperature of 150 °C. Animals were exposed to about 15 mg/m^3 for 3.5 or 6 hours per days, for 5 days. Controls were included. Study was performed to determine the acute pulmonary inflammatory response and alteration of cytochrome P450 metabolism in the lungs.	Exposure did not result in neutrophil infiltration, alterations in LDH activity or protein content, nor in changed alveolar macrophage function. Overall, no signs of acute pulmonary inflammation. However, exposure did increase the level and activity of CYP1A1, and markedly reduced the level and activity of CYP2B1 in the lungs.	Ma *et al*. 2003[80]
Female Sprague-Dawley rats (7/group)	Hot performance grade bitumen fume was generated at 170°C in a temperature-controlled kettle. The fumes passed through a heated pipe (inlet, 160°C; outlet 150°C). Animals were exposed to ambient air or to bitumen fume at a concentration of 16.0±8.1 mg/m^3 for 3.5 h/day for 5 consecutive days. Eighteen hours after final exposure nasal cavities were lavaged.	Nasal lavage in exposed animals showed the presence of inflammatory cells (increased number of neutrophils and macrophages compared to controls). Also sensory neuropeptide release in the nasal epithelium was enhanced, suggesting that neurogenic inflammation had occurred with nasal irritation.	Sikora *et al.* 2003[83]

Male Sprague-Dawley rats (4-6 animals at each time point).	Road paving bitumen fume was generated at 170°C in an oven and passed through a heated pipe with the temperature maintained at 150°C (inlet) and 120°C (outlet). Animals were exposed to filtered air or 72.6± 5.0 mg (bitumen fume) /m^3 for 6 h/ day for 5 days. One day after final exposure, rats were intratracheally inoculated with *Listeria* monocytogenes. Infection grade in the lungs and lung defence was measured up to 7 days after virus instillation.	Bitumen fume exposure did not cause lung injury or inflammation. Also the rate of pulmonary clearance and alveolar macrophage production were not affected. However, bitumen fume exposure did change lymphokin secretion. Overall, the authors concluded that the lung defences were sufficient to control the infection.	Antonini *et al*. 2003[81]
Intratracheal installation			
Male Sprague-Dawley rats (at least six animals per exposure group)	Intratracheal installation of condensate of road bitumen fumes taken from a tank (0.1, 0.5 or 2 mg in 0.25 mL sterile saline). A) One treatment; control animals received sterile saline or 0.25 mL 1% DMSO. Rats were killed 1 or 3 days after installation. B) Exposure on three subsequent days to same doses as in A).	No lung injury observed. Induction of acute inflammatory response. The amount of red blood cells and PMNs; LDH activity; and, protein content of bronchial lavage fluid were normal. Also alveolar macrophage function was normal.	Ma *et al*. 2000[82]
Dermal exposure			
New Zealand white rabbits (2 males and 2 females).	Residues of vacuum distillation (vacuum residuum samples API 81-13 and API 81-14; CAS 64741-56-6), warmed in water bath and applied occlusively for 24 hours to the shaved abraded skin. Dose applied topically was 2,000 mg/kg bw (single application). Observation period was 14 days.	One female had diarrhoea on day 1, and another female on days 6 and 7 after treatment with API 81-13. No to very slight erythrema was observed. Mortality was not increased. Estimated dermal LD_{50} was greater than 2,000 mg API81-13 or API81-14 per kg bw.	API 1982[78,79]

Oral exposure			
Sprague-Dawley rats (5 male and 5 females)	Residues of vacuum distillation (vacuum residuum samples API 81-13, API 81-14; CAS 64741-56-6) dissolved in corn oil (5,000 mg/kg bw) A single dose was given orally as a suspension. Animals were observed up to 14 days.	No mortality occurred during the test period. Hypoactivity and diarrhoea were observed. At necropsy, most animals did not show visible lesions. Lesions that were observed included: mildly reddened thymus (n=1, API 81-13); enlarged cervical lymph node (n=1, API 81-13); mild hydrometra uterus (n=1, API81-13); moderately dilated right kidney/renal pelvis (n=1, API 81-14). Authors reported also of an oral LD_{50} greater than 5,000 mg API81-13 or API81-14 per kg bw (males and females).	API 1982[78,79]
Short-term toxicity			
Inhalation exposure			
Wistar (WU) rats (n=16/sex/group). Controls included.	Exposure to bitumen fumes generated from a sample of bitumen tank condensate. The bitumen fume condensates were prepared in advance by collecting fume from a storage tank with paving bitumen (50/70, B65). The storage temperature of the bitumen was 160 – 180°C, the fume was collected at 180°C and a fraction of the vapour aerosol mixture was separated at 24°C. Animals were exposed nose only to clean air or to target concentrations of 4, 20 or 100 mg/m^3 THC (total hydrocarbon of bitumen fumes) for 6 hours/day, 5 days/week for 14 weeks. These doses correspond to actual concentrations (aerosol + vapour phase) of 4.0, 20 and 107 mg/m^3.	No mortality related to bitumen exposure was observed. At 100 mg/m^3 a significantly increased lower body weight in male rats was reported. Also, at this concentration statistically significant exposure-related histopathological changes (*e.g.*, hyalinosis, basal cell hyperplasia, mucous cell hyperplasia, inflammatory cell infiltration) in the nasal and paranasal cavities were observed. Under these experimental conditions a NOAEL of 20 mg/m^3 was established.	Fuhst *et al*. 2001[84], 2003[85]; Pohlmann *et al*. 2001[86]
Ingestion			
Pigs (n=4/group).	Hungarian bitumen products, one distillation bitumen and one extraction bitumen. A daily dose of 10 g for 63 or 71 days were given.	Appetite, body weight gains and state of health of the animals was unaffected. No pathological changes in liver and kidneys reported.	Köver and Zakar 1959[175]

Dermal exposure

New Zealand White rabbits (5 animals per sex per group. Also control animals included.	Two distillation residues (vacuum residuum samples API 81-13, API 81-14; CAS 64741-56-6). Undiluted doses of 200, 1,000 and 2,000 mg/kg bw were applied to the skin for 6 hours/day, 3 times/week for 4 weeks.	*1,000 mg/kg bw*: during treatment, reduced food consumption, desquamation of the skin, and wheezing were observed. *2,000 mg/kg bw*: on day 21 body weight gains were significantly lower than control group. Oedema formation was slight to moderate. Microscopic examination revealed minimal to moderate dermatitis and hyperkeratosis. The haematological and chemical parameters were unaffected.	API 1983 (source: DFG 2002)[2]

Long-term toxicity

Inhalation

C57 Black mice A) n=10/sex; n=6 male controls). B) 30 exposed animals; 6 control animals; sex not specified.	Bitumen-water aerosol produced by stirring and aerosolization of hot bitumen in hot water. Concentration not specified. Bitumen heated to 121°C. A) Total exposure period of 16.5 months in a whole animal exposure chamber. Exposure was for 30 min/day and 5 days/week. B) Total exposure period of 21 months. Exposure 6-7.5 hours/day for 5 days/week.	A) Exposure resulted in emphysema, bronchiolar dilation, and, in some animals, pneumonitis and severe localized bronchitis. Survival rate after 16.5 months was 3/20. B) Exposed mice developed bronchitis with peribronchial infiltration of large round cells; epithelial hyperplasia; loss of cilia; flattening and necrosis of the bronchial epithelium; loss of respiratory epithelium; and, atrophy and necrosis of the alveolar epithelium. Survival rate after 21 months was 2/30. Animals ate contaminated food, but did not suffer from weight loss.	Simmers 1964[87]
Bethesda Black rats (65 females). No controls.	Air-blown roofing bitumen from a commercial source (flash point 200°C). Bitumen was heated in evaporation vessel in the ventilated exposure chamber to 121-135°C. Concentration of brownish fumes not measured. 2-10 g bitumen evaporated daily. Animals were exposed 5 hours/day for 4 days/week for a total of 2 years.	Authors reported severe chronic fibrotic pneumonitis with peribronchial adenomatosis; epithelial metaplasia in the bronchial mucosa; and, bronchiectasis.	Hueper and Payne 1960[88]

Guinea pigs (strain 13; 30 animals, sex not specified). No controls.	Air-blown roofing bitumen from a commercial source (flash point 200°C). Bitumen was heated in evaporation vessel in the ventilated exposure chamber to 121-135°C. Concentration of brownish fumes not measured. 2-10 g bitumen evaporated daily. Animals were exposed 5 hours/ day for 4 days/week for a total of 2 years.	Authors reported severe chronic fibrotic pneumonitis with peribronchial adenomatosis; epithelial metaplasia in the bronchial mucosa; and, bronchiectasis.	Hueper and Payne 1960[88]
Dermal exposure			
C57 Black mice (n= 25 per sex).	Mixture of three steam-refined bitumens made from West coast crude oil, dissolved in toluene. Mixture of 75-100 mg was liquefied in a water bath. Mice were painted three times a week in the intrascapular area, without shaving. However, material was rubbed into the fur by applying it with a small glass-stirring rod. Exposure was up to 40 weeks.	Of the fifty animals, 30 animals were prepared for microscopical examination. Four mice showed skin changes of epilation, irregular thickening, slight hyperkeratosis and deeply placed hair follicles. The author did not report on positive and negative control groups.	Simmers 1965[89]
SS-57 white mice (n=40-52). Control, 23 animals. Sex unknown.	Three sludge bitumens (straight distillation (BN-2, BN-3 and BN-5). Also two bitumens from cracking-residue (BN-4, and BN-5). Origin oils from the Ukraine and Volga Region. Application: 40% in benzene (dose not specified), once weekly for 19 months.	Hyperkeratosis and inflammation of the skin reported in exposed animals.	Kireeva 1968[90] (source DFG)[2]
Swiss albino mice (n=12-14/sex/group). Control, 15 animals/sex.	Eight road paving grade bitumens, vacuum distilled, penetration 85/100 (according to ASTM). Bitumens were dissolved in benzene to give a 10% solution; 2.5 mg in 25 μL solution was applied twice weekly to shaved dorsal skin for more than 20 months.	Epidermal hyperplasia, and formation of ulcers and small abscesses reported in exposed animals. No further details given on non-carcinogenic effects.	Wallcave *et al*. 1971[91]

Male and female C3H/HeJ mice (25 animals per sex per group)	Test materials were liquids or semisolid petroleum refinery streams identified as API81-03, -07, -08, -09, 10, -13, -14, -15, -24, API83-01, -02, and -03. Dilutions were made with toluene. Test materials were applied twice a week to the shaved intrascapular region of the back (1 cm^2). Volume applied was 50 μL of undiluted solutions. Animals were sacrificed at 3 months and at 12 month in experiment (at each time point ten males and ten females). The sacrificed animals underwent gross pathological and histopathological examination.	All test materials were locally dermatotoxic (desquamation, alopecia or irritation). No other systemic non-carcinogenic toxic responses related to exposure were identified. See annex M for data on carcinogenicity.	API 1986[92]
C3H/HeJ male mice (n=30/ group). Controls included.	Bitumen source: standard commercial type III 'steep' bitumen, produced by distillation and air-blowing Arabian crude (for roofing purposes). Bitumen fumes were generated at 316 °C and collected by cold trap condensation. Condensates were fractionized in five different fractions (A – E). All these fractions were tested. Fume condensate fractions were applied twice weekly to the shaved dorsal skin. Fractions A through E were dissolved in solution of cyclohexane:acetone (1:1) to yield the following concentrations: 64.1%, 8.3%, 10.5%, 11.5%, and 5.6%, respectively. Test solvents were applied topically twice weekly for 104 weeks.	No effects on body weights observed after dermal exposure. In the group with the highest dose of BaP (0.01%) 80% of the animals had scabs and sores; the incidence was 50% for those animals receiving 0.01% BaP plus fraction E. None of the other fractions produced notable non-carcinogenic skin lesions.	Sivak *et al*. 1997[95]

Annex **M**

Animal carcinogenicity studies

species, strain and number	type of bitumen	observed effects	references
Inhalation exposure			
Bethesda Black rats (65 females). No controls.	Air-blown roofing bitumen from a commercial source (flash point 200°C). Bitumen was heated in evaporation vessel in the ventilated exposure chamber to 121-135°C. Concentration of brownish fumes not measured. 2-10 g bitumen evaporated daily. Animals were exposed 5 hours/day for 4 days/week for a total of 2 years.	No lung tumours found in treated animals. Authors suggested that tumours at other sites (3 liver tumours, 2 sarcomas, and 1 uterus tumour) were of spontaneous origin.	Hueper and Payne 1960[88]
Guinea pigs (strain 13; 30 animals, sex not specified). No controls.	Air-blown roofing bitumen from a commercial source (flash point 200°C). Bitumen was heated in evaporation vessel in the ventilated exposure chamber to 121-135°C. Concentration of brownish fumes not measured. 2-10 g bitumen evaporated daily. Animals were exposed 5 hours/day for 4 days/week for a total of 2 years.	No lung tumours found in treated animals.	Hueper and Payne 1960[88]

C57 Black mice A) n=10/sex; n=6 male controls). B) 30 exposed animals; 6 control animals; sex not specified.	Bitumen-water aerosol produced by stirring and aerosolization of hot bitumen in hot water. Concentration not specified. Bitumen heated to 121°C. A) Total exposure period of 16.5 months in a whole animal exposure chamber. Exposure was for 30 min/day and 5 days/week. B) Total exposure period of 21 months. Exposure 6-7.5 hours/day for 5 days/ week. IPCS commented that exposure condition did not represent real-world exposures.	A) 3/20 animals survived until the end of the study. One mouse of the twenty developed a papillary lung adenoma. Tumour incidence of controls was 0/6. B) 2/30 animals survived until the end of the study. Animals ate contaminated food, but did not suffer from weight loss. Of the 21 animals that were examined only 1 developed bronchial adenoma. Tumour incidence of control was 0/6.	Simmers 1964[87]
Male and female Wistar rats (50 or 86 per group/sex)	Bitumen fumes (particulate and vapour) were regenerated in the laboratory from bitumen fume condensate samples, which were collected from the headspace of hot bitumen storage tanks at road paving worksites. Animals were nose-only exposed to clean air, or to 6.8, 34.4 or 172 mg/m^3 (total hydrocarbon) for 6 hrs/day, 5 days/week for 2 year.	No increase in number of tumour-bearing animals were observed in the exposed groups compared to the control group, nor were there any treatment-related significant increases in organ-related tumour incidence found. One single animal in the highest dose group had a poorly differentiated adenocarcinoma in the nasal cavity. Concerning non-tumorigenic lesions, dose-related degenerative, inflammatory and proliferative lesions were observed in the nasal cavity and the lung.	Fuhst *et al.* (2007)[93]
Dermal application			
Male CD-1 (nonpigmented) and male C_3H/HeJ (pigmented) mice (50/ strain/ group).	Bitumen fume condensates generated in the laboratory at 232-316°C from type I and III roofing bitumen, and type I and III coal-tar pitch. Condensates were twice weekly topically applied to the skin for 78 weeks. Some groups received the condensate singly or in combination. Half of each group was exposed to simulated sunlight.	Fume condensates of both types of bitumen significantly produced more skin tumours (p=0.01) in both mice strains than in control animals. These concerned both benign tumours (papillomas) and malign tumours (squamous cell carcinomas). Other types of tumours observed included fibrosarcomas, kerato-acanthomas, fibromas, and unclassified benign epitheliomas.	Niemeier *et al.* 1988[94]
Male C_3H/HeJ mice (30/group) and male Sencar mice (30/group). Positive and negative controls were included. Study concerns a tumour-promoting activity study.	Bitumen source: standard commercial type III ‘steep’ bitumen, produced by distillation and air-blowing Arabian crude (for roofing purposes). Bitumen fumes were generated at 316 °C and collected by cold trap condensation. Condensates were fractionized in five different fractions (A – E). All these fractions were tested. Fractions A through E were dissolved in solution of cyclohexane:acetone (1:1) to yield the following concentrations: 64.1%, 8.3%, 10.5%, 11.5%, and 5.6%, respectively. Test solvents were applied twice weekly for 104 weeks.	Data were presented on the number of papillomas and carcinomas per group, the number of tumour-bearing mice, and the average time (in weeks) to carcinoma development. Raw roofing bitumen and neat bitumen fumes induced skin carcinomas (4/30 and 21/30 C_3H/HeJ mice, respectively). The residuum of the heated bitumen fumes did not induce any tumours. Skin carcinomas were only found when fractions B and C were used. These fractions contained high amounts of polycyclic aromatic hydrocarbons (PAH) and compounds (PAC).	Sivak *et al.* 1997[95]

Male and female C3H/HeJ mice (25 animals per sex per group)	Test materials were liquids or semisolid petroleum refinery streams identified as API81-03, -07, -08, -09, 10, -13, -14, -15, -24, API83-01, -02, and -03. Dilutions were made with toluene. Test materials were applied twice a week to the shaved intrascapular region of the back (1 cm^2). Volume applied was 50 μL of undiluted solutions. Animals were sacrificed at 3 months and at 12 month in experiment (at each time point ten males and ten females). The sacrificed animals underwent gross pathological and histopathological examination.	Exposure-related dermal and subcutaneous tumours were observed at the treatment site. This included one malignant tumour in each group API81-07, API81-15 and API81-10, various squamous cell tumours (API81-15 (10% solution),and 4 animals with squamous cell carcinomas (API81-15). Furthermore, a variety of internal neoplasms were found, including liver adenomas and carcinomas, pulmonary adenoma, mammary adenocarcinomas and monocytic leukemias, but none of these were related to exposure. See annex L for data on non-carcinogenic effects.	API 1986[92]
Male C3H/HeJ mice (50 animals per group)	Test materials were liquids or semisolid petroleum refinery streams identified as API81-03, -07, -08, -09, 10, -13, -14, -15, -24, API83-01, -02, and -03. Dilutions were made with toluene. Test materials were applied twice a week to the shaved intrascapular region of the back (1 cm^2). Volume applied was 50 μL of undiluted solutions. Animals were exposed for 2 years. Sacrificed animals underwent gross pathological and histopathological examination.	Dermal neoplasms (*i.e.*, fibromas, papillomas, squamous cell carcinomas, malignant melanomas) were seen in mice in all groups (incidence varied between 4 to 100% depending on type of test compound), except untreated controls. However, the authors noted that the incidence of dermal neoplasms at the non-test site was low (5 malignant and 3 benign neoplasms) and therefore they could not conclude whether this increase was treatment-related. Also non-dermal tumours, which could not be related to treatment, were found, such as malignant liver tumours (in all groups), a renal cell adenoma, pulmonary adenoma, an intestinal carcinoma, and fibrosarcomas.	API 1989[99]
Male C_3H/HeJ mice (50/group). Positive and negative control group included.	Standard roofing bitumen (type not provided), dissolved in redistilled toluene (ratio 1:1). 50 Mg of test compound was applied to the skin of the back twice weekly for 80 weeks.	No tumours were observed in mice treated with test compound or toluene (negative control); survival rates at week 60 were 26/50 and 37/50, respectively. 79% of positive control mice (receiving benzo[a]pyrene) developed tumours.	Emmett *et al*. 1981[101]

Female Sencar mice (30-40/ group). Positive and negative control groups included.	Four formulations of bitumen-based paints (A through D), and three coal tar based paints (E through G). The bitumen-based paints contained xylene, or xylene and mineral spirits with between 89% and 98% cutback bitumen. Volumes applied were 200-600 μL and 0.2-20 μL for bitumen-based and coal tar paints, respectively. 600 μL was applied as three weekly 200 μL doses. All animals were treated with 1 μg TPA/200 μL acetone, three times weekly for 20 weeks beginning 2 weeks after the last initiating dose. Total experimental period was 52 weeks.	Both types of paints initiated tumour development; for coal-tar paints this activity was about 100-fold greater than for bitumen-based paints. Only formulations D (bitumen-based) and E (coal-tar based) were analyzed for their ability to act as a compete carcinogen (exposure 30 weeks, observation period 52 weeks). Only the coal tar based formulation (E) acted as a complete carcinogen. No xylene-control was included in the test.	Robinson *et al.* 1984[96], Bull *et al.* 1985[176]
C57 Black mice (3males and 36 females). Control group included.	Commercially manufactured petroleum bitumen, mixture of steam and air blown bitumens from Californian refineries. Bitumen liquefied with benzene. Applied to the interscapular skin by painting twice weekly for more then 54 weeks. Dose not given.	Twelve squamous (epidermoid) cell carcinomas were reported in the exposed group at the site of painting. Five treated animals developed also papillomas. No skin tumours were detected in the control group. No data on the number of tumour bearing animals presented.	Simmers *et al.* 1959[97]
C57 Black mice (n=25 per sex). No control groups.	Mixture of three steam-refined bitumens made from West coast crude oil, dissolved in toluene. Mixture of 75-100 mg was liquefied in a water bath. Exposure was done by skin painting of steam- or air-refined bitumen, one to three times a week for up to 90 weeks. Bitumen application varied from 75 to 100 mg.	Low survival rate after 7 weeks, because of pneumonitis infection in the groups. Air-refined bitumen paint: one lung adenoma, one papilloma at the site of application. Steam-refined bitumen paint: three epidermoid cancers, two papillomas at the site of application. Control group (toluene only): nine epidermoid cancers.	Simmers *et al.* 1965[98]
C57 Black mice (n=25 per sex). No control groups.	Mixture of fractions “saturates” and “aromatics” from “steam-refined bitumen”. Mice were painted three times a week in the intrascapular area, without shaving. However, material was rubbed into the fur by applying it with a small glass-stirring rod. Exposure was up to 40 weeks. Test material was three times weekly applied to the interscapular area for up to 20 months. Dose per application was on average 33.4 mg.	The author did not report on the number of tumour bearing animals groups.13/50 animals developed skin tumours: 7 epidermoid carcinomas; 5 basal cell carcinomas; 1 sebaceous gland carcinoma; 13 papillomas, one mixed with leiomyosarcoma (in the small intestine).	Simmers *et al.* 1965[89]

C57 Black mice (n=25/sex). Control groups included.	Various types of bitumen used: 4 road bitumens, steam distillation products of 4 different crudes from various sources; petroleum roofing bitumen, blown; and, acetone (control). Bitumen was applied undiluted or diluted with acetone, twice weekly for 2 years. Application side was the skin of the neck, the shaved dorsal skin, or inside the ear. Dose not specified.	Concerning skin cancer: of the animals exposed to diluted road bitumen, 2 developed papillomas and 1 carcinoma. Of the animals exposed to petroleum roofing bitumen 1 had a questionable carcinoma. None of the animals that served as control (acetone alone) or were exposed to undiluted heated bitumen developed tumours. Authors suggest that absorbed bitumen components could stimulate development of leukaemia, because 7 animals developed this cancer in the group with diluted bitumen.	Hueper and Payne 1960[88]
SS-57 white mice (n=40-52). Control, 23 animals. Sex unknown.	Three sludge bitumens (straight distillation (BN-2, BN-3 and BN-5). Also two bitumens from cracking-residue (BN-4, and BN-5). Oils origin from the Ukraine and Volga Region. Application: 40% in benzene (dose not specified), once weekly for 19 months.	*BN-2*: no tumours observed. *BN-3*: 2/43 skin tumours (1 subcutaneous fibrosarcoma; 1 papilloma); 1 lung adenoma; 2 lymphoreticular sarcomas; 1 hepatic haemangioma. *BN-4*: 1 keratinizing squamous cell carcinoma; 1 non-keratinizing squamous cell carcinoma; 2 papillomas. All four animals with tumours also had lung adenomas. *BN-5 (sludge bitumen):* 1 keratinizing cell carcinoma, 1 sebaceous gland adenoma; 5 animals with lung adenomas and adenocarcinomas. *BN-5 (cracking-residue)*: 5 keratinizing cell carcinoma; 1 fibrosarcoma; 3 papillomas (all at the application site); 7 animals with lung adenomas and adenocarcinomas; 1 animal with stomach carcinoma.	Kireeva 1968[90](source DFG)[2]
Swiss albino mice (n=12-14/sex/group). Control: 15 animals/sex.	Eight road paving grade bitumens, vacuum distilled, penetration 85/100 (according to ASTM). Bitumens were dissolved in benzene to give a 10% solution; 2.5 mg in 25 μL solution was applied twice weekly to shaved dorsal skin (2.5 cm^2) for more than 20 months.	Of the total of 218 exposed animals 6 developed tumours: 5 papillomas and 1 skin carcinoma. The authors considered the number of tumours too low to conclude on tumourigenicity of bitumen. One control animal (benzene solution only) developed a skin papilloma.	Wallcave *et al.* 1971[91]
Male C3H/HeJ mice; n=50/group. Control group included (toluene).	Bitumen from Athabasca tar sands. Bitumen was dissolved in toluene. Dose applied to the shaved area of interscapular skin was 25 μL of a 70% suspension in toluene, thee times weekly for life.	Average survival was 19 months. Of the exposed animals, 1 had a benign skin tumour and 1 a malignant skin tumour. Of the control animals treated with toluene alone, 1 developed a skin papilloma.	McKee *et al.* 1986[102]
Male C3H/HeJ mice; n=50/group. Control group included (toluene).	Bitumen derived from the Cold Lake Oil Sands deposit, located in Alberta, Canada. Bitumen was obtained by steam injection *in situ*. Dose applied to the interscapular region of the skin was 25 μL of a 70% suspension in toluene for two years.	Average survival was 88 weeks compared to 83 weeks in the control group. 26% of the treated animals developed skin tumours (8 malignant and 5 benign). This was significantly more than in the control group (0/50).	McKee and Lewis 1987[100]

Male C3H mice; n=50 per group; positive control group included (benzo(a)pyrene).	Test compound: 1) naphtenic AC-20 bitumen produced from a mix of Nigerian light , Maya and Alaska North Slope crudes, and 2) a naphtenic Coastal Residuum. Test compounds were applied in aliquots of 37.5 L twice weekly on the shaved backs of mice. Experimental periode not given.	None of the test compounds produced tumours. Benzo(a)pyrene induced tumours in 46 of the 50 animals. No further de tails given.	McGowan et al., 1992[103] (abstract only)

Annex **N**

Mutagenicity and genotoxicity

Tabel N.1. Bitumen products (not heated)

test system	type of bitumen and concentration	result	reference
Mutagenicity			
Ames *Salmonella* mutagenicity assay using TA98 and TA100 with and without S-9 activation.	Road construction bitumen (petroleum derivate, 80-100 penetration grade) collected from the field was separated from aggregate with benzene, etc. Residue was dissolved in cyclohexane and extracted with DMSO. Doses: up to 50 µg/plate.	Negative results with and without S-9 activation. Total PAH content in bitumen sample was low compared to a pitch sample (0.218 and 38.75 mg/g, respectively).	Pasquini *et al.* 1989[33]
Ames *Salmonella* mutagenicity assay using TA98 and TA100 with and without S-9 activation.	Five whole bitumen samples (taken before mixing with the gravel aggregate) from actual road paving operations in Oklahoma. No details were given on the origin of the bitumen and composition of the samples. The samples were warmed to approximately 60°C to allow a less viscous flow. Samples were extracted with DMSO and distilled in water (pH 5.0). Concentrations tested: 50 to 10,000 µg extract/plate.	Overall, samples were not to weakly mutagenic. Only one out of the five samples tested positive (one DMSO extract in TA100 plus S-9; one water extract in TA98 plus S-9).	Gage *et al.* 1991[104]

Modified Ames *Salmonella* mutagenicity assay using TA 98 (no information on use of S-9 activation).	A) naphthenic AC-20 bitumen produced from a mix of Nigerian light, Maya and Alaska North slope crudes; B) Naphthenic coastal residuum (CR). All samples were dissolved in cyclohexane and extracted with DMSO. Concentrations applied were up to 1.0 µL AC-20 extract/plate, and up to 15 µL CR-extract/plate).	Negative results. Positive and negative controls tested appropriately. No further details presented.	McGowan *et al*. 1992[103] (abstract only).
Modified Ames *Salmonella* mutagenicity assay using TA98 and TA100 with and without S-9 activation.	Three different samples of penetration bitumens (80 to 100 penetration grades) were collected during paving operations. Four fractions (with different polarities) of DMSO extract were used. Also DMSO-extracts from bitumen fumes (particulates) collected by personal samplers were tested (1-65 mg/plate); no data presented on application temperature.	Neither the bitumen samples nor the bitumen fumes showed mutagenic activity. Levels of total PAH (sum of 16 single PAH) in the samples were very low.	Monarca *et al*. 1987[106]
Ames *Salmonella* mutagenicity assay using TA98, TA100, TA1535, TA1537 and TA1538 with and without S-9 activation.	Four different bitumen-based paints with a primary component of a bitumen cutback (derived from solid petroleum bitumen material cut back to 64% solid with mineral spirits). These bitumen cutbacks were diluted with xylene or additional mineral spirits before application. Final cutback ranged from 89% to 98%. Doses applied were 0.005 to 10 µL/plate.	No mutagenic activity observed (with or without a metabolic activations system). No evident toxicity was found. The authors did not detect PAH or only trace amounts (*i.e*., phenanthrene). The committee noted that the authors did not report on the exact chemical composition of the paint (except for PAH). Therefore, care should be taken in interpreting the data.	Robinson *et al*. 1984[96]
In vivo DNA mutagenic activity of the urine of male Sprague-Dawley rats (4/group) by Ames mutagenicity assay (TA98).	Bitumen from road construction (80-100 pen), extracted in benzene and dissolved in DMSO. Animals received a single intraperitoneal injection of 10, 50 or 100 mg/kg bw.	No mutagenic activity, with or without a metabolic activation system (S9).	Pasquini *et al.* 1992[107] (source DFG)[2]
DNA adducts, strand breaks and DNA-protein crosslinking			
In vitro 8-OH-dG formation (reactive oxygen species formation), DNA-protein crosslinks, DNA double- and single-strand break testing in HL60 cells.	Bitumen was obtained from the distillation of crude oil from Hanwha Energy (South Korea). Bitumen for testing was dissolved in tetrahydrofuran. Cells were treated with 10 µg bitumen/mL; for 8-OH-dG formation 100 µg bitumen/mL was used. Authors also investigated effects of combined exposure with UVA.	No single- or double strand breaks found in treated cells. Bitumen alone did not cause an significant increase of reactieve oxygen species. Also no significant increase in DNA-protein crosslinks was found. Authors did not report on statistical analysis.	Hong and Lee 1999[105]

In vitro lymphoma forward mutation assay with mouse lymphoma cell line L5178Y.	Vacuum petroleum residuum (CAS 64741-56-6; API #81-13 and API#81-14), dissolved in corn oil. Cells were exposed for 4 hours to a concentration range of 62.5 μgmL to 1,000 μg/mL, with or without S-9 activation.	Samples were weakly active in the mouse lymphoma assay (with S-9 activation).	American Petroleum Institute (API) 1984[109,177]
In vivo DNA-adduct formation (^{32}P-postlabeling) in female CD mice (5 animals per group).	Bitumen vacuum residuum (CAS 64741-56-6). Samples were extractions of the total PAC fraction. Extracts were dissolved in tetra-hydrofuran. Test compound (1 mg extract in 25 μL solvent (= 40 mg/ mL)) was once applied to the skin.	Adduct level only slightly above background. Comparison with other oil products revealed a correlation between DNA adduct content and the amount of polycyclic aromatic compounds.	Booth *et al.* 1998[108]
In vivo DNA strand breaks in the livers of female Sprague-Dawley rats (1 animal per test).	Road construction bitumen (petroleum derivate, 80-100 penetration grade) collected from the field was separated from aggregate with benzene, etc. Residue was dissolved in olive oil. A single intraperitoneal dose of 50 mg/kg bw was given. Negative and positive controls were included.	No significant increase in DNA strand breaks over a period of 72 hours after treatment.	Pasquini *et al.* 1989[33]
Chromosomal abberations and micronuclei formation			
In vivo chromosomal aberrations in male and female Sprague-Dawley rats (8-10 animals per group) using the bone marrow cytogenitic assay	Vacuum petroleum residuum (CAS 64741-56-6; API #81-13 and API#81-14), dissolved in corn oil. Oral administration (*per os*) of 0.3, 1 or 3 g/kg bw (five daily doses). Bone marrow was samples 6 hours after last dose. Control groups were included.	No significant increase in number and frequency of chromosomal aberrations in bone marrow compared to negative control.	American Petroleum Institute (API) 1984[109,177]

Tabel N.2. Bitumen fume and bitumen fume condensates (generated at temperatures below 230°C)

test system	type of bitumen and concentration	result	reference
Mutagenicity			
Modified Ames *Salmonella* mutagenicity assay using TA98 with S9 activation.	Paving bitumen fumes were generated at 163°C (one sample to 221°C). All fumes and vapours were condensed; in this study only the oil phase of the condensates were tested (200 mg in 1 mL DMSO). Data were compared with coal tar fumes (generated at 316°C).	Mutagenic activity of bitumen fumes was weak to moderate, and approximately 100-fold less than for coal tar fumes. No changes in mutagenic activity of roofing bitumen fumes were found by increasing generation temperature.	Machado *et al*. 1993[111]
Modified Ames *Salmonella* mutagenicity assay using TA98 and S-9 activation.	Field bitumen fume condensates were collected from the headspace above a hot mix bitumen storage tank. Tank temperatures ranged from 147 to 157°C during collection. Laboratory bitumen fume condensates were prepared by heating condensates to 149°C (and 316°C). Dose applied was up to 10 μg/plate.	Condensates collected from the hot mix tank were not mutagenic. Laboratory fume condensates were mutagenic; the 316°C samples being more mutagenic than the 149°C samples (mutagenicity index of 8.3 and 5.3, respectively). The authors reported that the 316°C samples contained more (three- to four-ring) polycyclic sulphur heterocyclic compounds than the 149°C samples. The laboratory-generated samples contained 5 to 100 times more of these compounds than the field generated samples.	Reinke *et al*. 2000[9]
Ames *Salmonella* mutagenicity assay using TA98, TA100, YG 1041 and YG 1042 with or without S-9 activation.	Laboratory fume condensates were prepared by heating bitumen ((45/60 pen and 160/210 pen) to 160°C and 200°C. Also coal-tar fume condensates were prepared by heating coal tar to 110°C and 160°C. Various amounts applied in 10 μL (no further details given).	With S-9 activation, all tested samples were mutagenic to all strains; the mutagenic potency of coal tar condensates were 15- to 600-fold higher than of the bitumen samples. The content of total PAH (sum of 16 single PAH) was much higher in coal-tar fume condensates than in bitumen fume condensates.	De Méo *et al*. 1996[178]

Ames *Salmonella* mutagenicity assay using TA98 and YG1024 with or without S-9 activation.	*Laboratory generated* bitumen vapours and particulates were obtained by heating bitumen to 170°C. Three different lab-generated fumes were tested: bitumen B120; bitumen B80 + coal fly ash (66%); and, bitumen B120 + waste plastics (10%). *Field generated* bitumen fume samples were collected on filters at paving sites (breathing zone samples). Samples of five different bitumens were tested (paving temp/remixing temp): stone mastic bitumen (SMA) + lime (10%) (175-200°C); SMA + coal fly ash (10%) (170-210°C); remixing of SMA + lime (10%) (180-207/150-260°C); remixing of SMA + coal fly ash (10%) (190/160-250°C); and, remixing of bitumen cement (160/310-350°C). Doses applied were 0.03 to 0.5 mg/plate. 4-nitroquinoline-1-oxide (without S9 activation) and 2-aminoanthracene (with S9 activation) served as positive control.	This study aimed at investigating the genotoxic potential of recycled additives and remixing of bitumen. All *laboratory generated* vapour fractions were negative, whereas particle fractions showed mutagenicity when strain TA98 was used (at maximum doubling or near doubling of revertants compared to negative control; with or without S9). Of the *field samples*, only particulate fractions were tested. In tests with strain TA98, the field samples tested positive (at maximum doubling or near doubling of revertants compared to negative control), with or without S9 activation. One sample (remixing of bitumen cement) scored very high. The committee, however, has some doubts about the relevance of this latter sample, because in this case an unusually high remixing temperature was used. Overall, the authors concluded that remixing fumes may have higher ability to induce mutagenic activity then normal paving fumes or laboratory generated fumes. Additional notes from the committee: the authors did not report on possible co-exposure with diesel exhaust, which is likely due to the nature of the work of the road pavers (diesel exhaust have been shown to test positive in Ames tests); in road paving only 1% of the bitumen that is used concerns mastic bitumen.	Heikkilä *et al*. 2003[110]
Ames *Salmonella* mutagenicity assay: TA97, TA98, TA100, TA1535.	Various condensates from welded polymer bitumen sheeting, and welded bitumen sheeting for roofing. Fumes were generated at 80°C. Extraction with acetone and pentane.	Negative results with and without a metabolic activation system (S9). For the committee the presented data were insufficient to make a conclusion.	Sonntag and Erdinger 1989[179] (short summary)
Ames *Salmonella* mutagenicity assay: TA98, TA100.	Condensates from bitumen E (Venezuela) and S (Middle-East); both oxidised bitumen 85/25. Fumes were generated at 190°C. Samples were extracted with acetone and dissolved in DMSO or in aqueous Tween solution.	Bitumen E was weakly positive (maximum effect: doubling of the number of revertants) with or without S9. Bitumen S was negative with or without S9, though an increasing mutagenicity was observed with T100 and no S9. For the committee the presented data were insufficient to make a conclusion.	Sonntag and Erdinger 1992[180] (short summary)

Spiral Ames *Salmonella* mutagenicity assay using TA98 and TA100 with and without S-9 activation.	Bitumen fume air samples were collected above an open port of the heated cement storage tank at seven hot-mix plants (application temperature between 99 and 147°C (211-296°F). Only whole fumes were tested in the first four plants, for the last three, whole and fractionated fumes were tested. In addition, at each plant, two samples were collected for mutagenicity testing, one with and one without crumb-rubber added to the bitumen formulation. Doses applied not reported.	No mutagenic activity observed in any of the samples. No further details given.	Burr *et al*. 2002[53]
In vivo DNA mutation and adduct testing in transgenic male *LacI* mice C57B1/6 (lambda *LIZ*, Big Blue®).	Bitumen (CAS 8052-42-4) of Venezuelan origin (50/70 pen). Fume was generated at 170°C. Five animals were nose only exposed to bitumen fume (100 mg/m^3 total particulate matter) for 6 hours/day, 5 days/week for 4 weeks. Six animals served as controls (clean air).	Authors did not demonstrate any mutagenicity in the lungs of these mice.	Micillino *et al*. 2002[113]
In vivo DNA mutation and adduct testing in transgenic male Fisher 344 rats (lambda *LIZ*, Big Blue®).	Bitumen (CAS 8052-42-4) of Venezuelan origin. Fume was generated at 170°C. Twelve animals were nose only exposed to bitumen fume (100 mg/m^3 total particulate matter) for 6 hours a day for 5 days. Control animals were exposed in similar conditions in clean air. The experiment was terminated 3 and 30 days after the last exposure.	Three and thirty days after ending exposure a DNA adduct was observed in exposed animals. However, at 30 days, the *cII* mutant frequency did not differ from those of control animals. In exposed animals a slight but non significant modification of the mutation spectrum associated with an increase of G:C to T:A and T:A to C:G was noticed. During exposure exposed animals had significantly higher concentrations of 1-hydroxypyrene in their urine than control animals.	Bottin *et al*. (2006)[181]
DNA adducts, strand breaks and DNA-protein crosslinking			
In vitro ^{32}P-post-labeling method using calf thymus DNA with S-9 activation.	Laboratory fume condensates were prepared by heating bitumen ((45/60 pen and 160/210 pen) to 160°C and 200°C. Also coal-tar fume condensates were prepared by heating coal tar to 110°C and 160°C. Concentration tested was 20 µg condensate/18 µL acetone (final volume 1 mL). BaP served as positive control.	All fume condensates produced the formation of DNA adducts. However, the amount of DNA adducts differed; the highest amounts were found for coal-tar, followed by bitumen 160/210 pen and bitumen 45/60 pen fume condensates. The pattern of DNA-adducts between the bitumen fume condensates en the coal tar fume condensates were qualitatively different. No specific adducts were identified.	De Méo *et al*. 1996[178]

In vitro ^{3}P-postlabeling method using calf thymus DNA and S-9 activation.	Various sources of bitumen fume condensates: road paving bitumen from hot storage tanks (156°C, 163°C or 146°C); and, type IV roofing bitumen from hot storage tank (227°C). Concentration tested was 25 mM (dissolved in DMSO).	DNA adduct formation by bitumen fume condensates was very low and comparable to severely hydrotreated naphtenic base-oils. Other oil-derived products, such as coal tar and crude oil distillates, showed a high amount of DNA adducts.	Akkineni *et al*. 2001[115]
In vitro ^{32}P-postlabeling method using cal thymus DNA with and without S-9 activation.	Condensates of bitumen from heavy Venezuela crude oil (45/60 pen), obtained at 160°C and 200°C. Condensates were dissolved in acetone (50 μg in 500 μL).	No DNA-adducts were detected without S-9 activation. DNA-adducts were found in the presence of microsomes from wild type mice and from mice deficient in AH-receptor and CYP1A2. Also adducts were found in the presence of microsomes from yeast expressing CYP1A1, 3A4 and 1A2.	Genevois *et al*. 1998[114]
In vivo DNA adduct formation (^{32}P-postlabeling) in female B6C3F1 mice (32 mice; an additional 16 mice served as control).	Hot performance Grade Asphalt PG 64-22 was preheated to 200°C. Fume was generated by passing heated air (180°C) over the upper surface of the bitumen. Animals were whole body exposed to the volatile fraction in an exposure chamber for 4 hours/day over 10 days. Concentrations of bitumen fume particulates in the animal chamber ranged from 152 to 198 mg/m^3.	The authors identified several types of DNA-adducts at very low levels. These adducts were significantly increased in the lung tissue of exposed mice compared to non-exposed mice.	Wang *et al*. 2003[116]
In vivo DNA-adduct formation (^{32}P-postlabeling) in BD4 rats (3 animals per group).	Condensates of industrial paving bitumen (45/60 pen and 160/210 pen). Samples obtained by heating at 160°C and 200°C. The condensates were the same as used by De Méo *et al*. (1996a). 100 μL (about 100 mg) of undiluted condensate was applied to the shaved dorsal skin twice in three days. The presence of DNA-adducts was examined in the skin, the lungs and lymphocytes.	DNA-adducts were found in the skin, the lungs and lymphocytes in the treated animals. No specific DNA-adduct was identified. Data are in agreement with data from De Méo *et al*. (1996a).	Genevois *et al*. 1996[44]
In vivo DNA-adduct formation (^{32}P-postlabeling) in Sprague-Dawley BD6 rats (3/group; 1 control per group).	Bitumen from Venezuelan (45/60 pen) or Middle East (160/210 pen) origen. In the laboratory, fumes were generated at 200°C. Animals were exposed nose only to 5 or 50 mg/m^3 (total particulate matter) for 6 h/day for 5 days.	At 5 mg/m^3 no adducts were formed in any of the tissues examined. At 50 mg/m^3, tissue analysis of the lungs, the liver, the kidneys and blood lymphocytes revealed that only in the liver DNA adducts were formed. Analysis of urinary 1-hydroxypyrene was negative at both concentrations.	Genevois-Charmeau *et al*. 2001[118]

In vivo DNA damage (Comet assay) in female Sprague-Dawley rats (number of animals not mentioned).	Bitumen (for road paving) was preheated to 170°C before it was passed through a heated pipe (150C, inlet; 120°C, outlet) into the animal exposure chamber. Before it entered the exposure chamber the air was humidified. Animals were exposed at 6 hours/day for 1 or 5 days. Daily bitumen fume concentrations were approximately 25, 38 and 58 mg/m^3. Control animals were exposed under the same conditions with air only.	Bitumen fume significantly induced DNA damage in alveolar macrophages and in lung tissue compared to controls ($p<0.05$).	Zhao *et al.* 2004[117]
Chromosomal abberations and micronuclei formation			
In vivo micronuclei formation in female Sprague-Dawley rats (6 animals per group).	Bitumen (for road paving) was preheated to 170°C before it was passed through a heated pipe (150°C, inlet; 120°C, outlet) into the animal exposure chamber. Before it entered the exposure chamber the air was humidified. Animals were exposed to approximately 58 mg/m^3 for 6 hours/day for 5 days. Control animals were exposed under the same conditions with air only.	Bitumen fume did not statistically significantly increase the number of induce micronuclei in bone marrow polychromatic erythrocytes. Values in controls were 0.9±0.8 micronuclei/1000bonemarrow polychromatic erythrocytes, those of exposed 1.6±0.9.	Zhao *et al.* 2004[117]
In vivo micronuclei formation in male Sprague-Dawley rats (5 animals per group).	Fume condensates from paving bitumen (PG 64-22) at 160°C. Condensates were dissolved in DMSO. Rats were exposed to saline, 0.45 or 8.9 mg/kg bw by intratracheal installation for 3 consecutive days.	Increased micronuclei formation in bone-marrow polychromatic erythrocytes was observed only in high dose group. Furthermore, exposure did not afffect total cytochrome P450 content, cytochrome c reductase, CYP2B1 levels and enzyme activity in the lungs. However, CYP1A1 level and activity was increased.	Ma *et al.* 2002[119]
In vitro chromosomal aberration assay using Chinese hamster ovary cells with or without S9-activation.	*Field* bitumen fume condensates were collected from the headspace above a hot mix bitumen storage tank. Tank temperatures ranged from 147 to 157°C during collection. *Laboratory* bitumen fume condensates were prepared by heating bitumen to 149°. Concentrations tested: 5-120 μg/mL.	Results were negative (both with and without a metabolic activation system). Authors suggested that this outcome may be explained by the fact that this assay was not optimized for these bitumen fumes.	Reinke *et al.* 2000[9]

Tabel N.3. Bitumen fume and bitumen fume condensates (generated at temperatures above 230°C)

test system	type of bitumen and concentration	result	reference
Mutagenicity			
Modified Ames *Salmonella* mutagenicity assay using TA98 and S-9 activation.	Laboratory bitumen fume condensates were prepared by heating bitumen to (149°C and) 316°C. Dose applied was up to 10 μg/plate.	Laboratory fume condensates were mutagenic; the 316°C samples being more mutagenic than the 149°C samples (mutagenicity index of 8.3 and 5.3, respectively). The authors reported that the 316°C samples contained more (three- to four-ring) polycyclic sulphur heterocyclic compounds than the 149°C samples. The laboratory-generated samples contained 5 to 100 times more of these compounds than the field generated samples.	Reinke *et al*. 2000[9]
Modified Ames *Salmonella* mutagenicity assay using TA98 with S9 activation.	Test material included: 2 coal tar pitches (ASTM type I), and 2 roofing bitumens (ASTM type III). Coal tar pitch and roofing bitumen fumes were generated in the laboratory at 232 or 316°C for 6 hours. All fumes and vapours were condensed; in this study only the oil phase of the condensates were tested (200 mg in 1 mL DMSO).	PAH content and mutagenicity was much higher for coal tar pitch than for roofing and paving bitumen fumes. Mutagenic activity of bitumen fumes was approximately 100-fold less than for coal tar fumes. No changes in mutagenic activity of roofing bitumen fumes were found by increasing generation temperature. For paving bitumen fumes, changes with generation temperature could not be assessed due to the limited data.	Machado *et al*. 1993[111]
Modified Ames *Salmonella* mutagenicity assay using TA98 and S-9 activation.	Roofing and neat (unfractioned) bitumen fume condensates from the study by Sivak *et al.* 1989. Bitumen fumes were regenerated at 316°C. The mitotic index is expressed as revertants x 10^{-5} per 10 kg, and contains the dose range 0.1 to 0.5 mg.	The mutagenicity index of whole bitumens was in the range of inactive to marginally active. Fume condensates were weakly positive. A coal tar pitch control was more than 100-times stronger than the bitumen samples.	Blackburn and Kriech 1990 (source NIOSH)[1]
DNA adducts, strand breaks and DNA-protein crosslinking			
In vivo DNA-adduct formation (^{32}P-postlabeling) in male CD rats (3 animals per group).	Whole fume condensates of type I and III roofing bitumens prepared in the laboratory. Fumes were regenerated at 316C; condensates were dissolved in DMSO. Exposure by intratracheal instillation at 8 hour intervals of 3 doses of 250-2,000 mg/kg bw. DNA-adducts determined in the lungs and white blood cells.	In the lungs, a dose-dependent increase in DNA-adducts was observed. No adducts were found in the white blood cells. DFG[2] noted that data for the doses in the tables did not agree with those in the text. The committee noted that the exposure route is not relevant for humans.	Qian *et al*. 1998[123]

Chromosomal abberations and micronuclei formation

In vitro micronucleus formation in Chinese hamster lung fiborblast (V79).	Condensates of type I and III roofing bitumen fumes generated in the laboratory at 316°C. Both whole fume condensates as well as condensates of fractions of type III bitumen fumes (A to E, different contents). Concentrations tested: 8-250 mg/mL.	A dose-related increase in micronucleus formation was found for whole bitumen condensates and all fractions, except for fraction A (*e.g.* alkanes, alkylated benzens, alkylated naphthalenes). Authors suggest that their test compounds possess some clastogenic activity.	Qian *et al*. 1996[121], 1999[122]
In vitro chromosomal aberration assay using Chinese hamster ovary cells with or without S9-activation.	Laboratory bitumen fume condensates were prepared by heating bitumen to 316°C. Concentrations tested: 5-120 μg/mL.	Results were negative (both with and without a metabolic activation system). Authors suggested that this outcome may be explained by the fact that this assay was not optimized for these type of bitumen fumes.	Reinke *et al*. 2000[9]

Intercellular communication

In vitro using Chinese hamster lung fibroblast (V79).	Fume condensates from air-blown Arabian crude bitumen (type III). Fumes were generated in the laboratory by heating to 316 °C. Fume condensates were then fractionated into five fractions (A to E, different contents). Concentrations applied: 0-50 μg/mL.	Fractions B to E were all cytotoxic at concentrations between 15 and 20 μg/mL (reduced colony formation). All fractions inhibited intercellular communication in a dose-dependent way, although there were some differences in activity (the least active was fraction A, containing mainly C3 to C35 alkanes, alkylated benzenes and alkylated naphthalenes).	Toraason *et al*. 1991[182]
In vitro using cultured human epidermal keratinocytes.	Fume condensates from air-blown Arabian crude bitumen (type III). Fumes were generated in the laboratory by heating to 316 °C. Fume condensates were then fractionated into five fractions (A to E, different contents). Concentrations applied: 0-50 μg/mL (fraction A also 100 μg/mL).	All fractions inhibited intercellular communication in a concentration-dependent manner. Statistical significance was reached at 10 (B, E) or 25 (A, C, D) μg/mL.	Wey *et al*. 1992[183]

Annex **O**

Classification of substances with respect to carcinogenicity

The committee expresses its conclusions in the form of standard phrases:

Judgement of the committee	Comparable with EU class
This compound is known to be carcinogenic to humans • It is genotoxic • It is non-genotoxic • Its potential genotoxicity has been insufficiently investigated. Therefore, it is unclear whether it is genotoxic	1
This compound should be regarded as carcinogenic to humans • It is genotoxic • It is non-genotoxic • Its potential genotoxicity has been insufficiently investigated. Therefore, it is unclear whether it is genotoxic •	2
This compound is a suspected human carcinogen. • This compound has been extensively investigated. Although there is insufficient evidence for a carcinogenic effect to warrant a classification as 'known to be carcinogenic to humans' or as 'should be regarded as carcinogenic to humans', they indicate that there is cause for concern. • This compound has been insufficiently investigated. While the available data do not warrant a classification as 'known to be carcinogenic to humans' or as 'should be regarded as carcinogenic to humans', they indicate that there is a cause for concern.	3 (A) (B)
This compound cannot be classified	not classifiable

Annex **P**

Guideline 93/21/EEG of the European Union

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.

Annex **O**

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 which 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_{10}	lowest lethal concentration
LD_{50}	lethal dose for 50% of the exposed animals
LD_{10}	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 (the USA)
FDA	Food and Drug Administration (the USA)
HSE	Health and Safety Executive (the 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 (the USA)
NTP	National Toxicology Programme (the USA)
OECD	Organisation for Economic Cooperation and Development
OSHA	Occupational Safety and Health Administration (the 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 (the UK)
WHO	World Health Organisation

Toxicological terms

bid	*bis in diem* (twice a day)
bw	body weight
CARA	chronic non-specific respiratory diseases
ECG	electrocardiogram
EEG	electro encephalogram
FEV	forced expiratory volume
FSH	follicle stimulating hormone
GD	gestation day(s)
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
PMR	proportional mortality ratio
RR	relative risk
SD	standard deviation
SEM	standard error of mean
SIR	standardized incidence ratio
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

AI	Asphalt Institute (the USA)
API	American petroleum Industry
AWE	asphalt worker exposure
B[a]P	benzo[a]pyrene
BSM	benzene soluble matter
FHWA	Federal Highway Administration (the USA)
PAC	polycyclic aromatic compound
PAH	polycyclic aromatic hydrocarbon
ROCEM	road construction workers' exposure matrix
TOM	total organic matter
TPA	12-*O*-tetradecanoylphorbol-13-acetate
TPM	total particulate matter
VOC	volatile organic compound