Asphalt and Asphalt Emissions Associated with Road Paving and Asphalt and Asphalt Emissions Associated with Roofing

Asphalt (bitumens) is produced from residues generated during the refining of petroleum crude oils. Asphalt is distinct from coal tars[1] and coal tar pitches[2]. Asphalt and asphalt emissions (i.e., gases, solid particulate matter, condensed vapor, and liquid asphalt droplets) are a complex mixture of aliphatic compounds, cyclic alkanes, aromatic hydrocarbons, polycyclic aromatic hydrocarbons (PAHs) and heterocyclic compounds containing nitrogen, oxygen and sulfur atoms, and metals.

The International Agency for Research on Cancer (IARC, 2013) recently grouped the different types of asphalt into six classes. Class 1 asphalt, also known as straight-run asphalt, is used in road paving. Class 2 asphalt includes oxidized asphalt and air-blown asphalt, and is used mostly in roofing[3]. Most of the asphalt in the US is used for either road paving (87%) or roofing (11%) activities (NIOSH, 2001a). Human exposure may occur in occupational settings, and the general public may be exposed as a result of breathing contaminated air.

Asphalt and asphalt emissions associated with road paving and roofing each passed the human and animal data screens, underwent preliminary toxicological evaluations, and are being brought to the Carcinogen Identification Committee for consultation. This is a compilation of the relevant studies identified during the preliminary toxicological evaluations. The CIC is being asked to advise OEHHA on whether either or both of these two classes of asphalt and asphalt emissions (i.e., those associated with road paving and those associated with roofing) should be considered for listing at a future CIC meeting.

Epidemiological data

The epidemiologic evidence for the carcinogenicity of asphalt and asphalt emissions was reviewed comprehensively in 2013 (See IARC, 2013, pp. 90-140). The IARC (2013) evaluation of the epidemiological evidence is as follows:

- "There is *inadequate evidence* in humans for the carcinogenicity of occupational exposures to bitumens and bitumen emissions during road paving."
- "There is *limited evidence* in humans for the carcinogenicity of occupational exposures to bitumens and bitumen emissions during roofing and mastic-asphalt work. A positive association has been observed between occupational exposures to bitumens and bitumen emissions during roofing and mastic-asphalt

[1] Coal tars are products of the destructive distillation of coals.
[2] Coal tar pitches are residues from the distillation of coal tars.
[3] Class 2 "oxidized asphalt" comprises two grades of oxidized asphalt, namely fully-oxidized (penetration index > 2) and air-rectified (semi-blown) (penetration index ≤ 2). These grades differ by their degree of oxidation during production, which leads to very different characteristics and uses. Air-rectified asphalt has applications similar to those of Class 1 asphalt (road paving).

work and cancers of the lung and the upper aerodigestive tract (buccal cavity, pharynx, oesophagus and larynx)."

Since the IARC review, one new epidemiology study and two new meta-analyses have reported findings for asphalt emissions and cancer risk:

- Occupational cohort study of asphalt roll (a type of asphalt membrane for roofing) workers in Italy: Zanardi *et al.* (2013)
    - *Increased risk of mortality from pharyngeal/tonsillar cancer, Standardized Mortality Ratio (SMR)=21 (95% Confidence Interval [CI] 8.8–51) among blue-collar workers on the production line (co-exposure to asbestos not adjusted for)*
    - *Increased risk of mortality from stomach cancer, SMR=5.3 (95% CI 2.2–12.8) among blue-collar workers on the production line (co-exposure to asbestos not adjusted for)*
- Meta-analyses of occupational exposure to PAHs and risk of cancer
    - Meta-analysis of 63 studies on the risk of laryngeal cancer in workers exposed to PAHs, including 12 risk estimates for asphalt exposed workers: Wagner *et al.* (2015)
        - *Pooled Effect Size (ES)=1.30 (95% CI 0.95–1.78) in the "asphalt exposed" subgroup*
    - Meta-analysis of 13 studies on the risk of respiratory and urinary tract cancers in workers exposed to PAHs, include three cohort studies of asphalt exposed workers: Rota *et al.* (2014)
        - *Pooled Relative Risk (RR)=1.89 (95% CI 0.45–7.95) for laryngeal cancer among asphalt workers (2 cohorts)*
        - *Pooled RR=1.59 (95% CI 0.68–3.76) for lung cancer among asphalt workers (3 cohorts)*
        - *Pooled RR=1.03 (95% CI 0.82–1.30) for bladder cancer among asphalt workers (2 cohorts)*

Animal carcinogenicity data

Asphalt and Asphalt Emissions Associated with Road Paving

- Long-term skin application studies in mice
    - Two-year study in male C3H/HeNCrl mice with daily applications of "field-matched" paving asphalt fume condensate: Clark *et al.* (2011), as reviewed in IARC (2013, pp. 143 and 151)
        - *No treatment-related tumor findings*
    - Two-year studies in male C3H/HeNCrlBR mice with 2x/week applications of paving asphalt or its vacuum residuum: Goyak *et al.* (2011), as reviewed in IARC (2013, pp. 143 and 151)
        - *No treatment-related tumor findings with paving asphalt or its vacuum residuum*
    - Two-year studies in C57 Black mice (male and female combined) with 2x/week applications of "road petroleum asphalt" obtained by steam

distillation of crudes from Mississippi, California, or Venezuela, and by steam-vacuum distillation of one Oklahoma crude: Hueper and Payne (1960), as reviewed in IARC (2013, p. 145)
    - *One skin carcinoma and one skin papilloma in mice treated with the Mississippi sample, and one skin papilloma in mice treated with the Oklahoma sample*
    - *No vehicle controls, although untreated controls were included*
  - 23-month study in C57 Black mice (male and female combined) with 3x/week applications of "steam-refined petroleum asphalts" (Class 1): Simmers (1965a), as reviewed in IARC (2013, p. 140)
    - *3 skin squamous cell carcinomas*
    - *2 papillomas and one adenoma of the lungs*
    - *High mortality in the early part of the study; 13 mice added to the study after one year*
  - >80-week study in female C57 Black mice with 3x/week applications of a mixture of "aromatics" and "saturates," isolated by fractionation of a "steam-refined asphalt" (Class 1) from a California crude petroleum: Simmers (1965b), as reviewed in IARC (2013, p. 145)
    - *Skin papillomas, epidermoid skin carcinomas, baso-squamous cell cancers and one sebaceous-gland carcinoma*
    - *No control*
  - ≥ 82-week study in Swiss albino mice (male and female combined) with 2x/week applications of "road-paving-grade asphalts" (Class 1) produced by vacuum distillation from well-defined crude sources and dissolved in benzene: Wallcave *et al.* (1971), as reviewed in IARC (2013, p. 146)
    - *No treatment-related tumor findings*
  - 19-month studies in SS-57 white mice (sex unreported) with 1x/week applications of four residual (straight distillation; Class 1) asphalt samples (BN-5, BN-4, BN-3 and BN-2): Kireeva (1968), as reviewed in IARC (2013, pp. 145-146)
    - *No treatment-related skin or lung tumors*

- Long-term skin application studies in rabbits
  - Two-year study in New Zealand rabbits (sex not reported) with 2x/week applications of "road petroleum asphalts" (Class 1) obtained by steam distillation of crudes: Hueper and Payne (1960), as reviewed in IARC (2013, p. 154)
    - *No treatment-related tumor findings*
    - *Small number of animals (six)*
    - *No control*

- Long-term subcutaneous/intramuscular injection studies in mice
  - Long-term study (duration varies, up to 26 months) in C57 Black mice (male and female combined) with subcutaneous injections (either a single injection, or 8 injections over a 16-week period, or 9–11 injections over the lifetime) of a mixture of "aromatics" and "saturates" isolated by

fractionation of a steam-refined asphalt (Class 1) from a California crude petroleum: Simmers (1966), as reviewed in IARC (2013, p. 152)
    - *Tumors of the lung (adenomas and adenocarcinomas) and "skin accessory organs" (adenocarcinomas) were observed in all treatment groups*
    - *Animals were lost and replaced in the middle of the experiment*
    - *No control*
  - Two-year studies in C57 Black mice (sex not reported) with six intramuscular injections (2x/week) of one of four "road petroleum asphalts" (Class 1) obtained by steam distillation of crudes from Mississippi, California, or Venezuela, and by steam-vacuum distillation of one Oklahoma crude: Hueper and Payne (1960), as reviewed in IARC (2013, pp. 152-153)
    - *Sarcoma at the injection site in one mouse in each of the groups treated with asphalt obtained from Mississippi, California, or Venezuela*

- Long-term intramuscular injection study in rats
  - Two-year study in Bethesda Black rats (sex not reported) with 12 intramuscular injections (2x/week) of "road petroleum asphalts" (Class 1) obtained by steam distillation of crudes: Hueper and Payne (1960), as reviewed in IARC (2013, pp. 153-154)
    - *Increase in sarcoma at the site of injection compared to untreated control*
    - *No vehicle control*

- Long-term inhalation studies in rats
  - Two-year studies in male and female Wistar rats exposed for 6 hours/day to 0-100 mg/m^3 asphalt fume condensate collected from a storage tank at 175^{o}C, resembling exposures during road paving): Fuhst *et al.* (2007), as reviewed in IARC (2013, pp. 153-154)
    - *One poorly differentiated adenocarcinoma (rare) of the nasal cavity in a high-dose male*
    - *No treatment-related tumor findings in females*

Asphalt and Asphalt Emissions Associated with Roofing

- Long-term skin application studies in mice
  - Two-year studies in male C3H/HeNCrl mice with 2x/week applications of "field-matched" or "lab-generated" built-up roofing asphalt fume condensate: Clark *et al.* (2011), see also IARC (2013, pp. 143, 149, and 151)
    - *Increases in skin squamous cell papilloma, skin squamous cell carcinoma, and skin squamous cell papilloma and carcinoma (combined) (each by pairwise comparison) with field-matched built-up roofing asphalt fume condensate*

        - *Increases in skin squamous cell carcinoma, and skin squamous cell papilloma and carcinoma (combined) (each by pairwise comparison) with lab-generated built-up roofing asphalt fume condensate*
    - Two-year studies in male C3H/HeJ mice with 2x/week applications of roofing asphalt fume condensates: Sivak *et al.* (1989) and Sivak *et al.* (1997), see also IARC (2013, pp. 147, 149, and 150)
        - *Increases in skin papilloma (by pairwise comparison) with the application of either neat fume condensates or reconstituted condensates, and skin carcinoma and combined papilloma and carcinoma (each by pairwise comparison) with the application of either neat fume condensates, fume condensate fractions B and C, or reconstituted condensates*
    - Two-year studies in male Sencar mice with 2x/week applications of roofing asphalt fume condensates: Sivak *et al.* (1989) and Sivak *et al.* (1997), see also IARC (2013, pp. 147, 149, and 150)
        - *Increases in skin papilloma and skin carcinoma (by pairwise comparison) with the application of neat fume condensates*
    - Two-year study in male and female C57 Black mice with 2x/week applications of "air-blown asphalt" used for roofing purposes: Hueper and Payne (1960), as reviewed in IARC (2013, p. 145)
        - *One skin carcinoma*
        - *No control*
    - 23-month study in C57 Black mice (male and female combined) with 3x/week applications of heated "air-refined (oxidized) petroleum asphalts: Simmers (1965), as reviewed in IARC (2013, pp. 140 and 145)
        - *Increase in skin squamous cell carcinoma (by pairwise comparison)*
        - *2 lung adenomas*
    - >80-week study in male C3H/HeJ mice with 2x/week applications of "standard roofing petroleum asphalt" (Class 2) dissolved in toluene: Emmett *et al.* (1981), as reviewed in IARC (2013, p. 146)
        - *No treatment-related skin tumor findings*
    - 78-week studies in male CD-1 mice with 2x/week applications of four types of roofing asphalt fume condensates: Thayer *et al.* (1981), see also NIOSH (2001b, pp. 81-82)
        - *Increases in benign skin tumors (by pairwise comparison) and benign and malignant skin tumors combined (the majority of these tumors were squamous cell papillomas and carcinomas) (by pairwise comparison) with all four types of roofing asphalt fume condensates*
    - 78-week studies in male C3H/HeJ mice with 2x/week applications of four types of roofing asphalt fume condensates: Thayer *et al.* (1981), see also NIOSH (2001b, pp. 81-82)
        - *Increases in benign skin tumors, malignant skin tumors, and benign and malignant skin tumors combined (the majority of these tumors*

were squamous cell papillomas and carcinomas) (each by pairwise comparison) with all four types of roofing asphalt fume condensates

- Long-term skin application studies in rabbits
  - Two-year study in New Zealand rabbits (sex not reported) with 2x/week applications of "air-blown asphalt" (Class 2): Hueper and Payne (1960), as reviewed in IARC (2013, pp. 154-155)
    - *No treatment-related tumor findings*
    - *Small number of animals (six)*
    - *No control*

- Long-term inhalation studies in rats or guinea pigs
  - Two-year study in female Bethesda Black rats with "fumes" of a "blown petroleum roofing asphalt" (Class 2) (5 hours/day, 4 days/week): Hueper and Payne (1960), as reviewed in IARC (2013, p. 154)
    - *No treatment-related lung tumor findings*
    - *No control*
  - Two-year study in Strain 13 guinea pigs (sex not reported) with "fumes" of a "blown petroleum roofing asphalt" (Class 2) (5 hours/day, 4 days/week): Hueper and Payne (1960), as reviewed in IARC (2013, p. 155)
    - *No treatment-related tumor findings*
    - *No control*

- Tumor initiation-promotion skin application studies in mice
  - 6-month initiation-promotion studies in male Crl:CD1 mice with skin applications of "field-matched" "BURA type III" (Class 2) fume condensate (collected at 199 °C) as (i) an initiator and 12-O-Tetradecanoylphorbol-13-Acetate (TPA) as tumor promoter, and (ii) a promoter with 7,12-dimethylbenzanthracene (DMBA) as an initiator: Freeman *et al.* (2011), as reviewed in IARC (2013, pp. 151-152)
    - *Apparent initiating activity, based on increased incidence of skin squamous cell papilloma*
    - *No apparent promoting activity*
  - Two-year initiation-promotion studies in male C3H/HeJ mice with benzo[a]pyrene as initiator and fractions of Type III roofing asphalt fume condensates as tumor promoters: Sivak *et al.* (1989) and Sivak *et al.* (1997)
    - *No apparent promoting activity*

Studies with Mixed Classes of Asphalt and Asphalt Emissions

- Long-term skin application studies in mice
    - 52-week study in female Sencar mice with 1x/week applications of "asphalt cutback" (Class 3, may contain Class 1 or 2 or a mixture)[4] for 30 weeks: Robinson *et al.* (1984), as reviewed in IARC (2013, p. 146)
        - *No treatment-related tumor findings*

- Long-term subcutaneous/intramuscular injection studies in mice
    - 54-week study in C57 Black mice (male and female combined) with injection of steam- and air-blown (oxidized) petroleum asphalts (Class 1 and 2) suspended in olive oil: Simmers *et al.* (1959), as reviewed in IARC (2013, p. 152)
        - *Increase in sarcoma at the injection site (by pairwise comparison)*

- Tumor initiation-promotion skin application studies in mice
    - 52-week initiation-promotion study in female Sencar mice with skin applications of cutback asphalt (Class 3, may contain Class 1 or 2 or a mixture) and TPA as tumor promoter: Robinson *et al.* (1984), as reviewed in IARC (2013, p. 147)
        - *Apparent initiating activity, based on increased incidence of skin squamous cell carcinoma*

Other relevant data

- Genotoxicity[5]: as reviewed by IARC (2013) (pp. 170-189)
    - Mutagenicity in bacteria:
        - Mutations in *Salmonella typhimurium* with various forms of asphalt and asphalt emissions (e.g., fume condensates generated in lab or collected from storage tanks, or asphalt paint) *(positive and negative)*
        - Mutations in *Salmonella typhimurium* with urine samples from exposed Italian road pavers *(positive)*

    - Genotoxicity in mammalian systems *in vitro*:
        - DNA strand breaks

[4] Cutback asphalt is produced by adding an agent to straight-run or oxidized asphalt for the purpose of reducing viscosity for ease of handling. Cutback asphalt contains different combinations of products (blends).

[5] With the exception of studies in human samples, the genotoxicity of asphalt and asphalt emissions associated with road paving and roofing are reported together, as studies often don't provide adequate information on whether the exposure resembles road paving or roofing activities. Identifying information on exposure is included when possible.

- In λ DNA with asphalt *(negative; tested in the absence of exogenous metabolic activation)*
- In BEAS 2B human bronchial epithelial cells with lab-generated asphalt fume with or without modification with waste plastic and tall oil pitch, and fume samples collected from stone-mastic asphalt or asphalt concrete paving sites *(positive only with lab-generated fume with modification and without exogenous metabolic activation; negative in all other cases)*

▪ DNA adducts
- In calf thymus DNA with asphalt fume condensate (160 °C or 200 °C), or with asphalt fume sampled from hot storage tanks *(positive with exogenous metabolic activation)*
- In adult and fetal human skin samples with asphalt paint *(positive without exogenous metabolic activation)*

▪ Oxidative DNA damage
- In λ DNA *(positive without exogenous metabolic activation)*

▪ Micronucleus formation
- In Chinese hamster lung V79 cells with asphalt fume condensate (316 ± 10 °C) *(positive without exogenous metabolic activation)*
- In BEAS 2B human bronchial epithelial cells with lab-generated asphalt fume with or without modification with waste plastic and tall oil pitch, and fume samples collected from stone-mastic asphalt or asphalt concrete paving sites
  - Lab-generated asphalt fume and fume samples collected from stone-mastic asphalt paving sites *(positive without exogenous metabolic activation; negative with exogenous metabolic activation)*
  - Fume samples collected from asphalt concrete paving sites *(negative with or without exogenous metabolic activation)*

▪ Chromosome aberrations (CA)
- In Chinese hamster ovary (CHO) cells with asphalt fume samples collected from storage tanks (147–316 °C) *(negative with or without exogenous metabolic activation)*

▪ DNA-protein crosslinks
- In HL60 human promyelocytic leukemia cell line with asphalt *(positive without exogenous metabolic activation)*

o Genotoxicity in mammalian systems *in vivo*:

▪ DNA strand-breaks
- In rat alveolar macrophages with asphalt (170 °C, Class 1) *(positive)*

▪ DNA adducts

- In mouse skin and lung with skin application of asphalt paint, or vacuum residue of asphalt *(positive)*
- In rat skin, lung and lymphocytes with skin application of asphalt fume condensate (160 and 200 ^{o}C, Class 1) *(positive)*
- In rat lung and blood leukocytes with intratracheally instilled asphalt fume condensate (316 ^{o}C) *(positive)*
- In rat lung with inhalation of asphalt fume condensates (three studies with various condensates generated at 170 - 200 ^{o}C) *(positive)*
- In mouse lung with inhalation of asphalt fume condensate (170 ^{o}C, Class 1)
  - In B6C3F1 mouse *(positive)*
  - In Big Blue mouse *(negative)*

▪ Mutations
- *cII* and *lacI* mutations in lung DNA from mice exposed by inhalation to asphalt fume condensate (170 ^{o}C, Class 1) *(negative)*
- *cII* mutation in lung DNA from rats exposed by inhalation to asphalt fume condensate (170 ^{o}C, Class 1) *(negative)*

▪ Micronucleus Formation
- In bone-marrow polychromatic erythrocytes from rats exposed to asphalt fume condensate
  - Exposure via intratracheal instillation of asphalt fume condensate collected at 160 ^{o}C *(positive)*
  - Exposure via inhalation of asphalt condensate collected at 170 ^{o}C, or unknown temperature, or roofing asphalt fume condensate *(negative)*
- In peripheral blood erythrocytes from rats exposed by inhalation to asphalt fume condensate *(negative)*

o Genotoxicity in workers (road pavers):

▪ DNA damage in blood cells
- In peripheral mononuclear blood cells
  - In pavers exposed to Class 1 asphalt *(positive)*
  - In asphalt painters exposed to Class 1 asphalt *(negative)*
- In leukocytes
  - In European pavers exposed to mastic asphalt *(negative)*
- In whole blood
  - In pavers *(positive)*

▪ Oxidative DNA damage
- In European pavers *(positive)*

▪ DNA adducts

        - In mononuclear blood cells of US and German pavers *(equivocal)*
        - In leukocytes of German pavers *(negative)*
    - Sister Chromatid Exchange (SCE) in lymphocytes
        - In Turkish and Hungarian pavers *(positive)*
        - In Sweden and Italian pavers *(negative)*
        - In pavers from the UK and Northern Ireland *(equivocal)*
    - CA in peripheral blood lymphocytes
        - In Hungarian pavers *(positive)*
    - Micronucleus formation in peripheral blood lymphocytes
        - In Turkish, Indian, and Australian pavers *(positive)*
        - In Sweden and German pavers *(negative)*
    - Unscheduled DNA synthesis
        - In peripheral blood lymphocytes of pavers and other asphalt-exposed workers *(negative)*

- Genotoxicity in workers (roofers):
    - DNA damage in blood cells
        - In peripheral mononuclear blood cells
            - In roofers exposed to Class 2 asphalt *(positive)*
        - In leukocytes
            - In US roofers *(positive)*
    - Oxidative DNA damage
        - In US roofers *(negative)*
    - DNA/protein adducts
        - DNA adducts
            - In mononuclear blood cells of US roofers *(positive)*
            - In leukocytes of US roofers *(positive)*
        - Albumin adducts in the blood plasma of US roofers *(equivocal, levels were marginally significant)*
    - SCE in lymphocytes
        - In roofers from the UK and Northern Ireland *(equivocal)*

- Other mechanistic considerations: as summarized and reviewed by IARC (2013, pp. 189-193)
    - Activation of aryl hydrocarbon receptor (AhR) associated pathways
    - Changes in gene and protein expression
        - In exposed workers: changes in expression of genes and proteins related to programmed cell death and cellular defense mechanisms
        - In experimental animals: changes in expression of genes involved in lung inflammatory and immune responses, PAH metabolism, and oxidative stress responses in experimental animals
    - Alterations in immune function and inflammation
    - Inhibition of gap-junction intercellular communication

- Structure-activity considerations
    - Asphalt and asphalt emissions are complex mixtures with individual constituents (e.g., benzo[*a*]pyrene and several other polycyclic aromatic hydrocarbons) found in some other complex mixtures, such as diesel engine exhaust and tobacco smoke, which are Proposition 65 carcinogens.

Reviews

- IARC (2013)[6]

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[6] IARC (2013) concluded:
"Occupational exposures to straight-run bitumens and their emissions during road paving are possibly carcinogenic to humans (Group 2B)." "Occupational exposures to oxidized bitumens and their emissions during roofing are probably carcinogenic to humans (Group 2A)."

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