Sinus Cavity Cancer

IARC 98

Pages 399, 400 & 401

IARC 100F

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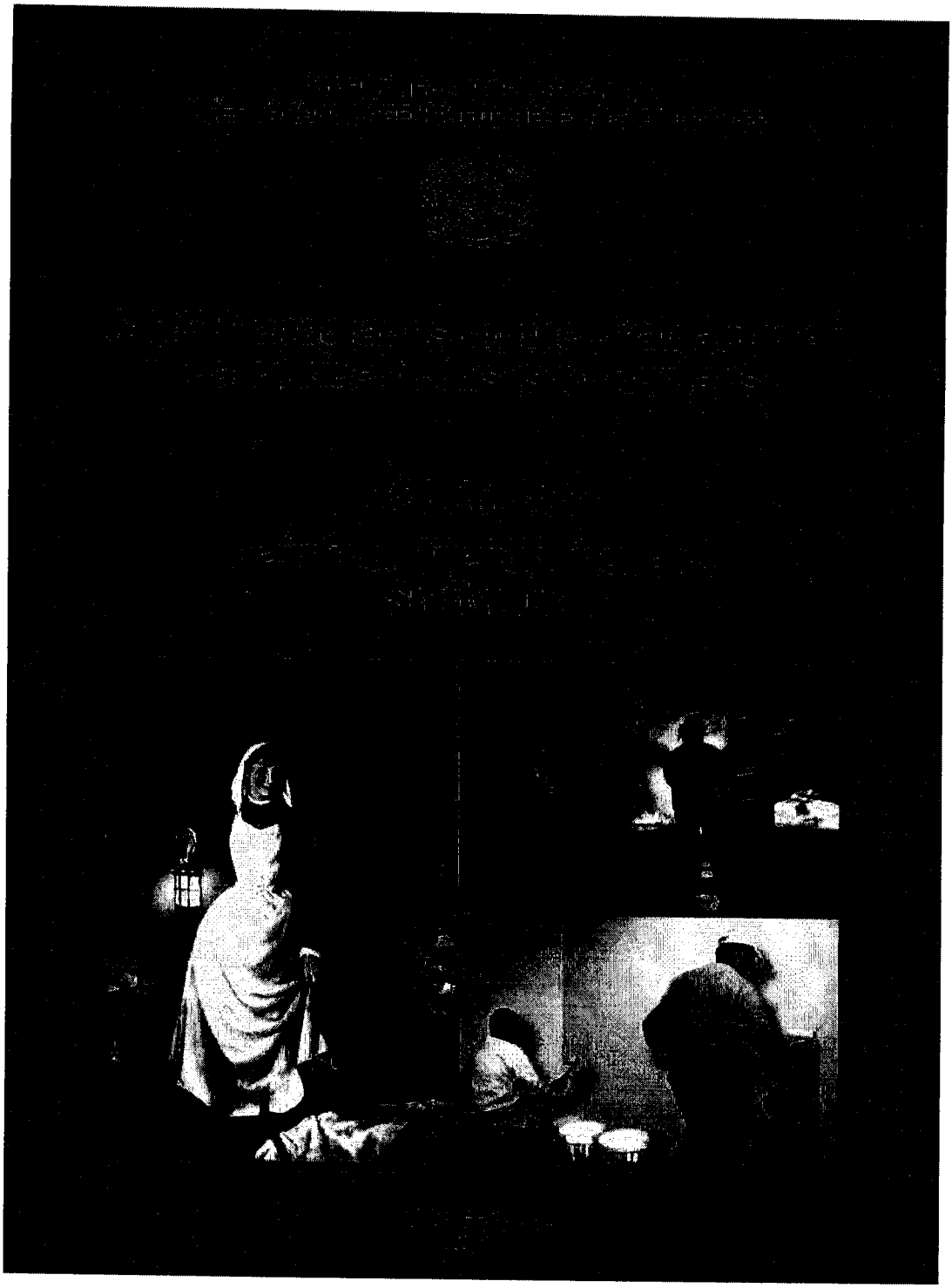
IARC 105

Pages 418, 419 and 421



1.2 Composition of fire smoke

1.2.1 *Fire chemistry*

Smoke from fires comprises suspended liquid and solid particulate matter, gases and vapours that result from the combustion or pyrolysis of material. There is a very large number of toxic components in smoke (for reviews, see Tuve, 1985; Meyer, 1989; DiNenno *et al.*, 2002; Côté, 2003). The basic form of the overall combustion reaction of organic (carbon-containing) compounds is illustrated by the burning of methane:

$$CH_4 + 2O_2 + \text{Energy of activation} \rightarrow CO_2 + 2H_2O + \text{Heat of combustion} + \text{Light}$$

Given the appropriate ratio of fuel (wood, solvent, plastic, rubber), oxygen, and combustion temperature, the products of combustion should be only water and carbon dioxide (CO_2).

Complete combustion is approached only under carefully controlled conditions. Uncontrolled or unintentional combustion tends to be "fuel rich" and therefore incomplete. The combustion of methane (CH_4) illustrates the formation of free radicals in an 11-step chain reaction, the first two of which are:

$CH_4 \rightarrow CH_3^{\bullet} + H^{\bullet}$

$H^{\bullet} + O_2 \rightarrow OH^{\bullet} + O^{\bullet}$

The free radicals formed during combustion are very reactive and side reactions are propagated to yield hundreds of chemical products, and smoke.

Most polymers found in buildings will burn or thermally degrade to simpler monomers. Thermal degradation products include methane, ethane, ethylene, benzene, toluene, and ethylbenzene in addition to the following monomers: ethylene, vinyl chloride, acrylonitrile, tetrafluoroethylene, styrene, methyl methacrylate, ethylene glycol, terephthalic acid, phenol, formaldehyde, hexamethylenediamine, adipic acid, propene, vinyl chloride, vinyl acetate, vinylidene chloride, chloroprene, 1,3-butadiene, ethyl acrylate, ethylene oxide, methylacrylate, urea, phenol, and isoprene.

The burning of plastics typically produces voluminous amounts of soot, together with higher levels of hydrogen cyanide (HCN), hydrochloric acid (HCl) and acrolein (CH_2=CHCHO) than the burning of materials such as wood, and fossil fuels. More smoke evolves from fires involving aromatic polymers, such as polystyrene, compared to aliphatic polymers, such as polyethylene.

In addition to the chemical agents described above, particulate matter is produced under conditions of incomplete combustion. The particulate matter is an aerosol consisting of condensed phase components of the products of combustion and finely divided carbon particulates that have not undergone combustion but remain suspended in the air. Although the particles themselves are microscopic in size (0.3–1.6 μm), they

rapidly coalesce and thereby become visible. These particles are also adsorbents (similar to activated charcoal) and are an additional vehicle for the transport and inhalation of toxic combustion products. Smouldering yields a substantially higher conversion of fuel to toxic compounds than does flaming, although it occurs more slowly (Ohlemiller, 2002).

1.2.2 *Modern versus pre-modern fires*

All types of fire release toxic and carcinogenic substances, including benzene, 1,3-butadiene, and formaldehyde. The focus has generally been on substances having short-term acute effects: carbon monoxide (CO), carbon dioxide, hydrogen cyanide, nitrogen oxides (NO_x), sulfur dioxide (SO_2) and hydrogen chloride. With the increasing use of polymers in building construction and furnishings, there is concern that the burning of these new materials might release large quantities of other highly toxic substances (Austin *et al.*, 2001b).

Combustion and pyrolysis products from newer building materials and furnishings were believed to be more toxic than smoke from fires in buildings built before these materials became commonplace, and more toxic than smoke from wildland fires (Betol *et al.*, 1983; Alarie, 1985). However, many of the carcinogenic products of combustion identified are volatile organic compounds and are common to most burning materials. In a more recent study, no new or unusual non-polar volatile organic compounds (VOCs) were observed in current structural fires compared to the combustion of wood (Austin *et al.*, 2001b, 2001c). Adding polyvinyl chloride (PVC) to the fire load at simulated apartment fires was observed to significantly increase levels of polychlorinated phenols (IARC Group 2B), while polycyclic aromatic hydrocarbon (PAH) levels remained essentially unchanged (Ruokojärvi *et al.*, 2000). The increases in levels of polychlorinated biphenyls (PCBs, 0.021 to 0.031 mg/m^3), polychlorinated benzenes (0.002 to 0.010 mg/m^3) and I-TEQs [or PCDD/F] (3.5 to 5.4 ng/m^3) as products of combustion were not significant [possibly due to the small sample size]. In another study, proportionately higher levels of ethyl benzene (IARC Group 2B) were found at an electronics factory fire when compared to levels at residential and mixed occupancy fires (Austin *et al.*, 2001b).

The emission of combustion products (in mg per kg of material burned) for the same material varies greatly depending on combustion conditions such as ventilation (oxygen supply), temperature, and heating rate. Nonetheless, the relative amounts of the various non-polar VOCs found in smoke at municipal structural fires have been found to be remarkably similar from fire to fire, namely with the same 14 of 144 target compounds, dominated by benzene (IARC Group 1), toluene and naphthalene (IARC Group 2B) (Austin *et al.*, 2001b, 2001c).

1.2.3 *Carcinogens found in smoke at fires*

Table 1.1 lists the agents in Groups 1, 2A, and 2B that have been detected at fires in one or more studies, together with corresponding IARC evaluations, human and animal evidence of carcinogenicity, and for the agents in Group 1, the cancer sites in humans.

Table 1.1. IARC evaluations and cancer sites in humans of chemicals measured at fires

Chemicals measured at fires	Overall evaluation	Human evidence	Animal evidence	Volume	Cancer sites in humans (For Group 1 agents only)
Acetaldehyde	2B	Inadequate	Sufficient	36, Suppl. 7, 71	
Arsenic	1	Sufficient	Limited	23, Suppl. 7	Skin, lung, liver (angiosarcoma)
Asbestos	1	Sufficient	Sufficient	14, Suppl. 7	Lung, mesothelioma, larynx, gastrointestinal tract
Benz[*a*]anthracene	2B	Inadequate	Sufficient	32, Suppl. 7, 92	
Benzene	1	Sufficient	Limited	29, Suppl. 7	Leukaemia
Benzo[*b*]fluoranthene	2B	No data	Sufficient	32, Suppl. 7, 92	
Benzo[*k*]fluoranthene	2B	No data	Sufficient	32, Suppl. 7, 92	
Benzofuran (coumarone)	2B	No data	Sufficient	63	
Benzo[*a*]pyrene	1	No data	Sufficient	32, Suppl. 7, 92	Lung, bladder, skin
1,3-Butadiene	1	Sufficient	Sufficient	71, 97	Lymphohaematopoietic system
Cadmium	1	Sufficient	Sufficient	58	Lung
Carbon black (total)	2B	Inadequate	Sufficient	65, 93	
Chrysene	2B	Inadequate	Sufficient	3, 32, Suppl. 7, 92	
Dibenz[*a*,*h*]anthracene	2A	Inadequate	Sufficient	32, Suppl. 7, 92	
Dichloromethane (methylene chloride)	2B	Indadequate	Sufficient	71	
Ethylbenzene	2B	Inadequate	Sufficient	77	
Formaldehyde	1	Sufficient	Sufficient	88	Nasopharynx; (nasal sinuses and leukaemia, suggested)
Furan	2B	Inadequate	Sufficient	63	

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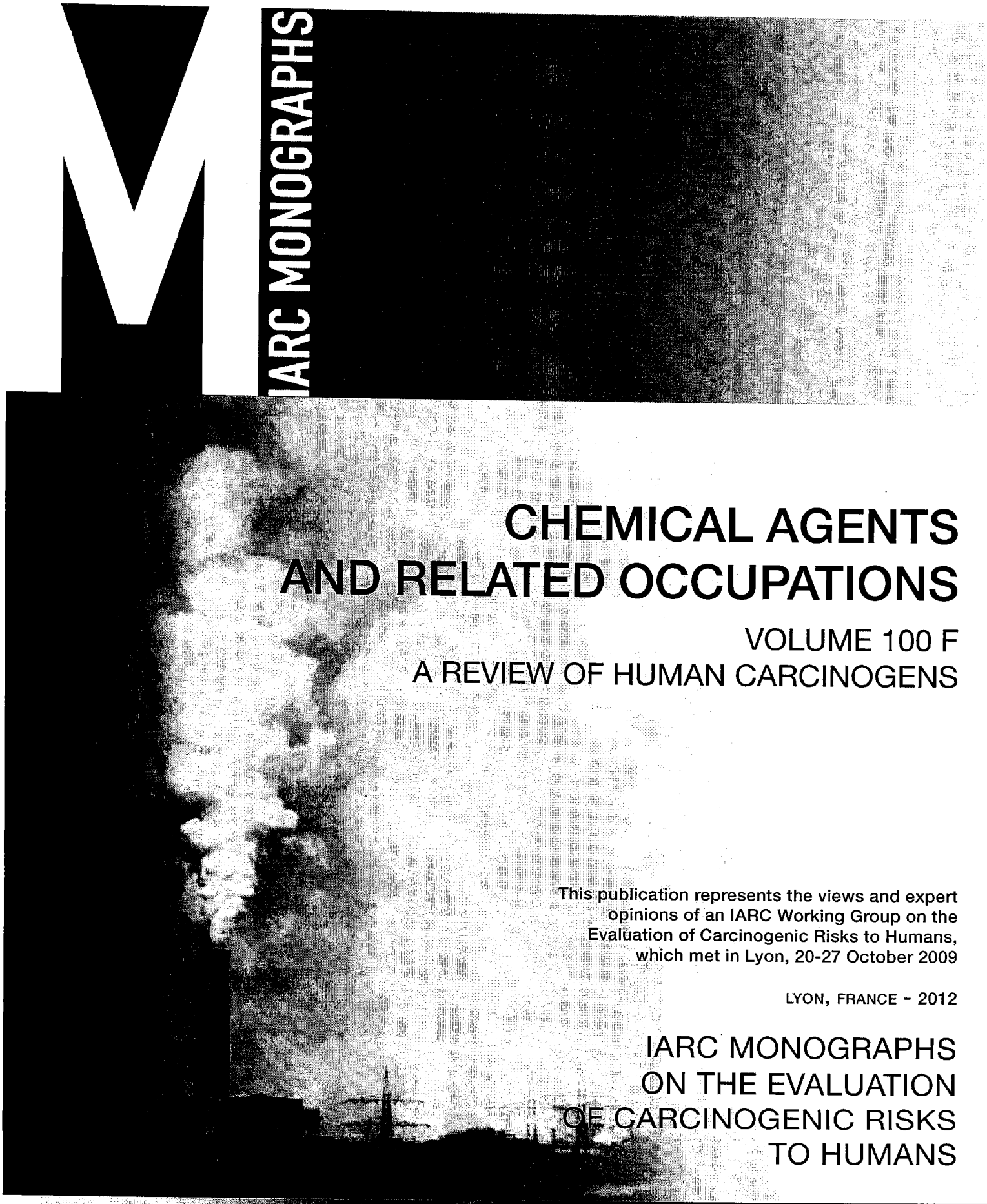

CHEMICAL AGENTS AND RELATED OCCUPATIONS

VOLUME 100 F
A REVIEW OF HUMAN CARCINOGENS

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, which met in Lyon, 20-27 October 2009

LYON, FRANCE - 2012

IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

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important in producing leukaemia in patients with Fanconi's anaemia, a genetic disorder that is characterized by progressive pancytopenia. DT40 cells with deficient repair mechanisms have also been shown to be more sensitive to other cross-linking agents such as cisplatin, a myelotoxic chemotherapeutic agent that leads to pancytopenia and acute myelogenous leukaemia (AML) (Nojima *et al.*, 2005).

4.4 Mechanistic considerations

4.4.1 Cancer of the nasopharynx and nasal sinuses

Mechanistic evidence supporting a causal relation between inhalation of formaldehyde and induction of cancer of the nasopharynx and nasal sinuses is based on the chemical reactivity of formaldehyde in producing DNA–protein cross-links, and its genotoxicity *in vitro* and *in vivo*, including in the nasal cells of exposed humans. Computational fluid-dynamic models of formaldehyde in the nasal passages of rats, monkeys and humans have generally been accurate in predicting the area in the nose with the highest number of DNA–protein crosslinks (Georgieva *et al.*, 2003). Local effects in the nasal passages, genotoxicity, and cell-proliferation rate appear to be the major determinants of nasal carcinogenicity after exposure to formaldehyde.

4.4.2 Leukaemia

The findings reviewed in *IARC Monograph* Volume 88 (IARC, 2006) pertaining to a potential mechanism for formaldehyde-induced leukaemogenesis were summarized as follows: "Based on the data available at this time, it was not possible to identify a mechanism for the induction of myeloid leukaemia in humans." The Working Group further stated that "It is possible that formaldehyde itself can reach the bone marrow following inhalation, although the evidence is inconsistent." Since that time, Zhang *et al.* (2009), reviewed potential pathways by which formaldehyde could act as a leukaemogen. Three mechanisms were suggested:

- by damaging stem cells in the bone marrow directly, as most other leukaemogens do;
- by damaging haematopoietic stem/progenitor cells circulating in the peripheral blood and
- by damaging the primitive pluri-potent stem cells present within the nasal turbinates and/or olfactory mucosa.

This subject was reviewed by Heck & Casanova (2004), Pyatt *et al.* (2008), and Goldstein (2011).

(a) Studies in animals

Studies of bone marrow cells in formaldehyde-exposed animals have been inconsistent. Kitaeva *et al.* (1990) described clastogenic and cytogenetic effects in the bone marrow of rats inhaling 0.5 mg/m^3 or 1.5 mg/m^3 of formaldehyde during four hours/day for four months. In contrast, Dallas *et al.* (1992) found no evidence of cytogenetic abnormalities in the bone marrow of rats exposed to 0.5, 3 or 15 ppm [0.62, 3.7 or 18.45 mg/m^3] formaldehyde for six hours/day, five days per week, for one or eight weeks. Mice that received up to 25 mg/kg bw formaldehyde in two intra-peritoneal injections within 24 hours showed no increase in chromosomal aberrations or micronuclei in the femoral bone marrow (Natarajan *et al.*, 1983). As described in section 4.1 above, no increase in formaldehyde-specific DNA–protein cross-links was observed in the bone marrow of Rhesus monkeys or rats under various experimental conditions (Heck & Casanova, 2004).

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determined by analysis of the urinary metabolites of caffeine.

Among policemen in Prague, Czech Republic, those who had both *CYP1A1* and *GSTM1* polymorphic variants had the lowest levels of DNA adducts in lymphocytes determined by postlabelling/thin-layer chromatography (Topinka *et al.*, 2007). The levels of DNA adducts were also highest in subjects with variants of *CYP1A1*, independent of *GSTM1* status, and were associated with the levels of carcinogenic PAHs in the air.

Subjects in Florence, Italy, who had occupational exposure to traffic exhaust and at least one variant of the DNA nucleotide excision-repair gene, *XPD-Lys751/Gln*, had increased levels of DNA adducts in their lymphocytes (determined by postlabelling/thin-layer chromatography; Palli *et al.*, 2001).

However, *GSTM1* and *NAT2* (*M1*, *M2* and *M3* alleles) had no effect on the levels of DNA adducts (measured by postlabelling/HPLC) in the lymphocytes of Copenhagen bus drivers (Nielsen *et al.*, 1996b). Also, *GSTM1*, *GSTT1* and *GSTP1* had no effect on the levels of DNA adducts (measured by postlabelling) or DNA damage (measured by the comet assay) in the lymphocytes of shale-oil mine workers exposed to diesel engine exhaust (Knudsen *et al.*, 2005).

CYP1A1 and *GSTM1* had no influence on the observed increase in micronuclei in the lymphocytes of road tunnel construction workers relative to office controls in Genoa, Italy (Villarini *et al.*, 2008). An *in vitro* study of diesel engine exhaust extracts in the *umu* gene expression assay in *S. typhimurium* TA1535/pSK1002 found that the extract was activated by CYP1B1 and CYP1A2 but not by CYP1A1 (Yamazaki *et al.*, 2000).

4.5.2 Vulnerable populations

Children represent a population that is vulnerable to exposure to diesel engine exhaust because they spend most of their time playing outside, have higher respiratory rates than adults and have underdeveloped lungs (Suwanwaiphatthana *et al.*, 2010). Alveolar development is arrested in the young due to underlying inflammatory disease (Bäckström *et al.*, 2011). An age-dependent theoretical model was developed to predict PM dosimetry in the lungs of children. The simulation predicted that the lung deposition of 2-μm particles was 38% in adults but was as high as 73% in 7-month-old children (Musante & Martonen, 2000). However, it is uncertain how these events may affect susceptibility to lung cancer later in life.

4.5.3 Underlying lung disease

While there is evidence that exposure to diesel engine exhaust may exacerbate asthma and chronic obstructive disease and increase lung injury, it is not known how these chronic conditions may affect susceptibility to lung cancer from this exposure.

4.5.4 Respiratory tract microbiome

The respiratory tract is lined with microflora that expresses enzymes which may increase the metabolic activation of some components of diesel engine exhaust, e.g. nitroarenes. The composition of the microbiome is also affected by the use of antibiotics for upper respiratory tract infections. Thus, the microbiome represents a changing microenvironment that may affect susceptibility to the carcinogenic constituents of diesel engine exhaust.

4.6 Mechanistic considerations

4.6.1 Diesel engine exhaust

Diesel engine exhaust is a complex mixture comprised of both gaseous and particulate components. The gaseous phase comprises nitrogen oxides, sulfur, ozone and organic compounds, such as acetaldehyde, acrolein,

benzene, 1,3-butadiene, formaldehyde, naphthalene and PAHs and nitro-PAHs. Benzene, 1,3-butadiene, formaldehyde and benzo[*a*]pyrene are carcinogenic in experimental animals and have been classified as human carcinogens (IARC, 2010a, 2012a). Naphthalene (IARC, 2002) and acetaldehyde (IARC, 1999) have been classified as possibly carcinogenic to humans, and several other PAHs (IARC, 2010a) and nitro-PAHs (see the *Monographs* in this Volume) have been classified as probably or possibly carcinogenic to humans.

The particulate phase contains organic compounds including PAHs (IARC, 2010a) and nitro-PAHs (see the *Monographs* in this Volume), many of which have been classified by the IARC as possible or probable carcinogens. It also contains trace metals, including lead, manganese, arsenic and chromium, and those from the catalyst aftertreatment systems – vanadium, copper and iron. Arsenic and arsenic inorganic compounds and chromium VI have been classified as human carcinogens (IARC, 2012c), whereas lead (IARC, 1987) and inorganic lead compounds (IARC, 2006b) have been classified as probably or possibly carcinogenic to humans, respectively. These components are adsorbed onto carbon core particles that vary in size from coarse to fine to ultrafine nanoparticles.

(a) *Organic solvent extracts of particulates from diesel engine exhaust*

Organic solvent extracts of particulates of diesel engine exhaust contain higher-molecular-weight organic compounds, including PAHs and nitro-PAHs. Organic compounds adsorbed on particles have been evaluated for genotoxicity in *in vitro* and *in-vivo* assays, and have a broad range of activities. They are mutagenic in bacterial assays and in mammalian cells, form bulky DNA adducts, and induce unscheduled DNA synthesis, sister chromatid exchange, chromosomal aberrations and morphological cell transformation (IARC, 1989). They also induce skin papillomas in mouse skin tumour–initiation studies and adenocarcinomas in mice after dermal application in cancer bioassays (IARC, 1989). More recent studies indicate that organic solvent extracts of diesel engine exhausts induce DNA strands breaks and oxidative damage, as well as increase the expression of genes involved in xenobiotic metabolism, oxidative damage, antioxidant responses and the cell cycle in mammalian cells in culture.

There is strong mechanistic evidence that organic solvent extracts of diesel engine exhaust particulates induce cancer in experimental animals by a genotoxic mechanism.

PAHs are biotransformed by phase I metabolic enzymes to a series of dihydrodiols, phenols, quinones and polyhydroxylated metabolites. Dihydrodiols can be metabolized further to chemically reactive intermediates (diol epoxides) that bind covalently to DNA to form DNA adducts. PAHs can undergo one-electron reduction to form radical cations that can adduct to DNA forming depurinating PAH adducts. PAH quinones can undergo redox cycling, generating ROS that damage DNA. Many of these DNA modifications have been associated with the induction of mutation and, eventually, tumour formation. Further metabolism of PAH metabolites by phase II enzymes converts many of the primary metabolites to glucuronic acid and sulfate and glutathione conjugates that are excreted in the faeces and urine. Nitro-PAHs can be reduced by nitroreductases to hydroxylamino and amino metabolites; the hydroxylamino intermediates have been shown to bind to DNA to form covalent DNA adducts. Some nitro-PAHs can undergo both oxidative and reductive metabolism, forming mixtures of metabolites and DNA adducts containing nitro, dihydrodiol or amino functionalities (IARC, 1989). The detailed mechanism(s) of the metabolic activation of PAHs have been described previously (IARC, 2010a) and in this *Monograph* (see Section 4.1). Detailed mechanism(s) of the