Myelodysplastic Syndrome

"MDS" Cancer

IARC 98

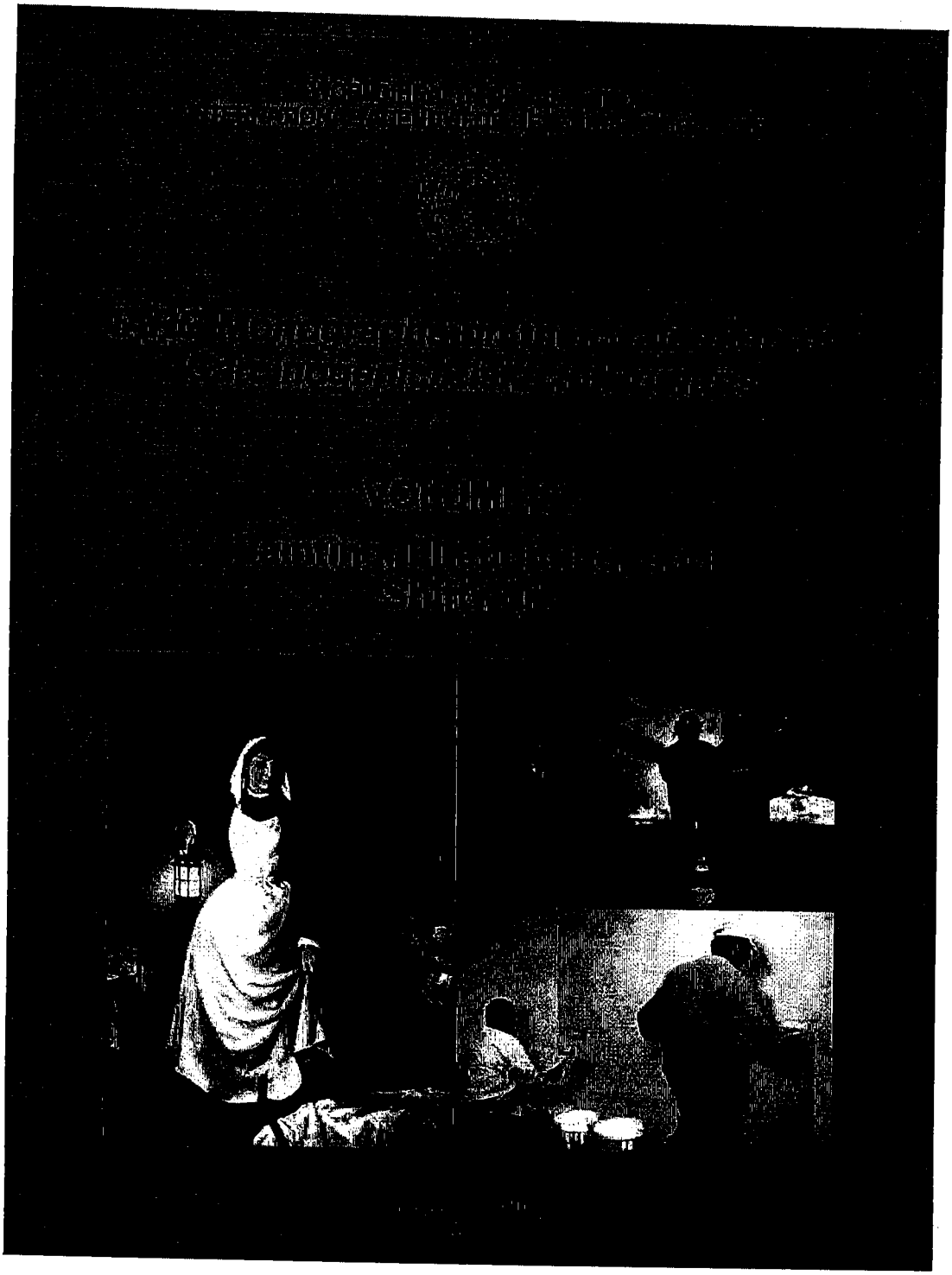
Pages 399, 400, 401 and 533

IARC 100F

Pages 276, 278, 279 and 280

IARC 105

Pages 418 and 419



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:

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

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

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	

For acetaldehyde, inhalation exposure leads to degeneration of nasal epithelium followed by hyperplasia and proliferation in rats (IARC, 1999). For acrolein, repeated inhalation results in changes in bronchiolar epithelial cells and emphysema in dogs (IARC, 1995). Dermal absorption does not appear to be important for acetaldehyde and acrolein.

Formaldehyde exposure results in DNA–protein cross-links and chromosomal abberations. Cell proliferation, which appears to amplify the genotoxic effects of formaldehyde, is increased at concentrations of around 6 ppm. No clear mechanism has been identified for the induction of myeloid leukemia in humans (IARC, 2006). Acetaldehyde causes gene mutations in bacteria; gene mutations, sister chromatid exchanges, micronuclei and aneuploidy in cultured mammalian cells; DNA damage in cultured mammalian cells and in mice in vivo. Acetaldehyde–DNA adducts have been found in white blood cells from human alcohol abusers (IARC, 1999). Acrolein induces gene mutation, sister chromatid exchange and DNA damage in cultured mammalian cells, but reportedly does not induce DNA damage in rats or dominant lethal mutations in mice treated in vivo (IARC, 1995).

Group 1
Product of
Combustion

4.1.3 *Benzene*

Benzene is systemically absorbed following inhalation, and due to rapid evaporation, dermal exposure should not be a significant source of systemic dose for firefighters. Benzene is oxidized primarily by CYP2E1 to benzene oxide, which exists in equilibrium with its tautomer oxepin (Kim *et al.*, 2006; 2007). Spontaneous rearrangement of benzene oxide produces phenol that is either excreted or oxidized by CYPs to hydroquinone, which is excreted or oxidized by myeloperoxidase in the bone marrow to 1,4-benzoquinone. Conversely, NAD(P)H quinone oxidoreductase 1 transforms 1,4-benzoquinone to hydroquinone. Hydroquinone and 1,4-benzoquinone are thought to influence the toxic effects of benzene through their ability to inhibit topoisomerase II and microtubule function, induce oxidative stress, and damage DNA. Other major metabolites include catechol, representing the pathway involving the hydrolysis of benzene oxide by epoxide hydrolases, and *trans,trans*-muconic acid, representing the pathway involving oxidation of oxepin and ring opening. Reaction between benzene oxide and glutathione, possibly mediated by glutathione-*S*-transferases (GSTM1, GSTT1), can produce the minor metabolite *S*-phenylmercapturic acid (Kim *et al.*, 2006; 2007). Although it is widely accepted that benzene toxicity is dependent upon metabolism, no single benzene metabolite has been found to be the major source of benzene haematopoietic and leukemogenic effects (ATSDR 2005). At low exposure levels, benzene is rapidly metabolized and excreted predominantly as conjugated urinary metabolites[The metabolism of benzene in the bone marrow is consistent with the increase in haematopoietic cancers seen in humans (ATSDR, 2005).]

Chromosomal aberrations in human peripheral lymphocytes have been associated with occupational exposure to benzene and include hypo- and hyperdiploidy, deletions, breaks, and gaps (ATSDR, 2005). Sister chromatid exchange was not found to be a significant effect of benzene exposure in humans. In-vivo animal studies provide convincing evidence of the genotoxicity of benzene. Benzene induced chromosomal aberrations, micronuclei and

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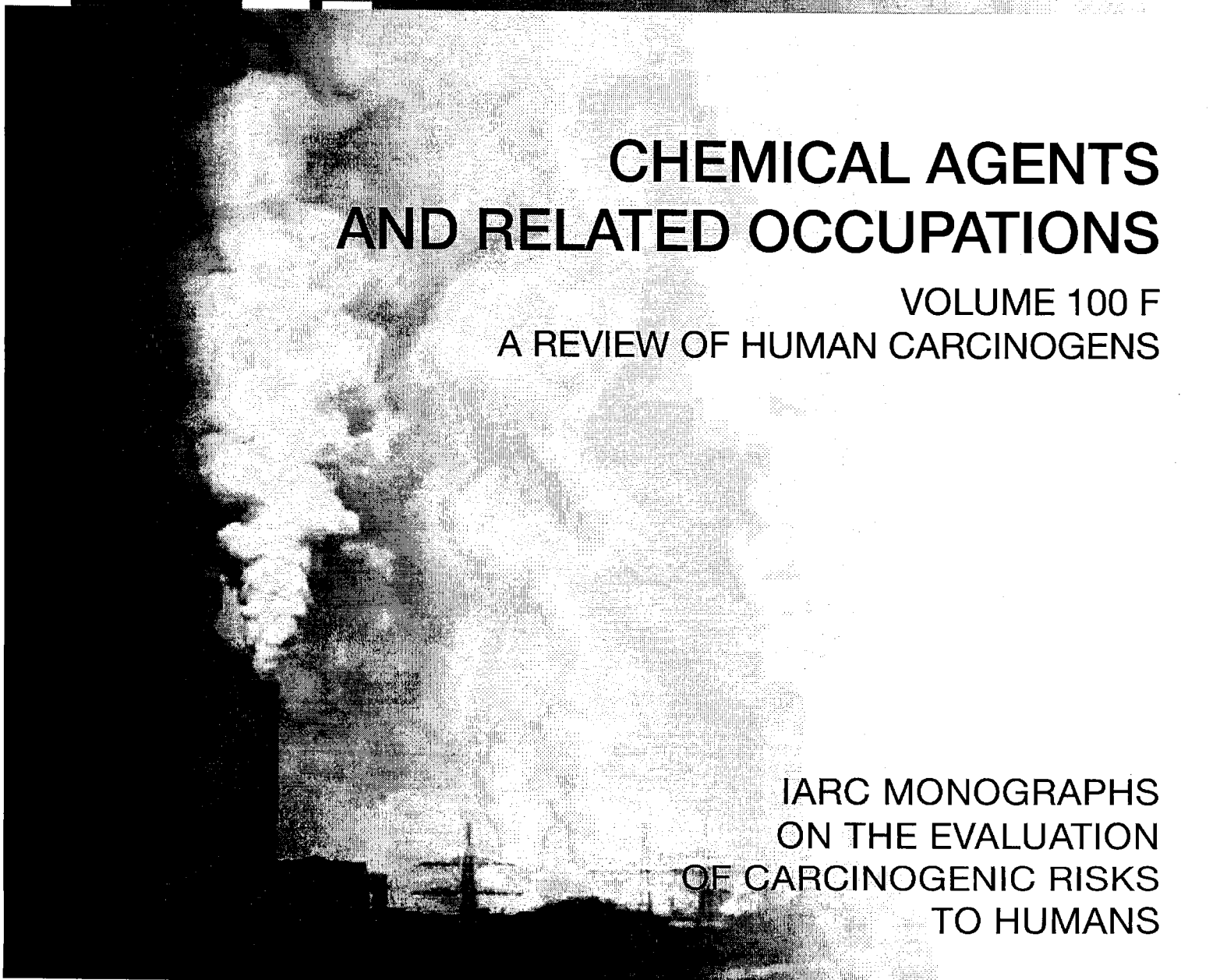

CHEMICAL AGENTS AND RELATED OCCUPATIONS

VOLUME 100 F
A REVIEW OF HUMAN CARCINOGENS

IARC MONOGRAPHS
ON THE EVALUATION
OF CARCINOGENIC RISKS
TO HUMANS

International Agency for Research on Cancer
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and of benign and malignant ovarian tumours, mammary gland carcinomas and carcinosarcomas, and Harderian gland carcinomas in female mice (NTP, 1986; Stoner *et al.*, 1986; Maronpot, 1987; Maltoni *et al.*, 1988, 1989; Huff *et al.*, 1989; Mehlman, 2002).

Increased multiplicity of lung adenomas was observed in male mice after intraperitoneal injection of benzene (Stoner *et al.*, 1986).

Exposure of genetically altered, tumour-prone mice to benzene by oral administration, skin application, or inhalation resulted in increased incidences of skin tumours (Blanchard *et al.* 1998; Holden *et al.*, 1998; French & Saulnier, 2000) and lymphohaematopoietic malignancies (French & Saulnier, 2000; NTP, 2007; Kawasaki *et al.*, 2009).

4. Other Relevant Data

4.1 Genetic and related effects

Benzene induced chromosomal aberrations, micronuclei and sister chromatid exchange in bone-marrow cells of mice, chromosomal aberrations in bone-marrow cells of rats and Chinese hamsters and sperm-head anomalies in mice treated *in vivo*. It induced chromosomal aberrations and mutation in human cells *in vitro* but did not induce sister chromatid exchange in cultured human lymphocytes, except in one study in which high concentrations of an exogenous metabolic system were used. In some test systems, benzene induced cell transformation. It did not induce sister chromatid exchange in rodent cells *in vitro*, but it did induce aneuploidy and, in some studies, chromosomal aberrations in cultured Chinese hamster ovary cells. Benzene induced mutation and DNA damage in some studies in rodent cells *in vitro*. In *Drosophila*, benzene was reported to be weakly positive in assays for somatic mutation and for crossing-over in spermatogonia; in single studies, it did not induce sex-linked recessive lethal mutations or translocations. It induced aneuploidy, mutation and gene conversion in fungi. Benzene was not mutagenic to bacteria (IARC, 1982, 1987). Chromosomal aberrations in human peripheral lymphocytes have been associated with occupational exposure to benzene for decades (Forni, 1979; IARC, 1982; Eastmond, 1993; Zhang *et al.*, 2002; Holecková *et al.*, 2004).

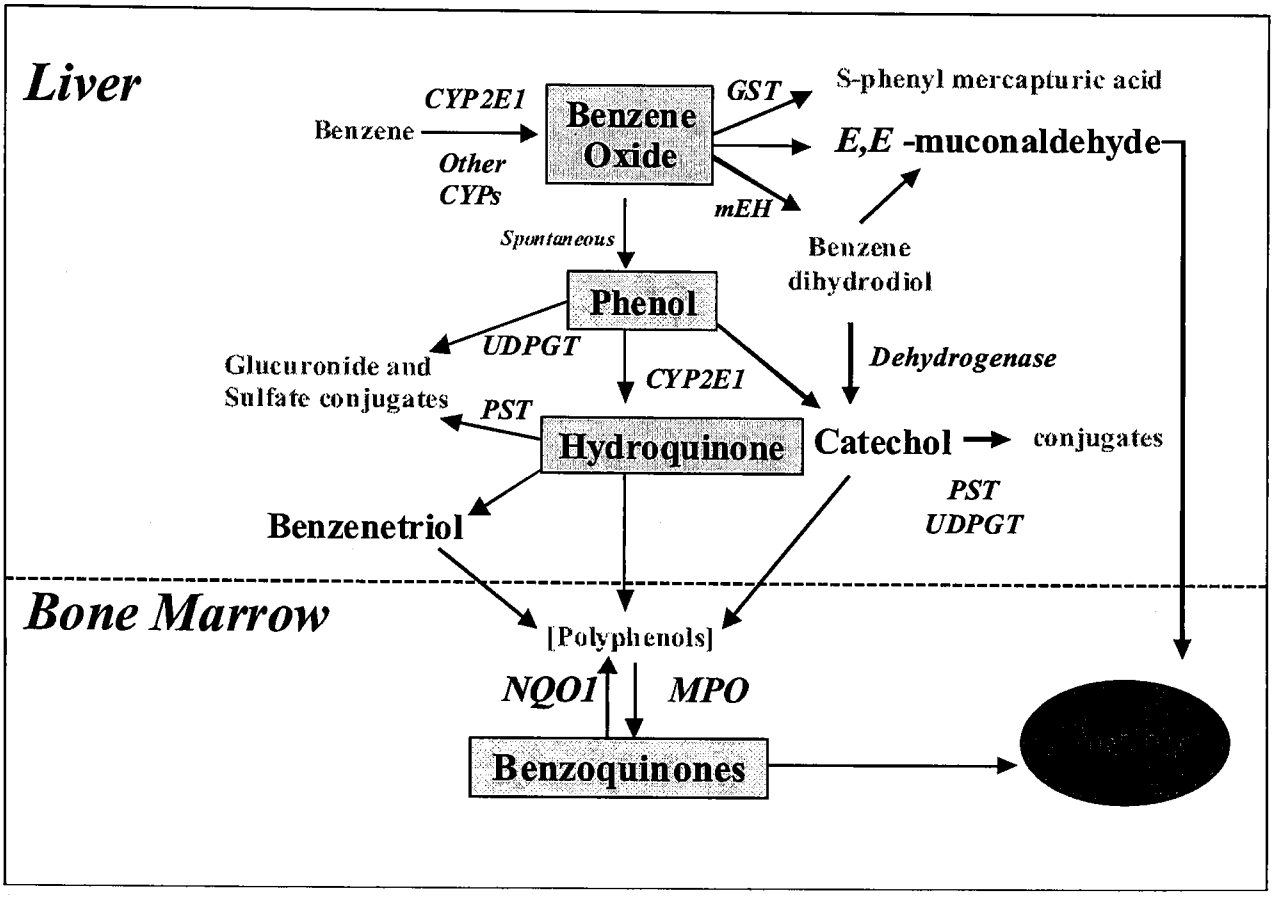
4.2 Leukaemogenic potential of benzene

Benzene is carcinogenic to the bone marrow causing leukaemia and myelodysplastic syndromes (MDS) and probably also to the lymphatic system causing non-Hodgkin lymphoma. Its carcinogenic mechanism of action is likely to be different for these two target tissues and probably multifactorial in nature. The metabolism of benzene will be summarized below and a review is presented of the current state of knowledge on the mechanisms of leukaemia and lymphoma induction by benzene. With regard to leukaemia, probable mechanisms of leukaemogenesis in the myeloid series, mainly acute myeloid leukaemia (AML) and MDS are discussed. Then, potential mechanisms by which benzene could cause acute lymphocytic leukaemia (ALL) in both adults and children are reviewed. Finally, mechanisms for the benzene-induced development of non-Hodgkin lymphoma are summarized, including that of chronic lymphocytic leukaemia (CLL), as it is now classified as a form of lymphoma.

4.2.1 Metabolism of benzene and its relevance to carcinogenicity

Benzene must be metabolized to become carcinogenic (Ross, 2000; Snyder, 2004). Its metabolism is summarized in Fig. 4.1. The initial metabolic step involves cytochrome P450 (CYP)-dependent oxidation to benzene oxide,

Fig. 4.1 Simplified metabolic scheme for benzene showing major pathways and metabolizing enzymes leading to toxicity. CYP2E1, cytochrome P450 2E1; GST, glutathione-*S*-transferase; NQO1, NAD(P)H:quinone oxidoreductase 1; MPO, myeloperoxidase; UDPGT, Uridine diphosphate glucoronosyl transferase; PST, phenol sulphotransferase; mEH, microsomal epoxide hydrolase



haematotoxicity (Hirabayashi *et al.*, 2008). The most likely explanation for these findings is that the absence of AhR removes haematopoietic stem cells from their quiescent state and makes them susceptible to DNA damage from benzene exposure and subsequent cell death through apoptosis. Further research is needed to examine the effects of benzene and its metabolites on cycling and quiescent haematopoietic stem cells.

4.2.2 Mechanisms of myeloid leukaemia development

(a) General

AML and MDS are closely-related diseases of the bone marrow that arise de novo (without an obvious cause) in the general population or following therapy with alkylating agents, topoisomerase II inhibitors, or ionizing radiation (therapy-related AML and MDS, i.e. t-AML and t-MDS) (Pedersen-Bjergaard *et al.*, 2006, 2008). Occupational exposure to benzene is widely thought to cause leukaemias that are similar to various forms of t-AML and t-MDS (Irons

& Stillman, 1996; Larson & Le Beau, 2005; Zhang *et al.*, 2007). AML and MDS both arise from genetically altered CD34+ stem cells or progenitor cells in the bone marrow (Morgan & Alvares, 2005; Passegué & Weisman, 2005) and are characterized by many different types of recurrent chromosome aberrations (Pedersen-Bjergaard *et al.*, 2006; Mrózek & Bloomfield, 2008). These aberrations have been shown to often develop into the genetic mutations that produce leukaemia. Cytogenetic analysis of chromosome number and structure has therefore become important in diagnosis and treatment of MDS and AML (Pedersen-Bjergaard *et al.*, 2006; Mrózek & Bloomfield, 2008). Recent research has shown that the chromosome aberrations and gene mutations detected in therapy-related and de novo MDS and AML are identical, although the frequencies with which they are observed in different subtypes may differ (Pedersen-Bjergaard *et al.*, 2008). Hence, therapy-related and de novo MDS and AML are considered identical diseases (Pedersen-Bjergaard *et al.*, 2008).

At least three cytogenetic categories of AML and MDS are commonly observed: those with unbalanced aberrations, with balanced rearrangements, and with normal karyotype:

Unbalanced chromosome aberrations comprise primarily the loss of various parts of the long arm or loss of the whole chromosome 5 or 7 (5q–/–5 or 7q–/–7) and gain of a whole chromosome 8 (+8) (Pedersen-Bjergaard *et al.*, 2006, 2007, 2008). These cases often have a complex karyotype and carry point mutations of *TP53* or *AML1*. Unbalanced chromosome aberrations are common after therapy with alkylating agents.

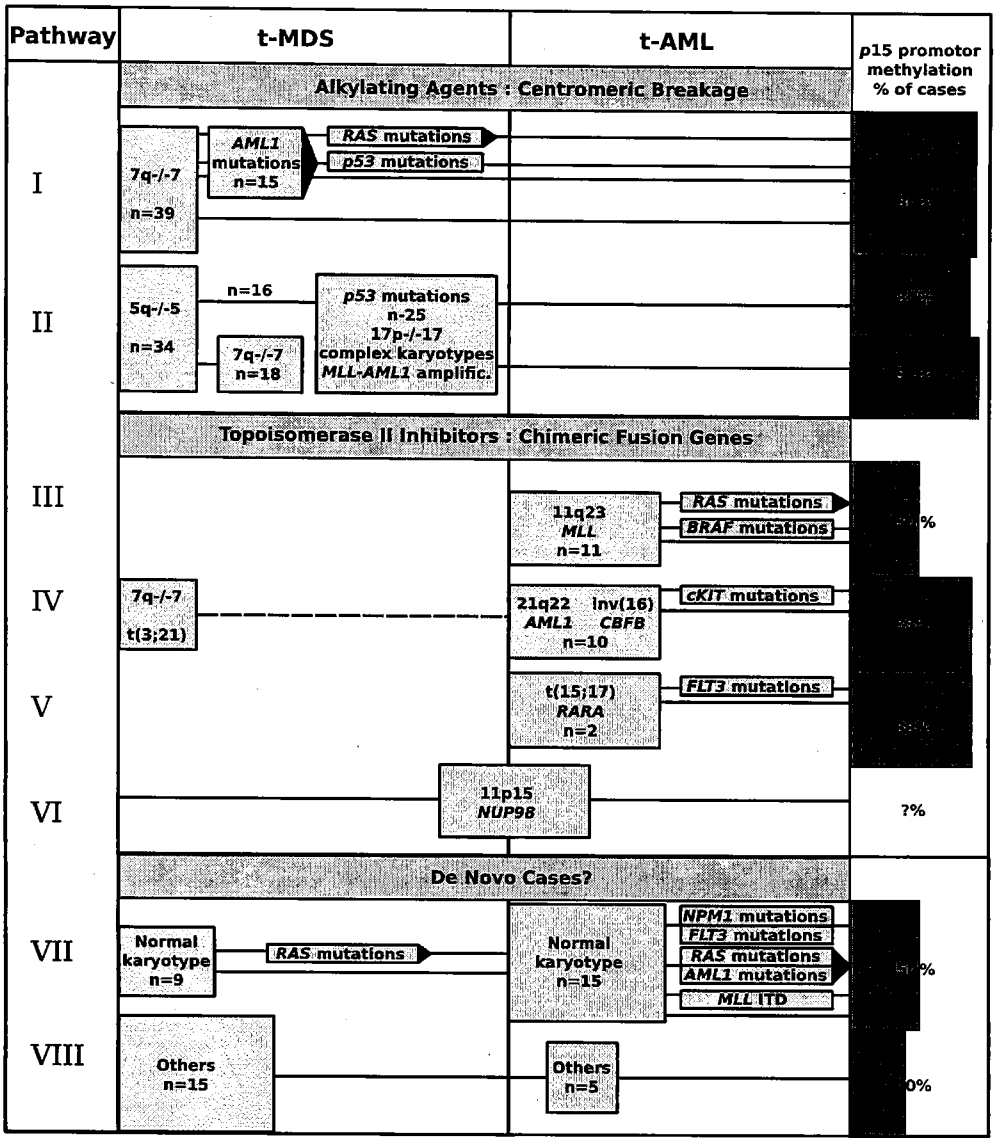
Balanced rearrangements are recurrent balanced translocations [e.g. t(11q23), t(8;21) and t(15;17)] or inversions [e.g. inv(16)], which arise, at least in the therapy-related subset of cases, as illegitimate gene recombinations related to functional inhibition of topoisomerase II (Pedersen-Bjergaard *et al.*, 2006, 2008). Among the most important rearranged transcription-factor genes are the mixed-lineage leukaemia (*MLL*) at 11q23, the *AML1* at 21q22, the retinoic-acid receptor-α *RARA* at 17q21 and the core-binding factor subunit-β (*CBFB*) at 16q22 (Pedersen-Bjergaard *et al.*, 2007).

Cases with a normal karyotype often harbour mutations of the *NPM1* gene (which encodes nucleophosmin), internal tandem duplications of the *FLT3* gene (which encodes fms-related tyrosine kinase), and/or point mutations or an altered methylation status of the *C/EBPα* gene (which encodes CCAAT/enhancer binding protein α) (Cuneo *et al.*, 2002; Pedersen-Bjergaard *et al.*, 2006, 2007, 2008; Hackanson *et al.*, 2008).

Within these three cytogenetic categories there are at least eight different genetic pathways that lead to MDS and AML, as defined by the specific chromosome aberrations present in each (Pathways I –VIII in Fig. 4.2). As more becomes clear about the molecular cytogenetics of leukaemia, it seems likely that many other pathways to AML and MDS will be discovered. For example, recent unbiased high-resolution genomic screens have identified many genes not previously implicated in AML that may be relevant for pathogenesis, along with many known oncogenes and tumour-suppressor genes (Ley *et al.*, 2008; Mardis *et al.*, 2009; Walter *et al.*, 2009).

Another classical pathway to AML is through the transformation of a myeloproliferative disorder (MPD) (Abdulkarim *et al.*, 2009), although there is less evidence for this pathway as a relevant mechanism to benzene-induced AML. MPDs include Philadelphia chromosome (Ph)-positive chronic myelogenous leukaemia (CML) and the Ph-negative conditions *polycythemia vera*, essential trombocythemia and idiopathic myelofibrosis. It is well established that AML may occur as a late complication in all these disorders. Over the first ten years after diagnosis, the incidence of leukaemic transformation is reported to be higher in patients with idiopathic myelofibrosis (8–23%) compared with

Fig. 4.2 Genetic Pathways to Myelodysplastic Syndromes (MDS) and Acute Myeloid Leukaemia



From Pedersen-Bjergaard *et al.* (2006)

IARC MONOGRAPHS

DIESEL AND GASOLINE ENGINE EXHAUSTS AND SOME NITROARENES

VOLUME 105

IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

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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