8. EFFECTS ON HUMANS

NitroPAHs, formed directly from diesel exhaust, heating stoves or other combustion processes, or formed through atmospheric transformation processes from PAHs, are ubiquitous atmospheric pollutants (see chapters 3 and 5).

Since the major route of exposure to nitroPAHs is through inhalation of complex mixtures (e.g., diesel exhaust, polluted urban air), the Task Group thought it appropriate to summarize the effects of diesel exhaust inhalation (for a more thorough treatise, see Scheepers & Bos, 1992b; IPCS, 1996; US EPA, 2000; Lloyd & Cackette, 2001; Sydbom et al., 2001). On the basis of available human and animal evidence, it is concluded that diesel exhaust can cause acute irritation (e.g., eye, throat, bronchial irritation), neurophysiological symptoms (e.g., lightheadedness, nausea) and respiratory symptoms (cough and phlegm). There is also evidence for possible immunological effects and exacerbation of allergic responses to known allergens. Chronic animal inhalation studies show a spectrum of dose-dependent chronic inflammation and histopathological changes in the lung in several studies (US EPA, 2000).

Exposure to diesel exhaust by inhalation has the potential to induce cancer in humans and animals. There is considerable evidence demonstrating an association between diesel exhaust exposure and increased lung cancer risk among workers in different occupations. The human evidence, although strong, is not sufficient to allow a definite conclusion that diesel exhaust exposure is associated with lung cancer, due to confounding factors such as smoking and further to the lack of exact diesel exhaust exposure data for workers (HEI, 1995; US EPA, 2000). However, there is extensive evidence for the induction of lung cancer in the rat from long-term inhalation exposure to high concentrations of diesel exhaust and supporting evidence of carcinogenicity from exposure to diesel particulate matter and associated organic compounds in rats and mice by non-inhalation routes of exposure (IPCS, 1996, 1998; US EPA, 2000).

Diesel vapour and diesel-exhaust derived particulate matter extracts are genotoxic to bacterial and mammalian cell systems and can induce adverse chromosomal changes in animals. Elevated levels of DNA adducts have been associated with occupational exposure to diesel exhaust.

Due to the complexity of diesel exhaust, it is likely that some effects are caused by the gaseous components, whereas other effects relate to the particle content. Approximately 50–90% of the number of particles in diesel exhaust are in the ultrafine size range, with the majority of diesel particles ranging in size from 0.005 to 0.05 µm and the mode at about 0.02 µm. These are believed to be aerosol particles formed from exhaust constituents during cooling and to consist of sulfuric acid droplets, ash particles, condensed organic material and maybe carbon spherules. Although ultrafine diesel exhaust-derived particulate matter accounts for the majority of the number of particles, it makes up only 1–20% of the mass of diesel exhaust-derived particulate matter. Between 80% and 95% of the diesel particle mass is in the size range from 0.05 to 1.0 µm, with a mean diameter of about 0.02 µm (US EPA, 2000). These particles have a very large surface area per gram of mass, which make them excellent carriers for adsorbed inorganic and organic compounds. These particles are respirable and penetrate deep into the lungs, carrying these compounds with them (US EPA, 2000).

Recent epidemiological studies have associated mortality and respiratory morbidity with exposure to ambient concentrations of ultrafine particles, raising concern that diesel exhaust could contribute to or be the cause of the observed health effects.

There have been many developments in recent years concerning changes in engines, fuel (e.g., decreasing sulfur content), particle traps, etc., all of which have had an effect on emissions, on particle size and on the relationship between the vapour and particulate phases of organic chemicals (see also chapter 3; CONCAWE, 1998; US EPA, 2000).

Some organic compounds associated with the particles, in particular PAHs and nitroPAHs, are known to show genotoxic properties, and some compounds show carcinogenic properties. It is not certain whether PAHs and their nitro, oxy-alkylated or heterocyclic derivatives or possibly other compounds or the particles themselves are principally responsible for the effects of diesel exposure. Either the effects of gas-phase constituents on the carcinogenic properties of the particles and/or particle-associated organics have not been investigated or the findings have been inconclusive (Scheepers & Bos, 1992b).

As can be expected, as nitroPAHs occur in complex mixtures, there are no reports on effects on humans from individual nitroPAHs. It can be expected that some of the effects reported to be due to exposure to diesel exhaust (see IPCS, 1996) or PAHs (see IPCS, 1998) may be due partly to the nitroPAHs in the complex mixture. Mutagenicity studies on atmospheric samples containing nitroPAHs (see section 7.6.8) suggest that nitroPAHs are responsible for at least part of the total mutagenicity and therefore should be considered of importance in the study of the carcinogenicity of atmospheric pollutants.

8.1 General population exposure

There are no case reports specifically on the effects of nitroPAHs.

It is presumed that carcinogens present in human lungs contribute to the incidence of lung cancer. Most of the carcinogens are inhaled with particulate matter via the respiratory tract into the lung alveoli. NitroPAHs have been detected in samples of resected lung tissue from tuberculosis patients, with and without carcinoma, in the period 1991–1996, in Japan (Tokiwa et al., 1993a, 1998a,b; Sera, 1998) (see chapter 5 and Table 27). For 112 non-smoking lung cancer patients from whom lung specimens were collected, 5-year survival rates after the operation were determined on the basis of the nitroarene concentration at the resection time. Lung specimens were divided into higher and lower chemical concentration groups at the levels of 18 pg/g for 1-nitropyrene, 15 pg/g for 1,3-dinitropyrene and 35 pg/g for 3-nitrofluoranthene, and the results were statistically analysed by the Kaplan-Meier method. The hazard ratio significantly increased in the higher

chemical concentration group if it was adjusted for age, gender and stage, and it also increased if it was adjusted for cell differentiation in addition to the other factors (Tokiwa et al., 1998a; Tokiwa & Sera, 2000).

8.2 Occupational exposure

Many workplaces have atmospheres with heavy loads of PAHs (see IPCS, 1998). In particular, workers exposed to diesel engine exhaust in the transport industry and in related occupations are exposed to nitroPAHs (section 5.3). 1-Nitropyrene has been used as a marker for exposure to nitroPAHs from diesel exhaust.

8.3 Indicators of exposure to nitroPAHs in diesel exhaust

8.3.1 Biomonitoring of exposure/effect

Although it is known that humans are exposed to nitroPAHs through their environment — e.g., diesel exhaust and cooking oil fumes — sensitive analytical methods for detection and quantification of nitroPAH adducts with protein and/or DNA or their metabolites in biological fluids are still being developed. First attempts were made with 1-nitropyrene, as this is the most abundant nitroPAH in numerous environmental sources (van Bekkum, 1999; Bos et al., 2000).

Biomonitoring studies in general appear to have a wide inter-individual variation (see below), and there is often a widely overlapping distribution of adduct concentrations in different exposure situations (e.g., occupational versus environmental), so that proving a cause–effect relationship in epidemiological studies is very difficult (Neumann et al., 1995b).

8.3.1.1 DNA adducts

Biomonitoring for nitroPAHs has proved more difficult than expected due to the many possible metabolic pathways and low yield of multiple DNA adducts measured by ^{32}P post-labelling (El-Bayoumy et al., 1994b,c; van Bekkum et al., 1999). Dinitropyrenes (in particular

1,6-dinitropyrene) have, as an alternative to 1-nitropyrene, also been suggested as biomarkers. Although they are present in much lower amounts (only 1% of that of 1-nitropyrene), they are more carcinogenic than 1-nitropyrene, and their DNA adducts are better characterized (Smith et al., 1993, 1995). A further development is the suggestion that T-lymphocyte mutations produced by the 1,6-dinitropyrene–DNA adducts may be more sensitive and longer-lived biomarkers than DNA adducts themselves in assessing previous exposures to nitroPAHs (e.g., from diesel exhaust) (Beland et al., 1994; Beland, 1995; Smith et al., 1995; see chapter 6).

8.3.1.2 *Protein adducts*

Another approach is to use protein (albumin or Hb) adducts of nitroPAHs as biomarkers of exposure, as suggested by El-Bayoumy et al. (1994a,c). Development of sensitive analytical techniques has enabled the study of nitroPAH–Hb adducts as biomarkers of nitroPAH exposure in rats (van Bekkum et al., 1997) and in human occupational exposure groups: coke oven workers assigned to different job categories (Neumann et al., 1995a,b) and bus garage workers, as well as control groups having urban and rural exposure (Zwirner-Baier & Neumann, 1999). In the human biomarker studies, five nitroPAHs were selected — 1-nitropyrene, 2-nitrofluorene, 3-nitrofluoranthene, 9-nitrophenanthrene and 6-nitrochrysene — and methods were developed to determine the sulfinic acid-type Hb adducts that they form *in vivo*. (Hydrolysis of the Hb adducts yields the respective arylamines, which were analysed by GC-MS. The detection limit was 0.01–0.08 pmol/g Hb.) In the more recent study (Zwirner-Baier & Neumann, 1999), three exposure groups (high, medium, low) were chosen, assessed from analysis of 1-nitropyrene extracted from total suspended particulate matter in air samples from the chosen locations. Blood samples were analysed from 29 bus garage workers (occupationally exposed to diesel exhaust) and from 20 urban hospital workers and 14 rural council workers as controls. Hb adducts above the detection limit were found in most blood samples. The most abundant adducts were from 1-nitropyrene and 2-nitrofluorene, but there were no differences between the groups, suggesting that both are widespread environmental contaminants (Zwirner-Baier & Neumann, 1999).

8.3.1.3 1-Nitropyrene metabolites

A sensitive and selective method of detecting 1-nitropyrene metabolites in urine after diesel exhaust exposure has been investigated in rats, with the aim of developing the method for biomonitoring of human exposure. 1-Nitropyrenols were reduced to 1-aminopyrenols prior to derivatization with heptafluorobutyryl imidazole (van Bekkum et al., 1998; van Bekkum, 1999).

Occupational exposure to diesel exhaust was studied using 1-nitropyrene as a biomarker. Air samples collected at fixed locations in a large trading and distribution centre for mixed cargo contained 1-nitropyrene at concentrations ranging from 270 to 7850 pg/m^3 and from 6.4 to 20.6 pg/m^3 for indoor and outdoor locations, respectively. The *N*-acetyl derivatives of 1-aminopyren-6-ol and 1-aminopyren-8-ol were identified in urine, but concentrations were at the limit of detection. Hb and plasma adduct levels ranged from non-detectable to 3380 fg 1-aminopyrene/mg and to 107 fg 1-aminopyrene/mg, respectively, and did not correlate with airborne 1-nitropyrene concentrations (van Bekkum, 1999; Bos et al., 2000).

Biomonitoring of workers occupationally exposed to diesel exhaust was performed to determine their internal burden of diesel-associated aromatic compounds. Personal air sampling also allowed the determination of exposure of the miners at their workplace to several PAHs and nitroarenes. The urine of 18 underground salt miners was collected during and after their shift for 24 h. Nine miners were smokers. The urinary levels of 1-hydroxypyrene and hydroxylated phenanthrene metabolites were determined as biomarkers of PAH exposure, whereas urinary levels of 1-aminopyrene and 3-aminobenzanthrone were chosen to monitor exposure to specific nitroarenes from diesel exhaust, such as 1-nitropyrene and 3-nitrobenzanthrone. It was found that concentrations of 3-aminobenzanthrone (1–143 ng/24 h urine), determined for the first time in this study as a urinary metabolite of diesel exhaust exposure, were similar to 1-aminopyrene concentrations (2–200 ng/24 h urine). The excreted amounts of aromatic amines found as metabolites of the nitroarenes were about 5- to 10-fold higher, as one

might expect from the levels determined by personal air sampling at the workplace of the individuals (Seidel et al., 2002).

8.3.1.4 Immunochemical determination

On the basis of an existing antibody developed against 6-amino-benzo[*a*]pyrene, an immunochemical assay (ELISA) was developed for the detection of metabolites excreted in urine as a result of occupational exposure to PAHs and nitroPAHs. The method was validated in a study on the occupational exposure of 28 railroad workers (Scheepers et al., 1995b).

8.3.2 Biomarkers of susceptibility

For a review of metabolic polymorphisms and susceptibility to cancer, see Vineis et al. (1999).

8.3.2.1 Cytochrome P450

The C-oxidative metabolism of individual nitroPAHs in different species is catalysed by different cytochrome P450s. In contrast to rat and rabbit (see chapter 6), the CYP3A subfamily (in particular CYP3A3 and CYP3A4) seems to be the enzymes involved in human metabolism of 1-nitropyrene and 4-nitropyrene in HepG2 cells and hepatic microsome samples. A minor role of CYP1A2 has also been suggested (Howard et al., 1990; Silvers et al., 1992; Chae et al., 1999a). None of the P450 enzymes tested (CYP3A4, CYP1A2, CYP2E1, CYP2A6, CYP2D6 and CYP2C9) appeared to be involved in the oxidation of 2-nitropyrene. Nitroreduction, through CYP3A4, was observed only for 4-nitropyrene, not for 1-nitropyrene or 2-nitropyrene (Chae et al., 1999a).

6-Nitrochrysene induced CYP1A1 but not CYP1A2 in human hepatoma HepG2 cells. 6-Nitrochrysene was also able to induce pulmonary CYP1A1 in human lung carcinoma NCI-H322 cells (Chen et al., 2000).

The genotoxicities of four samples of diesel exhaust particle extracts and nine nitroarenes found in diesel exhaust particle extracts were investigated after activation catalysed by human cytochrome P450 family 1 enzymes co-expressed with NADPH-cytochrome P450 reductase (NPR) in *Escherichia coli* membranes. The diesel exhaust particle extract samples induced *umu* gene expression in *Salmonella typhimurium* TA1535/pSK1002 without any P450 system and were further activated by human CYP1B1/NPR membranes. Moderate activation of the diesel exhaust particle extract sample by CYP1A2/NPR membranes, but not by either CYP1A1/NPR or NPR membranes, was also observed. 1-Nitropyrene was strongly activated by human CYP1B1/NPR membranes. 1,8-Dinitropyrene was most highly activated by CYP1A1 and CYP1B1 systems for the three dinitropyrenes tested. In contrast, 1,3-dinitropyrene was inactivated by CYP1A1/NPR, CYP1A2/NPR and CYP1B1/NPR systems and slightly activated by NPR membranes. 2-Nitrofluoranthene and 3-nitrofluoranthene showed activities similar to that of 1-nitropyrene after bioactivation by CYP1B1/NPR membranes. However, the genotoxicities of 6-nitrochrysene, 7-nitrobenz[*a*]anthracene and 6-nitrobenzo[*a*]pyrene were all weak in this assay system (Yamazaki et al., 2000).

Both the HPRT assay and the Ames test did not show any involvement of CYP3A in the activation of 1-nitropyrene to a mutagenic metabolite. In addition, a clear involvement of CYP1A2 in the activation of 1-nitropyrene was demonstrated in both mutation assays using eukaryotic cells. However, no activation of 1-nitropyrene was seen in the eukaryotic cell lines when expressing only CYP1A2 or acetyltransferase. No clear involvement of cytochrome P450 could be demonstrated for activation of 2-nitrofluorene to a mutagenic metabolite (Kappers et al., 2000).

8.3.2.2 *Influence of polymorphisms on biomarkers*

Of major importance in human biotransformation is the individual's capacity to metabolize certain xenobiotics. As a result of interindividual differences in metabolic capacity (polymorphisms), persons are slow, intermediate or rapid metabolizers. Some important enzymes involved in the biotransformation of xenobiotics such as PAHs and nitroPAHs

are polymorphic — e.g., some cytochrome P450s (CYP1A1, CYP1A2 and some CYP3A enzymes), NAT2 and GSTμ1.

CYP1A2 is a phase I enzyme involved in the biotransfomation of, for example, arylamines to reactive *N*-hydroxyamines. This enzyme is induced by various environmental factors.

NAT2 activity is genetically determined and polymorphic. Fast and slow acetylators are distinguished based on their ability to metabolize, for example, amines to *N*-acetyl derivatives. Two major alleles at a single autosomal gene locus are involved in the production of the *N*-acetyltransferase enzyme. Since CYP1A2 and NAT2 both convert arylamines, both polymorphisms need to be considered when understanding the toxicokinetics of such compounds.

The distribution of GSTμ1 is also polymorphic; approximately 50% of the human population is GSTμ1 deficient, as a result of a homozygous deletion of the GSTμ1 gene (Ketterer et al., 1992). GSTμ is an important subfamily of enzymes largely responsible for conjugation of electrophilic compounds with glutathione. Among the substrates for GSTμ1 are metabolites of arylamines and BaP such as benzo[*a*]pyrene-4,5-oxide and the ultimate carcinogen benzo[*a*]pyrene-diolepoxide. Hence, glutathione conjugation can prevent binding of such reactive metabolites with DNA.

In a study on 1-nitropyrene as an exposure marker in a large trading and distribution centre for mixed cargo, blood protein adduct levels were not influenced by NAT2 phenotype, CYP1A2 phenotype or GST phenotype (van Bekkum, 1999).

The Task Group was made aware that a large study is in progress in the European Union, looking at miners and the association of polymorphisms with biomarker development (Scheepers et al., 2002).

9. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

The Task Group realized that the biotransformation and DNA damage studies could have been included in earlier chapters (e.g., chapter 4 or 6); however, the Task Group felt that these studies should be combined and considered in this chapter.

9.1 Laboratory experiments

9.1.1 Aquatic species

Schultz & Moulton (1985) reported an EC_{50} of 17.3 mg/litre for growth inhibition of the ciliate *Tetrahymena pyriformis* exposed to 1-nitronaphthalene in a static test system at 28 °C for 60 h. The 95% confidence interval was 14.72–21.26 mg/litre.

A 96-h LC_{50} value of 9.0 mg/litre was reported for the fathead minnow (*Pimephales promelas*) exposed to 1-nitronaphthalene in a static renewal test system (Curtis & Ward, 1981). The 95% confidence interval was 5.4–15 mg/litre. The test was carried out using water with a hardness of 30–35 mg calcium carbonate/litre, pH 7.2–7.9 and temperature of 22 ± 1 °C.

Lysak & Marcinek (1972) reported a 24-h LC_{100} value of 25 mg/litre for rainbow trout (*Oncorhynchus mykiss*) exposed to 1-nitronaphthalene in a static renewal test system at a temperature ranging from 16 to 21.5 °C. The corresponding 48-h LC_0 concentration was 5 mg/litre. Mortality was reported in fish exposed to 7.5–15 mg/litre for 48 h.

9.1.2 Biotransformation studies in aquatic species

Post-mitochondrial supernatants (S9) of marine invertebrates from three phyla — mussel (*Mytilus edulis*), crab (*Carcinus maenas*) and starfish (*Asteria rubens*) — activated 1-nitropyrene to products that were mutagenic in *S. typhimurium* strain TA98NR (Marsh et al., 1992).

An NADPH-dependent two-electron nitroreductase activity, occurring only under anaerobic conditions, was detected in the microsomal and cytosolic fractions of the major digestive tissues of mussel (*Mytilus edulis*) (digestive gland) and crab (*Carcinus maenas*), but not in the gills of either species. 1-Aminopyrene was the only metabolite identified. No activity was detectable in the pyloric caeca or stomach region of the starfish (*Asteria rubens*). NAD(P)H-dependent one-electron nitroreduction was present in all subcellular fractions of the major digestive tissues of the three species (Hetherington et al., 1996).

1-Nitropyrene (8.3 mg/litre) was added to the water for goldfish (*Carassius auratus*). After 48 h, 1-aminopyrene, *N*-acetyl-1-aminopyrene and *N*-formyl-1-aminopyrene were detected in the water (Kitamura & Tatsumi, 1996), showing that goldfish can metabolize 1-nitropyrene via a nitroreduction pathway (Kitamura & Tatsumi, 1996).

In goldfish (*Carassius auratus*), 2-nitrofluorene is predominantly metabolized to and excreted as 2-aminofluorene and its acylated metabolites, but not as its hydroxylated metabolites (Ueda et al., 2001b).

9.1.3 DNA damage in aquatic species

1-Nitropyrene (100 µmol/litre) produced concentration-dependent increases in DNA strand breaks (using the "comet" assay) in isolated brown trout (*Salmo trutta*) hepatocytes incubated *in vitro* (17.1 ± 4.4 compared with control 3.7 ± 0.6), but no significant effects were found in blood cells (2.8 ± 0.4 compared with control 2.4 ± 0.4) (Mitchelmore & Chipman, 1998).

Isolated mussel (*Mytilus edulis* L.) digestive gland cells were analysed using the single-cell gel electrophoresis or "comet" assay (Mitchelmore et al., 1998a) to assess the ability of potential aquatic contaminants (e.g., BaP, 1-nitropyrene) to induce DNA strand breaks. There were significant concentration-dependent increases in the percentage of DNA in the comet tail (mean values ± standard deviation) for all doses compared with controls ($P < 0.05$) for BaP (up to 24.7 ± 5.1 at 100 µmol/litre) and 1-nitropyrene (up to 54.7 ± 5.0% at 200 µmol/litre).

There was a decrease ($P < 0.05$) in viability (eosin Y exclusion) of exposed compared with control cells at 200 µmol/litre with BaP but not with 1-nitropyrene.

In a further study using mussel (*Mytilus edulis* L.) digestive gland, isolated cells were exposed *in vitro* to sub-cytotoxic concentrations (50 µmol/litre) of BaP and 1-nitropyrene for 1 h in the dark at 15 °C in the absence or presence of various cytochrome P450 inhibitors, anti-oxidant enzyme inhibitors, the free radical scavenger *N*,*N*-*t*-butyl-a-phenylnitrone and other modulators. DNA strand breakage was measured using the "comet" assay (Mitchelmore et al., 1998b). BaP-induced strand breakage was indicated to be cytochrome P450 catalysed and to occur via the production of BaP quinones. 1-Nitro pyrene-induced strand breakage was indicated to occur via free radical mechanisms(s) (84% strand break inhibition by 50 mmol *N*,*N*-*t*-butyl-a-phenylnitrone/litre) and catalysis by different forms of cytochrome P450 than for BaP (61% strand break inhibition by 50 µmol a-naphthoflavone/litre, but none by clotrimazole at same concentration).

The ability of 1-nitropyrene to form DNA adducts in fish was investigated *in vitro* and *in vivo* using brown trout (*Salmo trutta*) and turbot (*Scophthalmus maximus*) and compared with that in Wistar rat (Mitchelmore et al., 1998c). Hepatic S9 fractions from brown trout, uninduced and induced with ß-naphthoflavone, and from ß-naphthoflavone-induced rat were incubated with calf thymus DNA and 1-nitropyrene. With all S9 fractions, the presence of three distinct 1-nitropyrene-related DNA adducts was detected using ^{32}P post-labelling. Turbot, rat and brown trout (uninduced and induced with ß-naphthoflavone) were dosed with 1-nitropyrene (i.p.; 100 mg/kg bw). Liver DNA from both turbot and rat exhibited a 1-nitropyrene-related adduct spot in a similar position to that seen in the incubations with S9 from rat and brown trout. The major DNA adducts in fish were consistent with the major 1-nitropyrene DNA adduct (dG-C8-AP), based on co-chromatography. However, in contrast to the *in vitro* studies, no 1-nitropyrene-related adducts were found in liver DNA from induced and uninduced brown trout, possibly reflecting the influence of detoxification systems.

9.2 Field observations

No information on the effects of nitroPAHs on organisms in the field was identified in the literature.

10. EVALUATION OF HUMAN HEALTH RISKS AND EFFECTS ON THE ENVIRONMENT

Compounds in ambient air that have been implicated as being mutagenic/carcinogenic include nitroPAHs and, more recently, the nitro-oxy compounds — nitroketones (in particular 3-nitrobenzanthrone) and nitrolactones (in particular 2-nitrodibenzopyranone and nitropyrene lactones).

10.1 Evaluation of human health risks

The Task Group was aware that changes in diesel fuel, engine technology, exhaust treatment and indoor heating may alter the relative concentration of nitroPAHs on the air particles, and the number and size of the particles may alter the bioavailability, and ultimately the impact, of the nitroPAHs.

There is increasing evidence in recent studies that nitroPAHs, in particular in volatile and semivolatile fractions, are still emitted in diesel exhaust emissions, even after use of catalysts, and their concentrations may in fact be increased by this process.

10.1.1 Exposure levels

10.1.1.1 NitroPAHs

NitroPAHs are found in the environment from combustion source emissions or as the result of gas-phase radical-initiated atmospheric formation. NitroPAHs that have been detected in diesel exhaust include primarily 1-nitropyrene, 9-nitroanthracene, 3-nitrofluoranthene, 6-nitrochrysene, 7-nitrobenz[*a*]anthracene, 2-nitrofluorene and dinitropyrenes.

The highest levels of nitroPAHs in the general environment have been found in urban air. The major contributor to the concentrations of dinitropyrenes and 1-nitropyrene in ambient air is traffic emissions.

Some nitroPAHs, notably 2-nitrofluoranthene and 2-nitropyrene, which are not found in diesel exhaust, have been detected in urban, suburban, forest and remote areas. The ubiquitous occurrence of these nitroPAHs is probably due to their photochemical origin from gas-phase radical-initiated reaction of the parent PAHs and subsequent attachment of the nitroPAHs to carbon particles, which can be widely distributed in the atmosphere.

NitroPAHs that have been detected in ambient air include 1- and 2-nitronaphthalene and methylnitronaphthalenes (predominantly in the vapour phase), 2-nitrofluorene, 9-nitroanthracene, 9-nitrophenanthrene, 2-, 3- and 8-nitrofluoranthene, 1- and 2-nitropyrene, 1,3-, 1,6- and 1,8-dinitropyrene and 6-nitrochrysene.

From worldwide surveys of mononitropyrenes and fluoranthenes from a number of urban, suburban and remote areas, it can be seen that the concentrations of 2-nitrofluoranthene (atmospheric formation) in ambient particulate exceeds several-fold that of 1-nitropyrene (from combustion) in almost all studies.

Seasonal studies on selected nitroPAHs show that the concentrations of 1-nitropyrene and dinitropyrenes (from combustion sources) in ambient air particulate are usually higher in winter than in the other months. In contrast, in most studies, levels of 2-nitrofluoranthene and 2-nitropyrene (atmospheric transformation) are less in winter months than in the warmer seasons. When vapour- and particulate-phase nitro-PAHs are monitored, it seems that the semivolatile nitroPAHs are the most predominant nitroPAHs.

It is difficult to give a comprehensive comparison of levels of the different nitroPAHs in rural and urban studies, as most studies have, for various reasons, concentrated on levels of a few selected nitro-PAHs. The levels of individual nitroPAHs in ambient air vary considerably, depending on place of measurement, season and time of day. In general, however, levels of total nitroPAHs measured range from picograms to several nanograms per cubic metre.

NitroPAHs have been found in some food samples. Levels do not usually exceed 5 µg/kg, with the exception of spices, smoked food, tea (in particular Mate tea) and peanuts. NitroPAHs in vegetables and fruits are probably due to atmospheric pollution. The average daily intake of nitroPAHs is negligible compared with that for PAHs.

Air concentrations of 1-nitropyrene have been measured in various workplaces associated with the use of diesel engines. The exposure levels of nitroPAHs vary depending on occupation, and the highest levels found have been in underground mining (mean 2.5 ng/m^3; maximum 42 ng/m^3).

10.1.1.2 Nitroketones

3-Nitrobenzanthrone was detected in diesel exhaust particulate (0.6–6.6 µg/g load) as well as in airborne particle extracts from urban samples (not detected to 12 pg/m^3).

10.1.1.3 Nitrolactones

2-Nitrodibenzopyranone has been detected in ambient air (0.05–1 ng/m^3) at about the same levels as 2-nitrofluoranthene, but at higher levels than 1- and 2-nitropyrene. 2-Nitrodibenzopyranone (0.8 µg/g) was also found in an urban dust sample, but much lower concentrations were found in diesel particulate material (0.2 µg/g), suggesting that nitrodibenzopyranones are formed in the atmosphere. Nitropyrene lactones have also been reported in ambient air.

1) Biomonitoring

Various reports have described the development of methods for and showed data on the evaluation of 1-nitropyrene as a biomarker for occupational exposure to diesel exhaust. 1-Nitropyrene has been measured in particulate matter as a marker for environmental exposure. Urinary metabolites of PAHs and nitroPAHs were determined in urine of diesel mechanics using an immunoassay (ELISA), and, in another study, metabolites of 1-nitropyrene (specifically *N*-acetyl-1-aminopyren-6-ol and *N*-acetyl-1-aminopyren-8-ol) were measured in urine of

workers in a shipping department. Additional studies have focused on measuring the Hb and plasma adducts of metabolites of 1-nitropyrene and other nitroPAHs and may provide appropriate biomarkers in future molecular epidemiological investigations.

10.1.2 Fate in the body

10.1.2.1 NitroPAHs

1-Nitropyrene and 2-nitrofluorene administered by various routes are rapidly absorbed and metabolized, and the metabolites are conjugated and excreted. Radiolabelled 1-nitropyrene was found to be widely distributed in the body of rats and mice after all routes of administration. Following intragastric and intraperitoneal administration and following inhalation of 1-nitropyrene or 1-nitropyrene coated on diesel exhaust particles, the majority, 50–60% of the administered dose, has been shown to be excreted in the faeces, whereas urine contained about 15–20% of the dose. In contrast, the major route of excretion of 2-nitrofluorene is the urine.

NitroPAHs constitute a complex group of chemicals showing different metabolic profiles. In mammals, there may be several metabolic pathways for a particular nitroPAH, often depending on the route of administration. Intestinal microflora play an important role in nitroreduction of nitroPAHs and in metabolism, by deconjugating metabolites, thereby enabling enterohepatic circulation. The metabolism of only a few nitroPAHs has been studied.

In vivo studies in mammals (e.g., 1-nitropyrene and 2-nitro fluorene) have shown that the metabolism of nitroPAHs occurs by both oxidative and reductive pathways, leading to several types of DNA adducts. Although the DNA adducts formed via nitroreduction pathways have mostly been identified and correspond to the DNA adducts found in *in vitro* studies (e.g., in particular the C8-substituted dG adduct), the DNA adducts resulting from oxidative pathways have not been thoroughly identified. There is increasing evidence to suggest that oxidative metabolic pathways are important in the biotransformation and

possibly macromolecular adduct formation by nitroPAHs, supported by observations *in vitro* in human cells and *in vivo* in rats.

10.1.2.2 Nitroketones

Using the ^{32}P post-labelling assay, 3-nitrobenzanthrone was found to bind covalently to calf thymus DNA after metabolic activation, forming multiple DNA adducts *in vitro*, all of which are reduction products. Multiple DNA adducts were also detected in cultures of rat lung alveolar type II epithelial cells treated with 3-nitrobenzanthrone.

10.1.2.3 Nitrolactones

2-, 3- and 4-nitrodibenzopyranones all formed multiple DNA adducts after incubation with xanthine oxidase and calf thymus DNA under anaerobic conditions. DNA adducts were detected in the liver, but not the lungs, of rats treated with 2-nitrodibenzopyranone. The migration of these adducts was similar to that observed in the *in vitro* experiment.

10.1.3 Toxic effects

10.1.3.1 Non-neoplastic effects

The limited data indicate that nitroPAHs have a moderate to low acute toxicity. For example, the oral LD_{50} for 2-nitrofluorene in mice was 1600 mg/kg bw, whereas gavaging up to 5000 mg 1-nitropyrene/kg bw resulted in no observable toxic effects.

Oral administration of up to 160 mg 1-nitronaphthalene/kg bw via diet revealed no clinical abnormalities in mice and rats. In contrast, lung (and liver) toxicity has been reported after single i.p. injections of 100 mg 1-nitronaphthalene/kg bw and effects in non-ciliated cells in the bronchioles at concentrations as low as 25 mg/kg bw. In a 13-week inhalation study on rats conducted according to current acceptable standards, exposure to 1-nitropyrene resulted in histopathological effects in the upper respiratory tract, leading to a lowest-observed-effect level (LOEL) of 0.5 mg/m^3.

There are few data on systemic or local non-neoplastic effects caused by short-term or long-term treatment with nitroPAHs. In most cases, non-neoplastic toxic effects were observed at doses at which carcinogenic responses are also manifested.

No data are available on skin and eye irritation, sensitization or reproductive toxicity.

There were no data available on the non-neoplastic effects of nitroketones and nitrolactones.

10.1.3.2 Genotoxicity

1) NitroPAH

Data on genotoxicity *in vitro* are available on 95 nitroPAHs (see Table 45), but only one or two end-points, mainly in bacterial test systems, were investigated for 74 nitroPAHs. A sufficient database, also including eukaryotic test systems, has been found only with 21 nitroPAHs. Sixty-seven of 95 nitroPAHs tested showed positive results, but these were derived from a small database. Clearly positive results were obtained for 19 nitroPAHs, and questionable results for 8 nitroPAHs. Clearly negative results were not obtained with any of the nitroPAHs.

For 86 nitroPAHs, data on the *Salmonella typhimurium* microsome test are available. In contrast to the parent PAHs, most nitroPAHs were clearly more effective in the *S. typhimurium* microsome test without metabolic activation. There are five nitroPAHs that showed exceptionally high mutagenic potency (≥100 000 revertants/nmol) in this test system: 3,7- and 3,9-dinitrofluoranthene, 1,6- and 1,8-dinitropyrene and 3,6-dinitrobenzo[*a*]pyrene (see also nitroketones and nitrolactones below).

Bacterial nitroreductase and acetyltransferase are involved in the metabolic activation of the nitroPAHs, but not all nitroPAHs follow the same metabolic activation pathways. For different nitroPAHs, both frameshift and base pair substitutions have been reported in the *S.*

typhimurium microsome test. There is evidence that nitroPAHs with nitro groups perpendicular to the aromatic ring are not as mutagenic as isomers having parallel nitro orientation.

Some nitroPAHs are extremely mutagenic in bacteria. This led to an earlier conclusion that nitroPAHs are among the most important mutagens in ambient aerosol samples. This sensitivity of *S. typhimurium* to nitroPAHs is attributed to the presence of native nitroreductase enzymes, which initiate the metabolism of nitroPAHs to their ultimate mutagenic metabolites (arylhydroxylamines). These results in bacteria may be misleading, as nitroPAHs as a group were found to be less mutagenic than PAHs in *in vitro* studies in human B-lymphoblastoid cells h1A1v2 and MCL-5. The most active nitroPAH tested (1,6-dinitropyrene) had a minimum mutagen concentration ~3-fold higher than that of BaP. However, these results in human cells must also be interpreted with caution, as they may underestimate the toxic potential of nitroPAHs; comparative carcinogenesis studies — e.g., the mouse newborn assay (Table 53) — show some nitroPAHs being more carcinogenic than BaP.

Data on the genotoxicity of nitroPAHs *in vivo* are available on 15 nitroPAHs. All nitroPAHs that gave positive results *in vivo* were also positive *in vitro* (Table 46). Four nitroPAHs that were positive in *in vitro* genotoxicity tests revealed inconsistent/inconclusive genotoxicity (2-nitronaphthalene, 5-nitroacenaphthene and 3-nitrofluoranthene) or negative genotoxicity (2,7-dinitrofluorene; limited validity) results *in vivo*.

Most of the tested nitroPAHs were positive in *in vivo* genotoxicity tests in somatic cells, and the data in *Drosophila* confirm that these compounds are *in vivo* somatic mutagens. There were no germ cell assays carried out in rodents, and the single germ cell assay in *Drosophila* was negative.

2) Nitrobenzanthrones

3-Nitrobenzanthrone, like 1,6- and 1,8-dinitropyrene, is highly mutagenic in bacteria through nitroreduction and *O*-esterification. 3-

Nitrobenzanthrone is also an effective gene mutagen and causes micronuclei formation in human cells *in vitro* and in mice *in vivo*.

3) Nitrodibenzopyranones and nitrolactones

2-Nitrodibenzopyranone was reported to be highly mutagenic in the *S. typhimurium* microsome test in strain TA98 (–S9), being more mutagenic than 2-nitrofluorene and 1-nitropyrene.

1- and 3-nitropyrene lactones have been found to be highly mutagenic in the *S. typhimurium* microsome test.

Studies on the *in vitro* genotoxicity of 2-nitrodibenzopyranone in forward mutation assays using two human B-lymphoblastoid cell lines are conflicting. However, nitropyrene lactones were found to induce mutations at the *tk* and *hprt* loci in both cell lines. Further, they induced kinetochore-positive and -negative micronuclei in the CREST modified micronucleus assay, which detects chromosomal loss and breakage events.

4) Complex mixtures

Studies on the genotoxicity of individual nitroPAHs are necessary for an understanding of the mechanisms of toxicity, but studies on the mutagenicity of environmental samples, although much more complex, are needed to examine the effect of actual exposure conditions.

Most studies have used the *S. typhimurium* microsome test, although more recent studies have used *Drosophila* and human cell lines for mutagenicity testing. Another issue is the possible additivity, antagonism or synergism of combined nitroPAHs in mixtures compared with individual nitroPAHs. There may also be problems with collection and stability of samples and the type of nitroPAH.

5) Diesel engine exhaust

Earlier studies found that in diesel engine exhaust, nitroPAHs accounted for 20–25% of the bacterial mutagenic activity (without

further enzymatic activation of the assay, i.e., –S9). Another study found that mono- and dinitroPAHs accounted for 30–40% of bacterial mutagenic activity (–S9) of diesel engine exhaust particles.

In a diesel exhaust particle extract (benzene–ethanol), nitroPAHs were found mostly in fraction 4 (solvent DCM), which contained 61.5% of the total activity. Of this fraction, 53.1% of the activity was attributed to nitroPAHs, with the greatest contribution being from 1-nitropyrene and 1,3-, 1,6- and 1,8-dinitropyrene.

Studies on ambient air showed that 1–8% of the mutagenic activity (–S9) in the *S. typhimurium* microsome test was due to nitroPAHs. In the benzene–ethanol extract of airborne particulate, the calculated mutagenic contributions of 1-nitropyrene and 1,3-, 1,6- and 1,8-dinitropyrene in the *S. typhimurium* YG1024 strain were 2.1, 2.5, 5 and 9%, respectively, assuming that the interaction between the compounds is negligible.

The 1-nitropyrene content in diesel exhaust particle samples correlates with the mutagenicity in four *S. typhimurium* strains.

6) Ambient air

Using a preincubation modification of the *S. typhimurium* microsome test, the vapour phase contributed substantially to the mutagenic potential of ambient air samples. The ambient mutagenicity concentration in the vapour phase was comparable with that in particulate matter. Nitronaphthalenes were thought to account for about 13% of the mutagenicity in the fraction where the mutagenicity of the vapour phase was highest for these nitroPAHs. About 10% of ambient particulate mutagenicity in the Ames test can be accounted for by nitrofluoranthenes and nitropyrenes, the dominant contributors to ambient particulate organic matter. These nitroPAH isomers were largely formed from the atmospheric gas-phase reactions of the parent PAH, rather than being directly emitted.

2- and 4-nitrodibenzopyranone were found in the most mutagenic HPLC fraction of ambient particle extracts collected from Riverside,

California, USA, when tested in a preincubation modification of the *S. typhimurium* microsome test (TA98 [–S9]). This fraction accounted for ~20% of the total mutagenic activity, with the 2-nitro isomer contributing to the majority of this mutagenicity.

A human cell mutagenicity assay at the *tk* locus was recently used on samples from various sites in the Los Angeles, California, USA, area collected in 1993. This assay has previously been shown not to be very sensitive to nitroPAHs. 2-Nitrofluoranthene was the only nitroPAH in this study that significantly contributed to the mutagenicity.

10.1.3.3 Neoplastic effects

1) NitroPAHs

Data on carcinogenic effects are available for 28 nitroPAHs (see Table 52). Although inhalation is the main exposure route in humans, no long-term inhalation study on any nitroPAH is available. Most studies examined the carcinogenic effects of nitroPAHs by oral, topical application, pulmonary implantation and intratracheal administration.

Owing to the limitations in experimental design, none of the negative studies confirmed the absence of carcinogenic effects in animals. However, results showed carcinogenic effects in experimental animals for 5-nitroacenaphthene, 2-nitrofluorene, 3-nitrofluoranthene, 3,7-dinitrofluoranthene, 3,9-dinitrofluoranthene, 1-nitropyrene, 4-nitropyrene, 1,3-dinitropyrene, 1,6-dinitropyrene, 1,8-dinitropyrene and 6-nitrochrysene. Some carcinogenic effects in experimental animals were observed for 2-nitropyrene, 7-nitrobenz[*a*]anthracene, 2-nitrobenzo[*a*]-pyrene, 6-nitrobenzo[*a*]pyrene, 3,6-dinitrobenzo[*a*]pyrene, 7-nitrodibenz[*a*,*h*]anthracene and 3-nitroperylene. For the remaining 10 nitroPAHs tested, not enough data were available to evaluate the carcinogenicity in experimental animals.

Besides local effects at the site of injection, nitroPAHs induced mainly systemic tumours in mammary tissue, lung, liver and the haematopoietic system. 6-Nitrochrysene appears to be the most carcinogenic of the nitroPAHs considered here. With systemic effects

after s.c. or i.p. injection, 1-nitropyrene was more carcinogenic than the dinitropyrenes. The carcinogenicity of 1-nitropyrene and dinitropyrenes varies, depending on the route of administration.

The substitution of the nitro group on the parent PAH does not alter the carcinogenicity and/or mutagenicity in a consistent manner (i.e., sometimes increases and sometimes decreases the effect). As examples, nitrated benzo[*a*]pyrenes were found to be generally less potent carcinogens than the parent compound BaP. However, the mono- or dinitrated pyrenes are more carcinogenic than pyrene, and 3-nitroperylene is more carcinogenic than perylene. 6-Nitrochrysene was more carcinogenic than chrysene after i.p. administration, but was less active with respect to local effects after dermal exposure.

2) Nitroketones and nitrolactones

There are no data on the carcinogenicity of these compounds.

10.1.4 Evaluation of nitroPAHs, nitroketones and nitrolactones that seem to be of importance in the environment

Table 58 shows a summary of the exposure and effects of nitroPAHs that are probably of special relevance to health and the environment.

10.2 Evaluation of effects on the environment

NitroPAHs are either formed in the atmosphere from PAHs or emitted directly into the atmosphere during combustion processes. They are transported in the vapour phase or adsorbed onto particulate matter. Those with liquid-phase vapour pressures greater than 10^{-4} Pa at ambient air temperature will exist at least partially in the gas phase — i.e., two- to four-ring PAHs and two-ring nitroPAHs.

Owing to their low aqueous solubility or insolubility, nitroPAHs are not expected to be transported in water. Data available give high values for log K_{oo}, suggesting that nitroPAHs, similar to PAHs, adsorb

Table 58. Overview on exposure, genotoxicity of nitroPAHs *in vitro* and *in vivo*, and carcinogenic effects of selected nitroPAHs

Substance	Human exposure		Genotoxicity *in vitro*	Genotoxicity *in vivo*	Carcinogenicity			
	Ambient air[a]	Diesel exhaust particles[b]	Result[c]	Result[d]	Indication[e]	Number of positive studies[f]		
						Rat	Mouse	Hamster
1-Nitronaphthalene	+[g,h]	+	**Positive**	Positive	Database insufficient			
2-Nitronaphthalene	**+**[g,h]	+	**Positive**	Inconclusive	Database insufficient			
5-Nitroacenaphthene			**Positive**	Inconclusive	Positive	2	1	1
2-Nitrofluorene	**+**	**+**	**Positive**	**Positive**	Positive	2		
2,7-Dinitrofluorene	+	+	**Positive**	(Negative)	Database insufficient			
9-Nitroanthracene	+	+	**Positive**	Positive	n.d.			
9-Nitrophenanthrene	+[g]	+	Positive	n.d.	n.d.			
2-Nitrofluoranthene	+[h]		Positive	n.d.	Database insufficient			
3-Nitrofluoranthene	**+**	**+**	**Positive**	Inconclusive	Positive	1	1	
3,7-Dinitrofluoranthene	**+**		**Positive**	Positive	Positive	2		
3,9-Dinitrofluoranthene	**+**		**Positive**	Positive	Positive	2		
1-Nitropyrene	**+**	**+**	**Positive**	**Positive**	Positive	8	1	
2-Nitropyrene	+[h]		**Positive**	n.d.	(Positive)	1		
4-Nitropyrene	**+**	**+**	**Positive**	n.d.	Positive	4	1	
1,3-Dinitropyrene	**+**	**+**	**Positive**	(Positive)	Positive	3		
1,6-Dinitropyrene	**+**	**+**	**Positive**	Positive	Positive	5	2	1
1,8-Dinitropyrene	**+**	**+**	**Positive**	Positive	Positive	5	1	

Table 58 (Contd).

Substance	Human exposure		Genotoxicity *in vitro*	Genotoxicity *in vivo*	Carcinogenicity			
	Ambient air[a]	Diesel exhaust particles[b]	Result[c]	Result[d]	Indication[e]	Number of positive studies[f]		
						Rat	Mouse	Hamster
7-Nitrobenz[*a*]anthracene	+	+	Positive	n.d.	(Positive)		1	
6-Nitrochrysene	+	+	**Positive**	Positive	Positive	2	15	
1-Nitrobenzo[*a*]pyrene			Positive	n.d.	Database insufficient			
2-Nitrobenzo[*a*]pyrene			Positive	n.d.	(Positive)		1	
3-Nitrobenzo[*a*]pyrene			Positive	n.d.	Database insufficient			
6-Nitrobenzo[*a*]pyrene	+	+	**Positive**	n.d.	(Positive)		1	
1-Nitrobenzo[*e*]pyrene			Positive	n.d.	Database insufficient			
3-Nitrobenzo[*e*]pyrene			Positive	n.d.	Database insufficient			
1,6-Dinitrobenzo[*a*]pyrene			Positive	n.d.	Database insufficient			
3,6-Dinitrobenzo[*a*]pyrene			Positive	n.d.	(Positive)	2[i]		
7-Nitrodibenz[*a*,*h*]anthracene			Inconclusive	n.d.	(Positive)		1	
9-Nitrodibenz[*a*,*c*]anthracene			Inconclusive	n.d.	Database insufficient			
3-Nitroperylene		+	Positive	n.d.	(Positive)		1	
3-Nitrobenzanthrone	+	+	**Positive**	Positive	n.d.			
2-Nitrodibenzopyranone	+[h]	+	**Positive**	n.d.	n.d.			

Table 58 (Contd).

[a] + = nitroPAHs detected in ambient air.
[b] + = nitroPAHs detected in diesel exhaust particles.
[c] Normal type: limited database (data on fewer than three end-points available) or inconsistent results; bold type: data on three or more end-points available and majority of end-points positive.
[d] Normal type: limited database (only data on one end-point available) or inconsistent results; bold type: data on two or more end-points available and majority of end-points positive; parentheses: limited validity; n.d. = no data.
[e] (Positive) = only one positive study with study design sufficient for assessment; n.d. = no data.
[f] Number of carcinogenicity studies with positive results and experimental design sufficient for assessment; separated for different species; detailed data presented in Tables 39 and 52.
[g] NitroPAHs predominant in the vapour phase.
[h] NitroPAHs formed by tropospheric transformation.
[i] Probably the same results are presented in two different publications.

onto soil and sediments. Leaching into groundwater is thought to be negligible. Some nitroPAHs may be slowly biodegradable under certain conditions.

The values for $\log K_{ow}$ range from 2.5 for 1-nitronaphthalene to 6.3 for 3-nitroperylene, suggesting a potential for bioaccumulation. There were no data available on biomagnification.

Calculated atmospheric lifetimes of nitroPAHs due to photolysis and gas-phase reactions with hydroxyl and nitrate radicals and with ozone under atmospheric conditions show that the main degradation process for nitroPAHs (e.g., 1- and 2- nitronaphthalene) is photolysis. Particle oxidation of nitroPAHs by ozone may be the main degradation process at night.

Most studies reporting nitroPAH concentrations have focused on air samples. There are a few studies that indicate the presence of nitroPAHs in other environmental media, including water (ng/litre range) and sediment, soil and sewage sludge (µg/kg range).

Organisms living in water, sediment or soil may potentially be exposed to nitroPAHs.

Data on the acute toxicity of nitroPAHs to aquatic organisms are available only for 1-nitronaphthalene. An LC_{50} (96 h) of 9.0 mg/litre was reported for the fathead minnow (*Pimephales promelas*). Furthermore, this nitroPAH inhibited the growth of the ciliate *Tetrahymena pyriformis*, with an EC_{50} (60 h) of 17.3 mg/litre.

With 1-nitropyrene, DNA adducts were detected *in vivo* using brown trout (*Salmo trutta*) and turbot (*Scophthalmus maximus*) that were comparable to those obtained in Wistar rats.

10.3 General considerations

1) The identification of all of the mutagenic compounds in urban air has not been achieved.

2) Most studies have concentrated on measuring concentrations of nitroPAHs on particulates and their levels of mutagenicity. Not enough data are available on the concentrations of nitroPAHs in, and mutagenicity of, the vapour phase.
3) There are not enough genotoxicity/carcinogenicity data on some nitroPAHs, such as the nitronaphthalenes, methylnitronaphthalenes, 2-nitrofluoranthene, 3-nitrobenzanthrone or nitrolactones.
4) The mutagenic responses of nitroPAHs in bacterial systems do not necessarily reflect those responses obtained in human cell lines or *in vivo*.
5) For certain nitroPAHs, there is increasing evidence for the role of oxidative metabolism *in vivo*, rather than nitroreductive biotransformation.
6) There is a lack of data on the biotransformation and genotoxicity (e.g., additivity, antagonism or synergism) of nitroPAHs when included in complex mixtures in which they exist (e.g., diesel and ambient particulates).
7) In addition, limited data are available on the toxic/genotoxic effects of nitroPAHs in target tissues of humans and animals and in human cell lines.

10.4 Overall evaluation

NitroPAHs, nitroketones and nitrolactones have been detected in ambient air and diesel exhaust.

Organisms living in water, sediment or soil may potentially be exposed to nitroPAHs. Some aquatic organisms are capable of metabolizing nitroPAHs to active intermediates that can damage DNA, and in certain cases nitroPAHs showed acutely toxic effects.

The nitroPAHs, nitroketones and nitrolactones listed in Table 58 are genotoxic. Many of the nitroPAHs are somatic mutagens in rodents and carcinogenic in more than one species. Even in light of a lack of human data, the overwhelming evidence supports a conclusion that the nitroPAHs are *probably human carcinogens.*

11. RECOMMENDATIONS FOR PROTECTION OF HUMAN HEALTH AND THE ENVIRONMENT

1) Reduce the overall concentration of PAHs in urban air, since they are a source of atmospheric nitroPAHs.
2) Reduce the level of nitroPAH emissions in diesel exhaust and other forms of combustion.
3) Improve the efficiency of exhaust catalysts and filters to remove PAHs and nitroPAHs.
4) Encourage development and implementation of less-polluting indoor heating sources.
5) Encourage power source development that does not require fossil fuel combustion.
6) Encourage improved industrial hygiene (ventilation, engine efficiency, personal protection) concerning fossil fuel engines.
7) Encourage increased examination by regulatory agencies of the occurrence of nitroPAHs in non-emission sources (e.g., Mate tea).
8) Improve communication on the risk of nitroPAHs by health agencies to industrial organizations (i.e., risk communication).

12. RECOMMENDATIONS FOR FURTHER RESEARCH

The following were identified by the Task Group as areas of basic research that required attention:

1. Obtain human epidemiological data on the role of nitroPAHs in human disease.
2. In the absence of human data, develop better risk assessment models for environmental genotoxic compounds (i.e., nitro-PAHs).
3. Assess the sensitivity of biomarkers for exposure to nitro-PAHs.
4. Determine the role of human polymorphism in the biotransformation and mutation burden of nitroPAHs.
5. Determine the exposure and accepted level of exposure to nitroPAHs from various sources.
6. Conduct mutagenicity/carcinogenicity studies on nitroPAHs in complex mixtures at levels that could mimic human exposure concentrations and routes.
7. Owing to limited data and ambient concentrations, generate more genotoxicity/carcinogenicity data on the nitronaphthalenes, methylnitronaphthalenes, 2-nitrofluoranthene, 3-nitrobenzanthrone and nitrolactones.
8. Determine the role of the matrix (aerosol versus particle-deposited) in the biotransformation and genotoxicity of nitro-PAHs.
9. Clarify if *in situ* formation of nitroPAHs occurs in humans exposed to nitrogen oxides.
10. Determine the impact of nutrition and antimutagens on nitro-PAH biotransformation and genotoxicity.
11. Determine the effect of engine design, fuel formulation and exhaust manipulation on nitroPAH emissions.

13. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

Some nitroPAHs have been evaluated by the International Agency for Research on Cancer (IARC, 1978, 1984, 1987, 1989, 1996). These are summarized in Table 59 below.

Table 59. Summary of previous evaluations of nitroPAHs by IARC

NitroPAH	Evidence for carcinogenicity in experimental animals	Evaluation in humans	Overall evaluation (group)[a]	IARC reference
1-Nitronaphthalene	Inadequate	No data	3	1989
2-Nitronaphthalene	Inadequate	No data	3	1989
5-Nitroacenaphthene	Sufficient	No data	2B	1978; Suppl. 7 (1987)
2-Nitrofluorene	Sufficient	No data	2B	1989
9-Nitroanthracene	No data	No data	3	1984; Suppl. 7 (1987)
3-Nitrofluoranthene	Inadequate	No data	3	1984; Suppl. 7 (1987)
3,7-Dinitrofluoranthene	Sufficient	Inadequate	2B	1989; revised 1996
3,9-Dinitrofluoranthene	Sufficient	Inadequate	2B	1989; revised 1996
1-Nitropyrene	Sufficient	No data	2B	1989
2-Nitropyrene	Inadequate	No data	3	1989
4-Nitropyrene	Sufficient	No data	2B	1989
1,3-Dinitropyrene	Limited	No data	3	1989
1,6-Dinitropyrene	Sufficient	No data	2B	1989
1,8-Dinitropyrene	Sufficient	No data	2B	1989
6-Nitrochrysene	Sufficient	No data	2B	1989
7-Nitrobenz[*a*]anthracene	Limited	No data	3	1989
6-Nitrobenzopyrene	Limited	No data	3	1989
3-Nitroperylene	Inadequate	No data	3	1989
Diesel exhaust (whole)	Sufficient	Limited	2A	1989

[a] Group 2A: probably carcinogenic to humans; Group 2B: possibly carcinogenic to humans; Group 3: not classifiable as to its carcinogenicity to humans.

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