WORLD HEALTH ORGANIZATION

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC MONOGRAPHS
ON THE
EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS

The Rubber Industry

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This section includes information on chemicals for which some data on carcinogenic, mutagenic or teratogenic effects were available to the Working Group. The selection of chemicals included in this section is not the result of an exhaustive screening of the literature on all chemicals used or formed in the rubber industry. Some of the chemicals have already been considered in previous IARC Monographs, and, for these, reference to the pertinent Monograph is given (see also Appendices 2 and 3). For a number of chemicals, information on carcinogenicity, mutagenicity or teratogenicity was derived from the literature and was not critically analysed or evaluated in the same way as that for chemicals previously considered in IARC Monographs. This section should therefore be read more as an introduction than as an exhaustive and complete review.

1. Carcinogenic, mutagenic and teratogenic effects

1.1 Accelerators, antioxidant and curing agents

Of the organic peroxides used as curing agents, dicumyl peroxide, bis(2,4-dichlorobenzoyl)peroxide and α,α'-bis(tert-butylperoxyisopropyl)benzene were reported to be skin irritants, while tert-butylperoxide was not. Their acute toxicity in animals has been summarized by Holmberg and Sjöstrom (1977), but virtually no evaluable data are available on their carcinogenic, mutagenic or teratogenic effects. Hydrogen peroxide was reported to be carcinogenic to mouse duodenum when administered at a concentration of 0.4% in drinking water for 108 weeks (Ito et al., 1981). It was also shown to induce DNA repair in Escherichia coli (Rosenkranz, 1973) and mutations in Saccharomyces cerevisiae (Thacker, 1975).

The accelerators and curing agents commonly used are thiuram compounds, inciuding tetramethylthiuram disulphide (thiram, TMTD), tetraethylthiuram disulphide (disulfiram, TETD) and tetramethylthiuram monosulphide (TMTM). (See also Appendix 1).

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TMTD and TETD were evaluated for carcinogenicity in an IARC Monograph (IARC, 1976b). The two carcinogenicity studies in experimental animals and the one case report of human thyroid cancer were considered an insufficient basis for evaluating the carcinogenicity of TMTD; the data for TETD were also too limited to evaluate carcinogenicity. In one study of oral administration to mice, the incidence of liver-cell tumours was increased in males of two strains, and the number of lung tumours was increased in males of one strain. Both TMTD and TETD react with nitrite to form carcinogenic nitrosodialkylamines. TETD is metabolized in rats and man to diethyldithiocarbamate, glucuronide and sulphate conjugates, diethylamine and carbon disulphide.

These compounds were investigated in a series of reactivity studies in vitro (Hemminki et al., 1980). TMTM, TMTD, TETD, zinc and copper dimethyldithiocarbamates, zinc, cadmium and tellurium diethyldithiocarbamates, and zinc dibutyldithiocarbamate were incubated with synthetic nucleophiles, 4-(para-nitrobenzyl)-pyridine and deoxyguanosine. The thiuram compounds were not reactive; copper dimethyldithiocarbamate, cadmium and tellurium diethyldithiocarbamate and zinc dibutyldithiocarbamate reacted slowly with both deoxyguanosine and 4-(para-nitrobenzyl)pyridine. There seemed to be no correlation between mutagenicity in Escherichia coli WP2 and chemical reactivity.

In a series of mutagenicity tests on rubber accelerators (Hedenstedt et al., 1979), TMTD and TMTM were mutagenic but TETD was non-mutagenic to Salmonella typhimurium. TMTD was the most active of the thiurams. Five out of nine tested dithiocarbamates were also mutagenic, ziram being the most active.

4,4'-Dithiomorpholine, zinc ethylphenyldithiocarbamate, N,N'-dicyclohexyl-para-phenylenediamine, N,N'-diphenyl-para-phenylenediamine, 4,4'-diaminodiphenylmethane, 6-ethoxy-1,2-dihydro-2,2,4-trimethylquinoline and N-methyl-N,4-dinitrosoaniline were all direct or indirect mutagens for S. typhimurium in another study (Hedenstedt, 1982). TMTD was also found to be mutagenic in another study on S. typhimurium TA100 (Shirasu et al., 1977).

TMTD, TMTM and TETD (in order of decreasing toxicity) produced deaths and malformations in chicken embryos (Korhonen et al., 1982a). The dithiocarbamates investigated were cadmium and zinc diethyldithiocarbamate, zinc ethylphenyldithiocarbamate,

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zinc dibutyldithiocarbamate, copper dimethyldithiocarbamate, tellurium diethyldithiocarbamate and piperidine pentamethylenedithiocarbamate. The cadmium and zinc salts were particularly embryotoxic (Korhonen et al., 1982b).

Ethylenethiourea has been judged to be carcinogenic in rats (IARC, 1974). It was also teratogenic in two studies in rats (Khera, 1973; Ruddick & Khera, 1975). When tested on chicken embryos, together with 1,3-dibutylthiourea, 1,3-diphenylthiourea, tetramethylthiourea, trimethylthiourea, 1,3-diethylthiourea and carbon disulphide, ethylenethiourea was the least embryotoxic compound in the series. Carbon disulphide was inactive at the concentrations tested. Tetramethylthiourea and 1,3-diphenylthiourea were the most active teratogens in this test system; ethylenethiourea was a weak teratogen (Korhonen et al., 1982c).

1.2 Solvents

Solvents that have been used or are used in the rubber industry include benzene, trichloroethylene, 1,1,1-trichloroethane and methylene chloride; 1,4-dioxane is used as a stabilizer in solvents. Generally, these compounds are not chemically reactive and do not appear to react with macromolecules, but their metabolites may do so.

Benzene is a known clastogen and has been considered to be carcinogenic in humans and rodents (IARC, 1982). It was teratogenic in rats (Kuna & Kapp, 1981). 1,4-Dioxane is carcinogenic in rats and guinea-pigs (IARC, 1976b).

The evidence for the carcinogenicity of trichloroethylene and 1,1,1-trichloroethane is limited; and the data on methylene chloride were inadequate for evaluation (IARC, 1979c). 1,1,1-Trichloroethane induced mutations in E. coli in the presence of a liver microsomal activation system; the increase was small but statistically significant (Norpoth et al., 1980). The data reported in the literature regarding the mutagenicity of trichloroethylene are conflicting. However, in the presence of a rodent liver activation system, a technical-grade product slightly increased mutagenicity in E. coli (Greim et al., 1975); and a product 99.5% pure increased mutagenicity in S. typhimurium TA100 (Bartsch et al., 1979). Irreversible binding of ^{14}C-trichloroethylene to mouse liver constituents, in vitro and in vivo, has been described (Uehleke & Poplawski-Tabarelli, 1977).

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Dichloromethane is weakly mutagenic in S. typhimurium TA98 and TA100, both in the presence and absence of a liver activation system (Jongen et al., 1978). Covalent binding and metabolism to carbon monoxide, both in vivo and in vitro, have been described (Ahmed et al., 1980).

Studies on the teratogenicity of trichloroethylene, 1,1,1-trichloroethane, methylene chloride and 1,4-dioxane were either inconclusive or failed to demonstrate skeletal or visceral malformations (IARC, 1976b, 1979c).

Dimethylformamide, also used in the rubber industry, is metabolized in rats to N-methylformamide (Barnes & Ranta, 1972), which is teratogenic and embryotoxic to rats (Stula & Krauss, 1977). Ethylene dichloride, which has been used as a solvent in the rubber industry, is carcinogenic to mice and rats and is mutagenic to S. typhimurium with or without metabolic activation (IARC, 1979c).

In human whole blood cultures, low concentrations (0.0125-0.05%) of a rubber solvent refined from a straight-run petroleum distillate of paraffin-based crude oil (consisting of a mixture of paraffins, monocycloparaffins, monoolefins, benzene and alkyl benzenes) caused an increased frequency of chromatid gaps and breaks; high concentrations (>0.05%) caused increases in the frequency of chromosome breaks. Concentrations up to a toxic level failed to produce sister chromatid exchanges (Altenburg et al., 1979).

1.3 Monomers

Small amounts of monomers, e.g., acrylonitrile, butadiene, chloroprene, ethylene, propylene, styrene, vinyl acetate, vinyl chloride and vinylidene chloride, may remain in solid rubber and could be released into the work environment. Most of these monomers do not bind directly with cellular macromolecules, but their metabolites may do so. Metabolic activation of acrylonitrile, chloroprene, styrene and vinyl chloride leads to reaction products which are mutagenic in S. typhimurium and in other bacterial test systems. In the case of acrylonitrile, chloroprene and vinyl chloride, a low mutagenic response was obtained in S. typhimurium and E. coli without metabolic activation (IARC, 1979b). Chloroprene, styrene and vinyl chloride also produce clastogenic effects.

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There is sufficient evidence for the carcinogenicity of acrylonitrile and vinyl chloride in experimental animals, and limited evidence for the carcinogenicity of styrene. The data were inadequate for an evaluation of chloroprene. Vinyl chloride is carcinogenic to humans, and there is limited evidence that acrylonitrile is too (IARC, 1979b,c). (See also Appendix 3.)

Acrylonitrile, chloroprene, styrene and vinyl chloride are teratogenic to experimental animals, and there is a suspicion that styrene and vinyl chloride have teratogenic effects in humans (IARC, 1979a,b)

Epichlorohydrin is used in the manufacture of elastomers. It reacts directly with macromolecules and it is mutagenic, clastogenic and carcinogenic in mice and rats (IARC, 1976a; Laskin et al., 1980). No adequate epidemiological observations on the carcinogenicity of epichlorohydrin to humans have been published (IARC, 1976a, 1979b).

1.4 Talc

French chalk (talc) is widely used as an antitacking agent. It has been used in many processes and is still used in substantial quantities. It is a major component of environmental dusts encountered in the rubber industry. Its composition is variable, being dependent upon the source of supply; for the most part, talc particles are 'platey' in character. Some talcs, however, may contain asbestos fibres, which are carcinogenic in both humans and animals (IARC, 1977). Prolonged and excessive exposure to talc has been shown to give rise to a number of documented cases of respiratory disease. (See section VI, .2.2).

1.5 Carbon blacks

Assessment of possible hazards from carbon black is difficult, because different preparations contain variable amounts of many compounds, some of which have still not been identified. The chemical composition and physical properties differ with methods of preparation and the nature of the starting material and, probably, from day to day.

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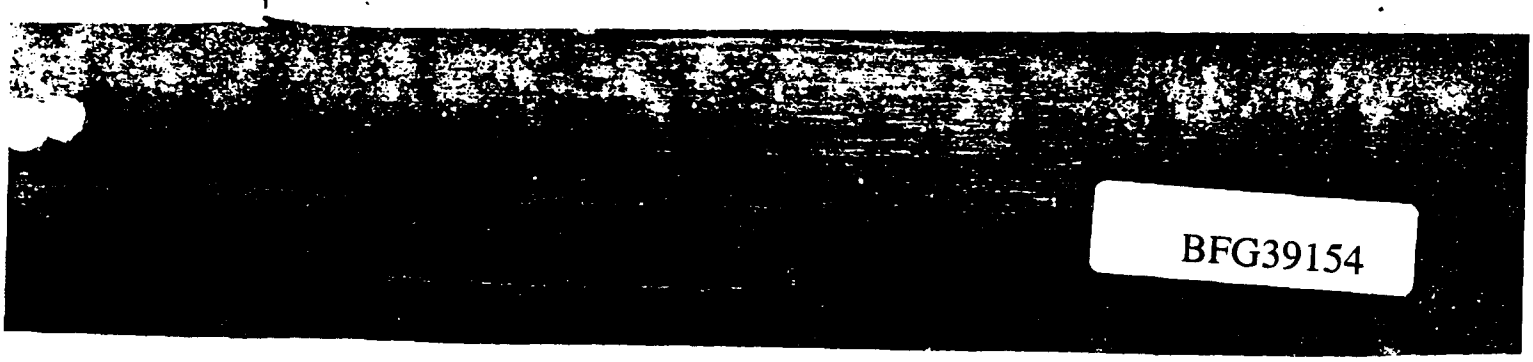

The most probable carcinogenic hazard is associated with the 'benzene extractables'. The material, extracted from furnace black, consists mainly of aromatic hydrocarbons and sulphur compounds. Some compounds have been identified by computerized gas-chromatographic mass spectrometry and high-resolution mass spectrometry (Lee & Hites, 1976). Among them, benz[a]anthracene, benzo[a]pyrene and indeno(1,2,3-cd)pyrene are known carcinogens (IARC, 1973); chrysene has been described as an initiating agent, and pyrene and fluoranthene as cocarcinogens for mouse skin (Van Duuren, 1976). Oxygen derivatives (Gold, 1975) and nitro derivatives (Fitch & Smith, 1979) of polycyclic compounds have also been found in extracts of commercial carbon blacks. Benzo[a]-pyrene was found in benzene extracts of all types of carbon black examined (Troitskaya et al., 1975). The amounts of some polycyclic hydrocarbons found in the benzene extracts of furnace carbon blacks are shown in Table 13 (from Locati et al., 1979).

Existing data indicate that the known carcinogens present in carbon blacks are strongly adsorbed but can be eluted by biological fluids. Although Neal et al. (1962) reported that polycyclic hydrocarbons, including benzo[a]pyrene, in furnace and channel blacks are not eluted by human blood plasma or gastric juice, Kutscher et al. (1967) found that bovine serum elutes 10-20% of benzo[a]pyrene from various types of carbon blacks within periods ranging from 4-60 hours depending upon the particle size. When a commercial carbon black (500-nm particle size) was incubated with sterile human plasma, several polycyclic aromatic hydrocarbons, including benzo[a]pyrene, were extracted within 16-192 hours. Elution of benzo[a]pyrene from fine-particle carbon black (80 nm) was more difficult, but 65% was extracted within eight days (Falk et al., 1958).

The rates of elution by benzene and the amounts of material extractable from carbon black vary with the type of carbon. Thus extraction of two carbon blacks which contained over 0.1% of extractable material, was almost complete in 150 hours (Locati et al., 1979). In a study using three organic solvents for extraction of adsorbates from five rubber-grade oil-furnace blacks, toluene was found to be a better extractant than benzene and both to be superior to cyclohexane (Taylor et al., 1980).

Table 13.
Values exp
black type

PAH
Phenanthre anthrac
Fluoranthe
Benzo[d,e, thiophe acenaph
Pyrene
Benzo[g,h fluoran
Cyclopent pyrene
Benzofluo (total
Benzopyre
Dimethyl and/or benzo[
Indenopyr
Benzo[g,h
Anthanth
Benzoacr deriv

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Table 13. Polycyclic aromatic hydrocarbons (PAH) identified in five types of carbon black. Values expressed as percent of benzene extract; mean value and range of 5 samples for each black type[3]

PAH	Sample				
	A	B	C	D	E
Phenanthrene and/or anthracene	0.07 (<0.05–0.1)	absent	<0.05	absent	0.2 (0.1–0.5)
Fluoranthene	4.1 (3.8–4.3)	3.7 (3.4–3.9)	3.5 (2.9–4.3)	4.1 (3.4–6.4)	4.3 (3.9–5.2)
Benzo[d,e,f]dibenzothiophene + benzo[a]acenaphthylene	<0.05	<0.3	<0.3	absent	<0.05
Pyrene	22.2 (21.3–24.9)	23.2 (21.6–24.0)	16.5 (13.4–18.7)	17.2 (14.3–18.1)	17.2 (14.3–20.1)
Benzo[g,h,i]fluoranthene	7.2 (5.9–7.6)	6.3 (5.6–7.2)	6.9 (6.5–7.3)	4.6 (4.2–5)	7.8 (7.5–8.1)
Cyclopenta[cd]pyrene	10.2 (5.6–14.7)	<0.3	7.0 (6.8–7.3)	4.4 (4.2–5)	6.5 (5.2–7.8)
Benzofluoranthenes (total)	0.7 (0.4–1.1)	absent	<0.3	1.2 (0.9–1.4)	0.6 (0.4–0.9)
Benzopyrenes (total)	1.4 (1.1–1.9)	0.5 (<0.3–0.7)	1.1 (0.4–2.1)	2.6 (1.5–3.2)	2.7 (2.0–3.9)
Dimethylcyclopentapyrene and/or dimethylbenzofluoranthene	2.5 (2.0–3.5)	0.5 (<0.3–0.7)	0.9 (0.3–1.3)	1.9 (1.7–2.3)	1.4 (1.1–1.7)
Indenopyrene	1.7 (1.5–2.2)	0.5 (<0.3–0.7)	0.1 (abs.–0.3)	2.3 (2.1–2.5)	2.9 (2.7–3.1)
Benzo[g,h,i]perylene	11.7 (10.9–13.8)	6.2 (5.5–8.5)	8.7 (8.2–9.5)	13.5 (12–16.5)	13.6 (12.8–17)
Anthanthrene	3.2 (2.8–3.5)	–	0.8 (<0.3–1.2)	2.3 (1.9–3.3)	3.5 (2.8–5.5)
Benzoacridine derivative	<0.05	absent	absent	absent	0.2 (abs.–0.5)

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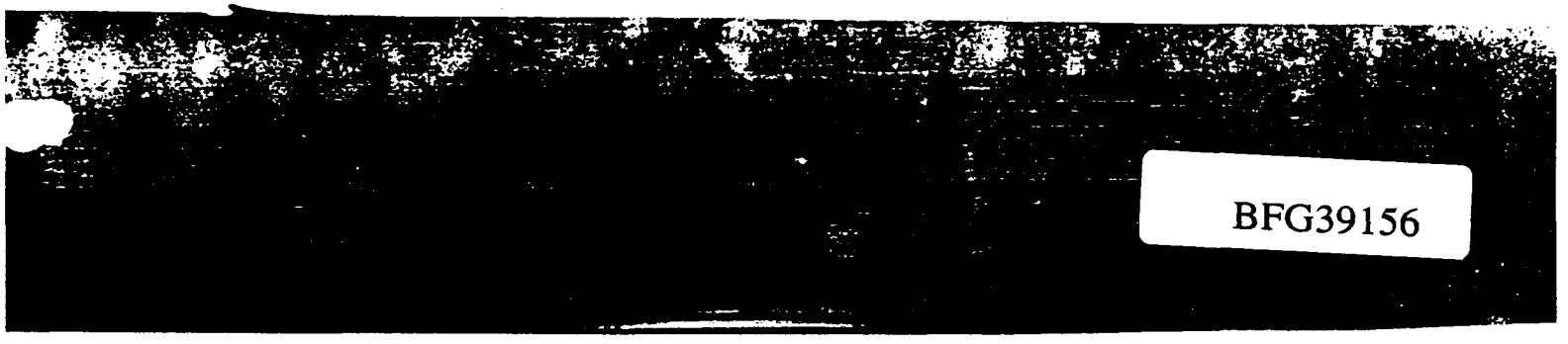

Table 13 (contd)

PAH	Sample				
Isomer of coronene	6.3 (5.1-7.2)	1.1 (abs.-2.2)	0.1 (abs.-0.3)	0.5 (abs.-1)	5.1 (4.6-5.7)
Coronene	7.2 (4.1-10)	1.2 (<0.3-3.2)	3.8 (3.5-4.4)	8.9 (8.5-9.8)	11.7 (9.5-13.8)
TOTAL	78.5	43.8	50.05	63.5	77.5

[a] From Locati et al. (1979)

Methylene chloride extracts of soots prepared by burning either kerosene or equal parts of pyridine, decaline and ortho-xylene or thiophene, were assayed in S. typhimurium in the presence of liver supernatant from Aroclor-induced rats for the induction of 8-azaguanine-resistant mutants. Mutation frequencies decreased in the following order: kerosene soot > furnace blacks > nitrogen-containing soot > sulphur-containing soot (Kaden et al., 1979). Several nitrated polycyclic aromatic hydrocarbons were mutagenic in S. typhimurium and induced unscheduled DNA repair in cultured human (HeLa) cells (Campbell et al., 1981). Samples of furnace blacks used as photocopy toners were found to be mutagenic in S. typhimurium, partly because of the presence in them of nitroaromatics (Rosenkranz et al., 1980; Löfroth et al., 1980).

Studies on the carcinogenicity of carbon blacks, by oral, skin, s.c. or inhalation exposure (Nau et al., 1958a,b, 1960, 1962, 1976), provided no evidence of carcinogenic effects; but the studies were inadequate in terms of number of animals and duration.

Furnace black (but not channel black) when suspended in tricaprylin induced sarcomas upon injection into mice. As it was not carcinogenic when implanted alone, it is probable that it became so when polycyclic aromatic hydrocarbon carcinogens were eluted by the tricaprylin. Injection of benzene extracts of furnace black also induced sarcomas (Steiner, 1954).

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When benzene-extractable materials from channel and furnace blacks were administered to mice by s.c. injection, skin application or feeding, malignant tumours were produced (Nau et al., 1958a,b, 1960). Malignant tumours were also produced following s.c. injections of cotton-seed oil in which the carbon blacks had been suspended for 1-6 months (Nau et al., 1960).

When 3-methylcholanthrene was adsorbed onto carbon black, its carcinogenic effect following s.c. administration to rats was reduced in comparison to that produced when the same dose was given alone (von Haam et al., 1958).

In a retrospective cohort study of workers involved in the manufacture of carbon black, no excess mortality from malignant neoplasms was noted; but the number of deaths considered was small (Robertson & Ingalls, 1980)

1.6 Aromatic amines

The metabolism and the nature of reactive intermediates formed from aromatic amines and their interaction with cellular macromolecules have been reviewed by Boyland (1958), Miller and Miller (1969), Clayson and Garner (1976), Miller (1978), Irving (1979) and Kriek and Westra (1979).

The carcinogenic or genotoxic activity of all aromatic amines that have been studied in detail is dependent on metabolic activation in vivo. Differences in these metabolic pathways largely account for the differences seen in tissue- and species-susceptibilities to cancer induction. The carcinogenicity of aromatic amines or amides is dependent on their oxidation to N-hydroxy derivatives, while the carcinogenicity of aromatic nitro compounds is linked to their reduction to hydroxylamines. Further conversion of the N-hydroxylamine or N-hydroxyamide to reactive intermediates can occur in several ways, including (1) esterification of the N-hydroxy group, (2) non-enzymic protonation of the nitrogen of the hydroxylamine, and (3) oxidation to a free radical of arylhydroxamic acids. Following generation of such reactive electrophilic intermediates in tissues or cells, macromolecular binding to nucleic aids and proteins has been observed. As a consequence, mutations (and other genotoxic effects, including malignant transformation) have been induced in a variety of cells and organisms when the reactive intermediates or the parent

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amines were assayed in the presence of a mammalian drug metabolizing system. In many cases, arylamidated and arylaminated products were formed with nucleic acid bases.

A great number of aromatic amines have now been studied for carcinogenicity, and considerable data have been reported in the first 27 volumes of the IARC Monographs. However, many of the aromatic amines considered in that series could not be evaluated for carcinogenicity, due to the inadequacy of experiments in animals and/or the lack of data concerning man. (See also Appendix 2.)

Naphthylamine–acetaldehyde condensates, of which the most important was known by the trade name 'Nonox S', were introduced around 1928 as antioxidants in the rubber product manufacturing industry. They were used in the UK and other countries (but apparently not in the US) for the production of tyres, tubes, air bags, electric cables and miscellaneous rubber goods, and were present in rubber compounds in concentrations of up to 1%. (It was the opinion of the members of the Working Group that concentrations of up to 4% may have been present in some products, particularly in air bags.) Their use was discontinued in the UK in 1949. Although the manufacturing process has changed several times, early products contained up to 2.5% 1–naphthylamine and up to 0.25% 2–naphthylamine. Exposure to Nonox S in rubber factories has been associated with an increase in the incidence of bladder cancer in workers (Veys, 1969).

4–Aminobiphenyl, benzidine and 2–naphthylamine are known to be carcinogenic for humans (IARC, 1979b). There is sufficient evidence of the carcinogenicity of 2,4–diaminotoluene and 4,4'–methylenebis(2–chloroaniline) in experimental animals. For 1–naphthylamine, 2,5–diaminotoluene, 4,4'–diaminodiphenylmethane and N–phenyl–2–naphthylamine, the available data were inadequate to assess carcinogenicity in experimental animals or in humans. (See Appendix 3.)

The experimental animal species most frequently used to investigate the carcinogenicity of aromatic amines are the dog and the hamster, in which the urinary bladder is the main target organ, as in humans. Aromatic amines have been shown to be carcinogenic in other rodent species, but the urinary bladder was not necessarily the target organ.

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Methods of analysis for aromatic amines of major industrial importance have been summarized (Egan et al., 1981).

1.7 Mineral oils, tar products and polycyclic aromatic hydrocarbons

Mineral oils (e.g., coal-tar oils, petrolatum) and tar products (e.g., bitumen, pitch) are widely used in the rubber industry as extenders. The amount of mineral oils (rich in aromatics), in tyres, for example, increased over past years up to about 20% or even more, since they are cheap and provide desirable properties to the finished rubber. Extenders such as the high-boiling mineral oil distillates (so-called aromatic oils), obtained from residues of solvent-refining and the manufacture of lubricating and cutting oils, contain relatively large quantities of polycyclic aromatic hydrocarbons (PAH), and 30% and more of the oil may consist of 4-6-ring PAHs. (See also section VI, 1.5.) PAHs may also be formed when tars and mineral oils are heated.

Although mineral oils and tar products vary in composition depending on their origin, the methods of production, etc., they all induce carcinogenic effects in mammals, including man. Their carcinogenicity may be dependent on the presence of carcinogenic PAHs (IARC, 1979b).

Benzo[a]pyrene is the carcinogenic PAH most widely investigated; benz[a]anthracene, benzo[b]fluoranthene, benzo[j]fluoranthene, chrysene, dibenz[a,h]anthracene, dibenzo[a,h]pyrene, dibenzo[a,i]pyrene and indeno[1,2,3-cd]pyrene) have also been considered by an IARC Working Group (IARC, 1973).

Mineral oils containing different amounts of PAHs have been found to be mutagenic in the Salmonella typhimurium/microsome test (Hermann et al., 1982).

1.8 Nitroso compounds

N-Nitrosodi-n-butylamine, N-nitrosodiethylamine, N-nitrosodimethylamine, N-nitrosomorpholine, N-nitrosopiperidine and N-nitrosopyrrolidine have been shown to be carcinogenic in various animal species, after administration by various routes. These compounds are metabolized to reactive metabolites, which are mutagenic in various experimental systems (IARC, 1978). There is

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limited evidence for the carcinogenicity of N-nitrosodiphenylamine in rats; but it was not mutagenic in prokaryote or eukaryote cells (IARC, 1982), although it is a transnitrosating agent in vivo (Ohshima et al., 1982). No carcinogenic effects were observed when dinitrosopentamethylenetetramine was tested in rats by oral administration and i.p. injection (IARC, 1976a); and in a cell-transformation assay, negative results were also obtained (Styles, 1978). The data on the carcinogenicity of N-methyl,N-4-dinitrosoaniline were considered to be inadequate for evaluation (IARC, 1972). para-Nitroso-N,N-dimethylaniline has produced oesophageal tumours in rats (Goodall et al., 1968).

1.9 Phthalate and adipate esters

Among the phthalic acid esters used in the rubber industry, di(2-ethylhexyl) phthalate has been most extensively investigated for its toxicological properties and is the most widely used. It inhibits mitochondrial function and causes peroxisome proliferation, hepatomegaly and testicular atrophy in rodents. Various mutagenicity tests in bacteria and mammalian cells showed negative or contradictory results. Long-term administration of di-(2-ethylhexyl) phthalate to rats and mice resulted in hepatocellular tumours. Di(2-ethylhexyl) adipate produced hepatocellular tumours in mice; but di(n-butyl) phthalate was apparently negative when tested for carcinogenicity in mice and rats (IARC, 1982).

1.10 Curing fumes and other emissions

The compounds present in the air during vulcanization (curing fumes) are mainly produced by the volatilization of rubber chemicals and their impurities and of the products of chemical reactions occurring during curing. (See also Sections IV and V.)

Air samples from industrial curing of acrylonitrile-butadiene styrene copolymer, ethylene-propylene rubber and chloroprene rubber were mutagenic in S. typhimurium (Hedenstedt, 1982). In laboratory model systems, the curing of ethylene propylene rubber and chloroprene rubber produced mutagenic gases and vapours. On the basis of these and other series of tests of condensates from cured rubber material, it was concluded that its mutagenicity was dependent to a large extent on the composition of the polymer (Hedenstedt, 1982).

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In other model systems, in which mixing and curing conditions were simulated (Hedenstedt et al., 1981), air samples from the curing of styrene-butadiene rubber and from the mixing and curing of chloroprene rubber and ethylene-propylene rubber were mutagenic to S. typhimurium.

No experimental data are available concerning the long-term toxicity of curing fumes.

2. Effects in humans (other than cancer)

In this part, some effects in humans are described which are indicative of exposures that occurred within the working or general environment. Some of the data may be useful in assessing that exposure levels were sufficiently high to produce the adverse effect. However, such effects may have no relation per se to the existence of a carcinogenic risk.

2.1 Dermatological effects

Dermatological effects resulting from exposure to rubber and rubber chemicals have been known for years in rubber goods manufacture (Cronin, 1980) and have been described in consumers. Non-specific dermatological reactions to rubber gloves and to footwear were reported many years ago (Downing, 1933; Marcussen, 1943). 'Accelerator agents', especially mercaptobenzothiazole, were described as the specific cause (Bonnevie & Marcussen, 1945). Shortly thereafter, seven cases of dermatitis of the eyelids were reported, due to the use of eyelash curlers and to the presence in them of the antioxidant, N-phenyl-2-naphthylamine (Curtis, 1945). In a case report of 42 individuals with dermatitis due to rubber gloves, mercaptobenzothiazole, TMTD and dipentamethylenethiuram disulphide were identified as the causative agents (Wilson, 1960). Of 100 cases of 'shoe dermatitis', 94% were attributed to exposure to mercaptobenzothiazole or TMTD or both (Cronin, 1966). Another report indicated that TMTD was responsible for a number of cases of rubber-glove dermatitis (van Ketel, 1968). Another series of 104 cases were attributed to exposure to thiuram accelerators or mercaptobenzothiazole (Wilson, 1969). N-Isopropyl-N'-phenyl-para-phenylenediamine has been reported to be responsible for 23 cases of dermatitis following exposure to rubberized fabrics (Batschvarov & Minkov,

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1968) and for dermatitis due to contact with automobile tyres (Jordan, 1971). It has also been reported to produce cross-sensitivity to the hair dye, *para*-aminodiphenylamine (Schønning & Hjorth, 1969).

Alkyl phenols and hydroquinone have been reported to cause leucodermas in rubber workers (Calnan, 1973). Phenylenediamines in rubber products are common causes of dermatitis (te Lintum & Nater, 1974; Nater, 1975), and a cross-reactivity occurs between different phenylenediamines (Rudzki *et al.*, 1976). 4,4'-Dithiodimorpholine, another rubber chemical, has been reported to be a skin sensitizer (Heydenreich & Ølholm-Larsen, 1976). Sensitivity to *N*-isopropyl-*N*'-phenyl-*para*-phenylenediamine, *N*-phenyl-*N*-cyclohexyl-*para*-phenylenediamine and *N*-dimethyl-1,3-butyl-*N*'-phenyl-*para*-phenylenediamine has been reported in workers handling tyres. All subjects sensitive to the first were also sensitive to the second, and 37% of them to *para*-phenylenediamine. The last-mentioned was the most powerfully allergenic compound (Herve-Bazin *et al.*, 1977).

Disulfiram (TETD) and thiram (TMTD), like most dithiocarbamates, alter ethanol metabolism (van Logten, 1972); there has been a report that in three patients with eczema from rubber gloves the condition was aggravated after consumption of ethanol (van Ketel, 1968).

Superficial keratitis has been observed in rubber workers exposed to ethyl isothiocyanate (Groves & Smail, 1969).

The International Contact Dermititis Research Group has proposed the following patch-test allergens in relation to exposure to rubber chemicals:

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N-cyciohexylbenzothiazylsulphenamide
hydroquinone monobenzylether
1,3-diphenylguanidine
phenyl-β-naphthylamine
N-phenyl-N'-isopropyl-para-phenylenediamine
4,4'-dihydroxydiphenyl
2-mercaptobenzimidazole
hexamethylenetetramine
tetramethylthiuram monosulphide
bis(diethyldithiocarbamato)zinc
mercaptobenzothiazole
tetramethylthiuram disulphide
phenylcyclohexyl-para-phenylenediamine
diphenyl-para-phenylenediamine
dibenzothiazyldisulphide
morpholinylmercaptobenzothiazole
tetraethylthiuram disulphide
dipentamethylenethiuram disulphide
di-β-naphthyl-para-phenylenediamine
bis(dibutyldithiocarbamato)zinc (Malten et al., 1976).

2.2 Respiratory effects

In a study of 239 Egyptian rubber workers in three factories, chronic bronchitis and chronic bronchial asthma were found among mixing and compounding workers exposed to dust and rubber additives, while workers exposed only to by-product gases had bronchial asthma (Noweir et al., 1972; Osman et al., 1972).

In a Swedish report (Fristedt et al., 1968), five cases of talcosis were described in one rubber factory. The mean average exposure to respirable dust (37-66 million particles per cubic foot) was twice to three times above the occupational standard at that time, which was 20 million particles per cubic foot.

The substitution for talc of powder with a fine particle size and containing a high content of crystalline silica in a rubber processing plant resulted in the development of silicosis in a number of exposed workers. The average time of exposure was 6.8 years (Gaubatz & Gaubatz-Trott, 1973).

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Workers exposed to curing fumes had a higher prevalence of chronic bronchitis than controls. Respiratory morbidity was related to both intensity and length of exposure to fumes. In addition, forced vital capacity was significantly decreased in curing workers; and those workers re-examined one year later suffered an excessive loss in pulmonary function compared with those not exposed (Fine & Peters, 1976a,b).

Sixty-five men exposed to dust in the processing area of three rubber factories had a higher prevalence of chronic productive coughs and a decrease in the ratio of forced expiratory volume:forced vital capacity when compared with controls. The effects on pulmonary function were related to length of exposure. The authors concluded that exposures to processing dusts at the level measured produced chronic respiratory disease (Fine & Peters, 1976c).

Eighty talc workers were also studied in the three rubber manufacturing plants. Although exposure to talc was below the current threshold limit value (20 million particles per cubic foot), workers exposed for 10 years had statistically significantly decreased forced expiratory volume and an increase in respiratory morbidity, despite the absence of changes in chest X-rays (Fine et al., 1976).

Rubber workers exposed to the hexamethylenetetramine-resorcinol adhesive system had an excess of acute respiratory symptoms and statistically insignificant reductions in forced expiratory volume and forced vital capacity. However, statistically significant decreases in pulmonary function were seen over a six-hour period of a work shift (Gamble et al., 1976).

A questionnaire on respiratory symptoms was answered by 1820 of 2856 white male production workers. The data were analysed according to where the individuals worked in rubber production. The prevalence of respiratory symptoms was high in those workers currently involved in milling, tube building, tube curing and tube inspection (McMichael et al., 1976). Another study of chronic respiratory disease in the rubber industry was based on a cohort on 4302 male rubber workers, of whom 73 terminated their employment with pulmonary disability. These 73 workers had spent significantly longer in curing preparation, curing and finishing and inspection work areas, each of which implied exposure to particulate material and/or to solvents. The authors concluded

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that a significant risk of developing a pulmonary disability was associated with smoking and exposure to dust and fumes, and in particular to talc and carbon black (Lednar et al., 1977).

Two further studies (Weeks et al., 1981a,b) revealed that employment in curing departments was associated with shortness of breath, chest tightness, wheeze, reduced forced expiratory volume and forced vital capacity and a decline in the ratio of forced expiratory volume:forced vital capacity. In addition, tingling and numbness occurred in the extremities. All of these associations became stronger with increase in duration of employment in the curing department. Exposure to respirable particulates causes not only increased symptoms of respiratory disease but also nausea and abdominal pain. Workers exposed to emissions from heated uncured rubber reported chest tightness on return to work.

At a US tyre factory, 210 workers (172 men and 38 women) developed a syndrome related to exposure to the volatile products released from a synthetic rubber formulation, first used in 1960. The factory employed approximately 2200 workers at the time of the outbreak, about 600 of whom were repeatedly exposed to the new formulation in their daily work. Symptoms occurred most frequently in workers in the Banbury-calender and tyre-building areas, where 32% and 22%, respectively, of the workers were afflicted. The symptoms included severe respiratory irritation, weakness, weight loss and general malaise. Fever and radiographic and pulmonary function abnormalities were also noted in many of those affected. More than 17% of the affected employees were permanently disabled. A similar syndrome was reported in at least four other factories in which the adhesive system had been introduced. After the system was modified, in late 1962, the prevalence of symptoms remained low, and no new cases appeared (doPico et al., 1975).

Chronic lung diseases (pneumoconiosis, pulmonary fibrosis, bronchitis and emphysema) occur in workers exposed to carbon black (National Institute for Occupational Safety & Health, 1978); and a higher incidence of pneumoconiosis has been reported in those exposed to channel black than in those exposed to thermal or furnace black (Troitskaya et al., 1975).

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2.3 Effects on reproduction

Data on hospitalized patients who had had miscarriages (spontaneous abortions) were analysed in conjunction with membership files of the Union of Rubber and Leather Workers (about 10 000 women) and records of the personnel of a rubber factory (about 1600 women) in Finland. Spontaneous abortions were calculated in two ways for each population analysed: rate (no. of spontaneous abortions x 100/no. of pregnancies) and ratio (no. of spontaneous abortions x 100/no. of births). The two frequencies were slightly increased for all Union members, as compared with all Finnish women. Moreover, age-standardized frequency was higher when the pregnancy occurred during Union membership than when it occurred before or after joining the Union. The frequency of spontaneous miscarriages among Union members employed only in the rubber industry was higher among those employed for 3 to 35 months than for those employed for longer periods of time. The employees of the rubber factory had slightly fewer spontaneous abortions on average than did the community population. However, women employed for 3 to 23 months had markedly higher frequencies of spontaneous abortion than those employed for longer times (Hemminki et al., 1982). [Because the data in these two studies present a conflicting picture with respect to the relation between rubber work and spontaneous abortions, no conclusions can be drawn.]

3. Summary

The number and diversity of chemicals used or formed and the multiplicity of exposures experienced within the rubber industry make it difficult to attribute a particular toxic effect to a given exposure.

Carbon blacks and mineral oils are major constituents in such products as rubber tyres. Data on the carcinogenicity of carbon blacks in experimental animals are inconclusive. Carbon blacks contain varying amounts of polycyclic aromatic compounds, some of which are carcinogenic and which may become bioavailable through elution. Solvent extracts of carbon blacks have been found to be mutagenic and carcinogenic in experimental systems. The mutagenicity and carcinogenicity of mineral oils are also

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