OCCUPATIONAL EXPOSURES IN THE RUBBER-MANUFACTURING INDUSTRY

Occupational exposures in the rubber-manufacturing industry were considered by previous IARC Working Groups in 1981 and 1987 (IARC, 1982, 1987). Since that time new data have become available, which have been incorporated in this *Monograph,* and taken into consideration in the present evaluation.

1. Exposure Data

In the context of this *Monograph*, the rubber industry is restricted to the rubber-manufacturing industry, including the production of tyres and general rubber goods and the process of re-treading. The production of synthetic polymers in chemical plants is not discussed.

1.1 Manufacturing process

Rubber manufacturing generally comprises the following operations: raw materials handling, weighing and mixing; milling; extruding and calendering; component assembly and building; 'curing' or vulcanizing; inspection and finishing; storage and dispatch. A detailed description of these steps in the production process can be found in IARC (1982).

Although the stages described below are applicable to the majority of rubber goods manufactured from solid polymer, a substantial proportion of rubber production involves the use of liquid latex. This applies to the manufacture of dipped rubber goods (such as rubber gloves and some footwear), foam-latex products (such as mattresses, cushions, etc.), and extruded thread products (such as elasticated fabrics and surgical hose).

1.1.1 Raw materials handling, weighing and mixing

All the materials required for the manufacture of the finished product are assembled. The raw polymer, either natural or synthetic is brought together at this stage with a variety of compounding chemical additives before being introduced into a mixer. The extensive range of chemicals required and the volume of raw material handled can give rise to substantial quantities of airborne dust.

1.1.2 Milling

From the mixer, the uncured rubber compound usually passes to one or more milling machines, where it is thoroughly blended to ensure an even dispersion of its chemical constituents. At this stage, considerable heat is generated, and, although many technical improvements have been introduced in recent years, the job of mill operator still involves a considerable degree of physical exertion and exposure to fumes arising from the heated compound.

1.1.3 Extruding and calendering

The extruders force the rubber compound through a die into various forms, which are then cut to appropriate lengths. Strips of softened rubber compound are fed into multiple-roll milling machines (calenders) to form rubber sheeting, or to apply the rubber directly onto woven textile fabric, which can then be wound off onto a roll. During such manufacturing operations, fumes are often generated.

1.1.4 Component assembly and building

At this stage, solvents are frequently used, with the possibility of inhalation of solvent vapours or of direct effects of the solvent on the skin of the operator.

1.1.5 Curing or vulcanizing

Heat is applied to the product, usually by use of steam, in a curing mould, press, or autoclave. Operators working in the area are exposed both to heat from the presses and to fumes from the heated rubber products. Chemical reactions take place throughout the manufacturing process, and may give rise to new, more volatile chemicals.

1.1.6 Inspection and finishing

This involves the handling of cured rubber products, often while still hot. It usually involves direct and extensive skin-contact with the surface of the finished article (during inspection) and may also involve exposure to vulcanizing fumes. Grinding, trimming, repair, painting and cleaning may also entail exposure to rubber dust, fumes and solvents.

1.1.7 Storage and dispatch

Large quantities of stored rubber goods may release considerable amounts of toxic substances, either as vapours or as constituents of the 'bloom' on the surface of finished goods.

1.2 Chemicals used in the rubber-production process

A wide variety of natural or synthetic elastomers, fillers (e.g. carbon black, precipitated silica or silicates) and additives are used in compounding to create the necessary properties of the final rubber product. The actual chemicals used in this process have changed over time and vary extensively depending on the manufacturing sector (e.g. tyres, general rubber goods, re-treading), and on the specific plant.

Compounding ingredients are classified as vulcanising agents (e.g. elemental sulfur, sulfur donors such as organic disulphides and higher sulphides, peroxides, urethane cross-linking agents); vulcanization accelerators (e.g. sulphenamides, thiazoles, guanidines, thiurams, dithiocarbamates, dithiophosphates, and miscellaneous accelerators such as zinc isopropyl xanthate and ethylene thiourea); vulcanization activators (e.g. zinc oxide, magnesium oxide, lead oxide); retarders and inhibitors of vulcanization (e.g. benzoic acid, salicylic acid, phthalic anhydride, *N*-nitrosodiphenylamine (NDPA), *N*-(cyclohexylthio)phthalimide); antidegradants; antioxidants (e.g. phenolics, phosphites, thioesters, amines, bound antioxidants such as quinone-diimines, miscellaneous antioxidants such as zinc and nickel salts of dithiocarbamates); antiozonants (e.g. *para*-phenylenediamines, triazine derivatives, waxes); anti-reversion agents (e.g. zinc carboxylates, thiophosphoryl derivatives, silane coupling agents, sulphenimide accelerator, hexamethylene-1,6-bis thiosulphate disodium dehydrate, and 1,3-bis(citranimidomethyl) benzene); plasticisers and softeners (e.g. petroleum products such as petroleum waxes and mineral oils, coal-tar products such as coumarone resin, pine products, synthetic softeners, and other products such as vegetable oils and fats); and miscellaneous ingredients (such as peptising agents, blowing agents, bonding agents, and pigments) (Datta & Ingham, 2001).

1.3 Human exposure

Workers in the rubber-manufacturing industry are exposed to dusts and fumes from the rubber-making and vulcanization processes. Potential exposures include *N*-nitrosamines, polycyclic aromatic hydrocarbons, solvents, and phthalates. Inhalation is the main route of exposure, although workers may have dermal exposure as well (e.g. to cyclohexane-soluble compounds). Details on historical occupational exposures in the rubber-manufacturing industry can be found in the previous *IARC Monograph* (IARC, 1982).

Data from studies published since the previous evaluation (IARC, 1982) are summarized below. These are mainly from Europe and North America. Hardly any current exposure data from Asia, where production of rubber goods has increased considerably during the last two decades, was available to the Working Group.

Several industry-wide surveys have been carried out in the United Kingdom (Dost *et al.*, 2000) and in the Netherlands (Kromhout *et al.*, 1994; Vermeulen *et al.*, 2000). In these studies, inhalable dust concentrations, curing-fume concentrations and solvents were measured. A recent European Concerted Action created a large exposure database for the rubber-manufacturing industry in five countries (the United Kingdom, Germany, the Netherlands, Poland, and Sweden). The Improved Exposure Assessment for Prospective Cohort Studies and Exposure Control in the Rubber-Manufacturing Industry (EXASRUB) database contains results of 59609 measurements collected from 523 surveys in 333 factories between 1956 and 2003. The database consists primarily of measurements of *N*-nitrosamines ($n = 21202$), rubber dust ($n = 13655$), solvents ($n = 8615$) and rubber fumes ($n = 5932$) (de Vocht *et al.*, 2005). The long timespan and the presence of longitudinal data from several countries provide insight into long-term temporal trends in exposure concentrations in the rubber-manufacturing industry.

1.3.1 Dust from rubber processing

An industry-wide survey in the Netherlands in 1998 showed geometric mean concentrations of inhalable dust that varied from 0.8 to 1.9 mg/m^3 and from 0.2 to 2.0 mg/m^3 when analysed by plant and by department, respectively. Actual inhalable dust concentrations depended to a large extent on specific conditions within the departments of the 10 plants involved in the study (Kromhout *et al.*, 1994). Comparison of the exposure levels nine years later revealed a reduction rate of 5.7% per annum for exposure to inhalable particulate matter. On average, median inhalable dust concentrations went down from 1.00 mg/m^3 to 0.59 mg/m^3 between 1988 and 1997. The steepest decline was observed in companies and departments with the highest exposure levels in 1988 and in workers with long employment. However, the highest concentrations were still seen in the compounding and mixing departments (Vermeulen *et al.*, 2000).

Dost *et al.* (2000) reported on exposure data collected in an industry-wide inventory in the United Kingdom during 1995–97 from 29 re-treading plants, 52 producers of general rubber goods, and seven producers of new tyres. The results show similar patterns at somewhat elevated levels.

These findings were confirmed in an analysis of dust-exposure data (13380 inhalable and 816 respirable dust measurements collected between 1969 and 2003) in the EXASRUB database. Geometric mean inhalable dust concentrations changed by −4% (range −5.8 to +2.9%) per year. Significant reductions were found in all five participating countries for 'handling of crude materials and mixing and milling' (–7% to –4% per year) and for 'miscellaneous workers' (–11% to –5% per year). Average geometric mean personal exposure levels ranged from 0.72 mg/m^3 in the Netherlands to 1.97 mg/m^3 in Germany. Up to 4–5-fold differences were observed between the countries in the early eighties, but these

differences diminished considerably in the two decades afterwards. In most countries, personal measurements appeared to be on average 2–4 times higher than stationary measurements (de Vocht *et al.*, 2008).

1.3.2 Fumes from rubber curing

Heating and curing of rubber compounds generates a visible fume. This fume has a complex chemical composition, which makes detailed analysis rather difficult. The cyclohexane-soluble fraction (CSF) of total particulate matter has been used as an indicator of fume contamination in the areas in which the samples were taken. Such monitoring studies are reviewed below.

In the 1988 Dutch industry-wide survey, Kromhout *et al.* (1994) reported a geometric mean CSF concentration of 0.39 mg/m^3 (n = 163) in the curing departments of 10 factories. Considerable variation was seen between the companies, with a range of geometric mean concentrations of 0.21–1.16 mg/m^3.

Median exposures reported for the United Kingdom industry-wide study were highest in the general rubber goods companies at 0.40 mg/m^3, intermediate for re-treading plants at 0.32 mg/m^3 and lowest for manufacturers of new tyres at 0.22 mg/m^3. Process-specific CSF concentrations in rubber goods production were as follows: 0.40 mg/m^3 in moulding, 0.33 mg/m^3 in extrusion, 0.18 mg/m^3 in milling. For re-treading, levels were 0.32 mg/m^3 for pressing, 0.19 mg/m^3 for extruding and 0.10 mg/m^3 for autoclaving (Dost *et al.*, 2000).

Analysis of 5657 CSF measurements in the EXASRUB database collected between 1977 and 2003 showed an annual decrease in concentration of 3% (range –8.6% to 0%). Steepest declines were seen in curing (–8.6% per year) and maintenance and engineering departments (–5.4% per year) (de Vocht *et al.*, 2008).

1.3.3 N-nitrosamines

Nitrosamines in the rubber-manufacturing industry are formed in the vulcanising process, with its extensive use of chemicals such as tetramethyl thiuram disulfide, zinc-diethyldithiocarbamate and morpholinomercaptobenzothiazole.

Exposures to volatile nitrosamines were measured at 24 French rubber-manufacturing plants from 1992 to 1995. A total of 709 exposure measurements (109 in the personal breathing zone, and 600 area samples) were collected. The following five different nitrosamines were identified: *N*-nitrosodimethylamine (NDMA), *N*-nitrosodiethylamine (NDEA), *N*-nitrosodibutylamine, *N*-nitrosopiperidine, and *N*-nitrosomorpholine (NMor). Eighty samples, in which the concentrations were either zero or not quantifiable were excluded. NDMA was the most frequently encountered nitrosamine (detected in 98% of the remaining 629 samples) and represented the most important fraction of the total nitrosamine concentration. For all nitrosamines present, 141 of the concentrations measured exceeded 2.5 µg/m^3. The salt-bath curing process generated particularly high nitrosamine levels, with 90% of the 96 measurements showing concentrations higher than 2.5 µg/m^3, many values even exceeding 20 µg/m^3 (Oury *et al.*, 1997).

Time trends of personal exposure to NDMA and to NMor over two decades (1980–2000) in the German rubber-manufacturing industry were analysed and compared with exposures observed in the Netherlands, Poland, Sweden, and the United Kingdom over the same time period. A total of 2319 NDMA and 2316 NMor measurements contained in the EXASRUB database were analysed. Results from Germany accounted for 88% and 85% of the data for these two amines, respectively. For both NDMA and NMor, the average geometric mean concentration in Germany was 0.13 µg/m^3. Geometric mean concentrations of NDMA ranged from

0.05 μg/m^3 in the Netherlands to 0.34 μg/m^3 in Sweden, while those of NMor ranged from 0.03 μg/m^3 in the United Kingdom to 0.17 μg/m^3 in Poland and Sweden. Exposure to NDMA and NMor decreased on average 2–5-fold in the German rubber-manufacturing industry over this time period, mainly due to the introduction of modern curing systems. Comparable levels were observed in the other European countries (de Vocht *et al.*, 2007).

In a study from Italy, personal exposures to nine airborne *N*-nitrosamines (NDMA, NDEA, *N*-nitrosodi-*n*-propylamine, *N*-nitrosodiisopropylamine, *N*-nitrosodi-n-butylamine, N-nitrosopiperidine, N-nitrosopyrrolidine, and NMor) were measured in 34 workers from four Italian factories that manufactured rubber drive belts for automobile engines. Airborne levels were very low and, in most cases, below the limit of detection of 0.06 μg/m3 (Iavicoli & Carelli, 2006)

Personal exposures to six nitrosamines (NDMA, NDEA, *N*-nitrosodi-*n*-butylamine, *N*-nitrosomorpholine, *N*-nitrosopiperidine, and *N*-nitrosopyrrolidine) were measured in the rubber-manufacturing industry in Sweden (Jönsson *et al.*, 2009). The exposures ranged from less than the limit of detection to 36 μg/m^3, and differed with the vulcanization method used. Workers involved in salt-bath vulcanization had the highest level of exposure (median, 4.2 μg/m^3).

Although average levels of *N*-nitrosamines are nowadays well below the current exposure limits, exposure to these chemicals has not been eliminated and incidental high exposures do still occur.

1.3.4 PAHs

In a 1997 cross-sectional study of 116 Dutch male workers in the rubber-manufacturing industry, Peters *et al.* (2008) collected urine samples on weekdays and on Sundays, and determined the concentration of 1-hydroxypyrene. The concentrations were significantly higher in workweek samples compared with those collected on Sunday. However, this increase was not uniform across tasks and only reached statistical significance for the curing department ($P = 0.003$).

1.3.5 Solvents

Kromhout *et al.* (1994) measured exposures to solvents in 10 rubber-manufacturing plants in the Netherlands in the late 1980s. The extent of use of individual solvents varied widely and total solvent concentrations were reported. The quantitative assessment of exposure to solvents was restricted to paraffins (hexane, heptane and octane); aromatic compounds (toluene, xylene, trimethylbenzene, naphthalene and isopropylbenzene); chlorinated hydrocarbons (trichloroethylene and 1,1,1-trichloroethane); ketones, alcohols and esters (methylisobutylketone, 2-ethoxyethanol and isobutylacetate). These were chosen on the basis of information on solvents, cements, and release and bonding agents used in the 10 plants. The geometric mean concentration by plant varied from 0.5–46.9 mg/m^3 and ranged from 0.4–34.6 mg/m^3 by department, with the highest exposures reported in the pretreating departments.

1.3.6 Phthalates

Two studies reported on exposure to phthalates, which are used as plasticizers in the rubber-manufacturing industry. A total of 386 spot-urine samples were collected from 101 Dutch workers employed in nine different factories, and analysed for the presence of phthalic acid and 2-thiothiazolidine-4-carboxylic acid. Samples were collected on Sunday and during the workweek on Tuesday, Wednesday, and Thursday. Geometric mean concentrations of phthalic acid showed a significant 2-fold increase (paired *t*-test; $P < 0.05$) during the workweek compared with the concentrations measured on Sunday

(GM, 83 µg/l), with absolute increases of approximately 70 µg/l. The concentrations did not differ markedly between Tuesday, Wednesday and Thursday (GM, 148 µg/l, 152 µg/l and 164 µg/l, respectively). Increases seemed to be restricted to specific factories and/or departments (e.g. moulding and curing) (Vermeulen *et al.*, 2005).

In a pilot biomonitoring study in several industries, Hines *et al.* (2009) reported that workers from a rubber boot manufacturing plant had 3-fold higher geometric mean concentrations of diethylhexyl-phthalate metabolites in post-shift urine than the concentrations measured in the general population.

1.3.7 Dermal exposure

Kromhout *et al.* (1994) and Vermeulen *et al.* (2000) reported on dermal exposures to cyclohexane soluble compounds in the rubber-manufacturing industry in the Netherlands. Dermal CSF levels decreased in a similar pattern as inhalation exposures over a 9-year period (1988–1997).

2. Cancer in Humans

The literature reviewed in previous *IARC Monographs* (IARC, 1982, 1987) provided *sufficient evidence* of a causal association between exposures in the rubber-manufacturing industry and cancer. The recent Working Group decided to review evidence from individual studies that appeared after the earlier evaluation (IARC, 1982) making use of a systematic review by Kogevinas *et al.* (1998). Evidence from meta-analyses published by Stewart *et al.* (1999), Borak *et al.* (2005) and Alder *et al.* (2006) was not considered since these studies combined a variety of exposure circumstances that would tend to dilute any observed effect. The Working Group realized that the complexity of occupational exposure in the rubber-manufacturing industry had so far precluded a clear conclusion about an association between increased cancer mortality and incidence and exposure to particular chemicals (except historically well known associations between 2-naphthylamine and bladder cancer, and benzene and leukaemia). Future studies in the rubber-manufacturing industry may overcome this problem by making use more systematically of the wealth of exposure data available in the industry (de Vocht *et al.*, 2005, 2009).

2.1 Cancer of the bladder

In the previous *IARC Monograph* (IARC, 1982) it was concluded that there was *sufficient evidence* of an excess occurrence of urinary bladder cancer in workers in the rubber-manufacturing industry. The first evidence appeared when a substantial excess of bladder cancer was noted among workers in this industry in the United Kingdom (Case *et al.*, 1954).

2.1.1 Cohort studies

Among workers in the British rubber-manufacturing industry, the death rate from bladder cancer during 1936–1951 was almost twice that of the general population (Case & Hosker, 1954). Studies in other countries also showed an excess of bladder cancer in workers in this industry, but these studies were based on small numbers.

Kogevinas *et al.* (1998) conducted a systematic review of epidemiological studies on cancer in the rubber-manufacturing industry. This review included cohort and case–control studies published after the previous evaluation (IARC, 1982), which were conducted in facilities that manufactured and repaired tyres, manufactured cables and other rubber goods. The authors found that moderately increased risks for bladder cancer were reported in 6 of 8 cohort studies of workers employed in the rubber-manufacturing industry in different regions of the world. In four studies that reported results by calendar period, the risk was highest among workers employed before 1950 (Delzell & Monson, 1984a,

b, 1985a, b; Gustavsson *et al.*, 1986; Negri *et al.*, 1989; Szeszenia-Dabrowska *et al.*, 1991). One of these studies reported potential co-exposure to 2-naphthylamine (Szeszenia-Dabrowska *et al.*, 1991).

Two cohort studies of Polish workers published before 1998 were updated and an excess mortality risk for bladder cancer was reported (see Table 2.1, available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-31-Table2.1.pdf). In the most recent follow-up of a cohort of Polish workers involved in the manufacture of rubber footwear, non-statistically significant increased risks for bladder cancer were found among men and women (Szymczak *et al.*, 2003). In a cohort study among workers in rubber-tyre manufacture in Poland (Wilczyńska *et al.*, 2001), no increased risk for bladder cancer was observed among all workers, but analysis of a subcohort of men involved in mixing and weighing of raw materials, milling, extruding and calendaring, showed a non-significantly increased risk. A job-exposure matrix (JEM) for occupational exposure to aromatic amines was used in the analysis of this cohort (de Vocht *et al.*, 2009). This JEM was set-up with data from EXASRUB, which provided estimates of geometric mean concentrations for airborne chemicals in each department in the factory during the study period. Internal analyses showed an increased risk in the highest two quartiles of exposure to aromatic amines.

2.1.2 Synthesis

Studies in the rubber-manufacturing industry with documented exposure to 2-naphthylamine clearly show an increased risk of cancer of the urinary bladder. More recent studies that included workers with no recorded exposure to 2-naphthylamine identified moderately increased risks for bladder cancer. [The Working Group could not rule out that the increased risks in recent studies were attributable to exposure to 2-naphthylamine, or whether other exposures in this industry contributed to this risk.]

2.2 Leukaemia

It was concluded in the previous *IARC Monograph* (IARC, 1982) that there was *sufficient evidence* of an excess occurrence of leukaemia in workers in the rubber-manufacturing industry.

2.2.1 Cohort studies

Kogevinas *et al.* (1998) noted four cohort studies that found moderately increased risks for leukaemia among workers in the rubber-manufacturing industry in the USA (Norseth *et al.*, 1983; Delzell & Monson, 1984a, b, in two departments of a rubber plant in Akron, Ohio), in Italy (Bernardinelli *et al.*, 1987), and in Germany (Weiland *et al.*, 1996), while four studies did not report an excess risk (Gustavsson *et al.*, 1986; Negri *et al.*, 1989; Sorahan *et al.*, 1989; Carlo *et al.*, 1993). The magnitude of the risk varied between studies, with the highest risks found in studies conducted in North America. The results supported the conclusion that the excess risk for leukaemia was attributable to exposure to solvents, particularly benzene. The authors indicated that a variety of solvent mixtures, with or without benzene, had been used in rubber cements, glues, binding agents, and release agents.

Cohort studies on leukaemia that were published since the review paper mentioned above (Kogevinas *et al.* (1998) are summarized in Table 2.2 (available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-31-Table2.2.pdf). Straif *et al.* (1998) reported an excess risk for leukaemia in a cohort of male workers employed in one of five large plants in Germany that produced tyres or general rubber goods (SMR, 1.5; 95%CI: 1.0–2.1). An increased risk was observed in work area I (Preparation of Materials) where solutions were made up,

and in work area II (Technical Rubber Goods). Non-significant excesses were also seen in other areas. Longer duration of employment was associated with increased incidence of leukaemia in work area I, particularly among those workers with 10 or more years of employment (SMR, 3.0; 95%CI: 1.5–5.6).

Li & Yu (2002a) conducted a nested case–control study (7 cases of leukaemia, 28 controls) in a rubber-manufacturing facility, and reported an excess risk for leukaemia in workers of the inner-tube department, but not in other departments of the plant. The odds ratio for leukaemia was 7.81 (95%CI: 0.8–78.8) for one or more years of work in the inner-tube department.

2.2.2 Case–control study

McLean *et al.* (2009) conducted a population-based case–control study in New Zealand, with 225 cases of leukaemia and 471 controls. Full occupational histories were obtained by interview. Among those reporting working as rubber/plastics machine-operators (9 cases, 4 controls), the age-, sex- and smoking-adjusted risk estimate was 3.8 (95%CI: 1.1–13.1). The strongest findings, nonetheless, were for plastics rather than for the rubber-manufacturing industry.

2.2.3 Synthesis

The Working Group concluded that there was an increased risk for leukaemia among workers in the rubber-manufacturing industry. The excess risks may be associated with exposure to solvents, in particular benzene.

2.3 Malignant lymphoma including multiple myeloma and other lymphopoietic cancers

It was concluded in the previous review (IARC, 1982) that there was *limited evidence* of an excess occurrence of lymphoma among rubber-manufacturing workers. Excess occurrence of lymphoma had been noted in workers exposed to solvents in departments like footwear production and tyre manufacture (Veys, 1982).

2.3.1 Cohort studies

Kogevinas *et al.* (1998) reported excess risks for malignant lymphoma, including multiple myeloma, ranging from 1.7 to 3.6 in three cohort studies in the USA (Norseth *et al.*, 1983; Delzell & Monson, 1984a, b, in a rubber plant in Akron, Ohio) and Italy (Bernardinelli *et al.*, 1987), while there was no excess risk in two other cohort studies, in Italy and the United Kingdom (Negri *et al.*, 1989; Sorahan *et al.*, 1989). Delzell & Monson (1984b, 1985b) reported excess risks for multiple myeloma in certain departments of a rubber plant in Akron, Ohio, as did Gustavsson *et al.* (1986) in Sweden.

Cohort studies published since 1998 are included in Table 2.2, on-line. In Germany, Mundt *et al.* (1999) observed an increased risk for lymphatic system cancers among women employed in one of five large plants that produced tyres or general rubber goods. All cases were seen among women hired after 1950. In the United Kingdom, an increased mortality risk for multiple myeloma was found among men and women in 41 British rubber factories that manufactured tyres and general rubber goods (Dost *et al.*, 2007). Women also had increased multiple-myeloma incidence (SRR, 8.1; 95%CI: 1.7–23.7). Excess mortality was observed among workers in the general rubber sector (seven deaths observed, one expected).

Wilczyńska *et al.* (2001). did not find an overall increase in mortality risk for cancers of lymphatic and haematopoietic tissues in a rubber-tyre plant in Poland.

2.3.2 Synthesis

The Working Group concluded that there is *sufficient evidence* of excess malignant lymphoma among workers in the rubber-manufacturing industry.

2.4 Cancer of the lung

In the previous *IARC Monograph* (IARC, 1982) it was concluded that there was suggestive evidence of an excess incidence of lung cancer among rubber-manufacturing workers, but that the evidence for a causal association with occupational exposures was *limited*.

2.4.1 Cohort studies

Kogevinas *et al.* (1998) noted that the more recently reviewed studies tended to confirm a moderate excess risk for lung cancer. Positive findings were reported in five cohort studies (Delzell & Monson, 1985a, in the curing department; Gustavsson *et al.*, 1986; Zhang *et al.*, 1989; Szeszenia-Dabrowska *et al.*, 1991; Solionova & Smulevich, 1993). These risks were found among workers in tyre-curing departments, mixing and milling, in vulcanization workers, and in a study on jobs with high exposure to fumes or solvents. In three studies excess risks up to 1.5 were reported (Delzell & Monson, 1984b, in the aerospace-product department; Sorahan *et al.*, 1989; Weiland *et al.*, 1996), while in five cohort studies excess risks were not found (Norseth *et al.*, 1983; Delzell & Monson, 1984a, 1985b, in industrial-products and reclaim departments; Bernardinelli *et al.*, 1987; Negri *et al.*, 1989; Carlo *et al.*, 1993).

Cohort studies on lung cancer published after the above-mentioned review (Kogevinas *et al.*, 1998) are listed in Table 2.3 (available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-31-Table2.3.pdf). In most studies moderate but consistent increases in risk for lung cancer were found; two studies reported no increase in risk (Dost *et al.*, 2007; deVocht *et al.*, 2009).

From a study of a cohort of German women employed in rubber-manufacturing plants, Mundt *et al.* (1999) reported an increased risk for lung cancer mortality. Stronger associations were observed for certain periods of employment. Among a cohort of German men, a significantly increased risk for lung cancer mortality was observed (Straif *et al.*, 2000a). Using internal comparisons, the authors showed increased risks among those employed during one year or more in work areas that involved preparation of materials, technical rubber goods and tyre production (Straif *et al.*, 1999). Through retrospective, semiquantitative estimates of exposures to nitrosamines, asbestos and talc, an increased risk for lung cancer in association with high exposure levels for asbestos was observed. An exposure characterization in which categories of medium and high exposure levels of talc were combined with medium exposure to asbestos revealed an exposure-response relationship with lung-cancer incidence (Straif *et al.*, 2000a).

Szymczak *et al.* (2003) reported excess lung-cancer mortality among men and women employed in a rubber-footwear plant in Poland. There were increased risks by duration of employment, but no trend was observed. A population-based cohort study of non-smoking women in China also showed an increased risk for lung cancer, after controlling for exposure to second-hand smoke, education level and family history of lung cancer (Pronk *et al.*, 2009).

2.4.2 Case–control studies

The findings of population-based case–control studies are listed in Table 2.4 (available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-31-Table2.4.pdf). Most notably, in two large multicentre studies of non-smokers, increased risks for lung cancer were found among

women who reported having been employed in the rubber-manufacturing industry (Pohlabeln *et al.*, 2000; Zeka *et al.*, 2006).

2.4.3 Synthesis

Overall, the cohort studies suggest an increased lung-cancer risk among workers in the rubber-maufacturing industry. This conclusion is supported by the findings of population-based case–control studies. The Working Group concluded that there is evidence of excess lung cancer among workers in the rubber-manufacturing industry.

2.5 Cancer of the larynx

In a previous *IARC Monograph* (IARC, 1987) it was indicated that cancer of the larynx had been reported as occurring in excess in workers in the rubber-manufacturing industry, but this excess was not consistent.

2.5.1 Cohort studies

In his review, Kogevinas *et al.* (1998) reported a small but consistent excess risk for laryngeal cancer in seven cohorts, but indicated that the available evidence did not permit an evaluation to be made of the specific agents that may be associated with the increased risk for this cancer.

Straif *et al.* (2000a) found increased mortality from laryngeal cancer among workers in the German rubber-manufacturing industry (see Table 2.3, on-line). The authors indicated that the excess risk may be associated with employment in weighing and mixing and with exposure to asbestos, talc or carbon black. Dost *et al.* (2007) did not find an increased risk for laryngeal cancer mortality and incidence among workers in the British rubber-manufacturing industry. De Vocht *et al.* (2009) did not find increased mortality from laryngeal cancer in a plant that manufactured rubber tyres. They also did not find an association with exposure to aromatic amines or inhalable aerosol.

2.5.2 Synthesis

The Working Group concluded that there was inconsistent evidence of excess laryngeal cancer among workers in the rubber-manufacturing industry. [Tobacco smoking is a risk factor for laryngeal cancer, yet in many studies no adjustment for smoking status was made.]

2.6 Cancer of the stomach

In the previous *IARC Monograph* (IARC, 1982) it was concluded that there was *sufficient evidence* of an excess of stomach cancer among workers in the rubber-manufacturing industry, and limited evidence of a causal association with occupational exposures.

2.6.1 Cohort studies

The conclusions of the previous Working Group (IARC, 1982) were supported by cohort studies of male workers in specific rubber factories. A study in a rubber plant in Akron, Ohio (USA) showed an excess of stomach cancer primarily among workers involved in jobs early in the production line, where exposures are mainly to particulate matter, but also to some fume from uncured rubber (Delzell & Monson, 1982). A case–control analysis of stomach cancer among male workers in the same plant showed a positive association with work early in the production line and with jobs in curing and maintenance (McMichael *et al.*, 1976). Further analysis, according to estimated exposure to specific agents, showed a positive association with exposure to talc (Blum *et al.*, 1979). In one study in the United Kingdom, mortality from stomach cancer was increased among all workers, but particularly among men in jobs early in the production process (Parkes *et al.*, 1982). In a second study in the United Kingdom,

excess mortality from stomach cancer was also observed among all workers, but not among particular occupations (Baxter & Werner, 1980).

Kogevinas *et al.* (1998) reported low excess risks for stomach cancer in seven cohort studies. The risk was elevated mainly in mixing and milling departments in two studies (Wang *et al.*, 1984; Gustavsson *et al.*, 1986) and in jobs with high exposure to dust in a third study (Sorahan *et al.*, 1989). Kogevinas *et al.* (1998) indicated that cohort studies published after 1982 either did not confirm the presence of an excess risk or suggested the presence of only a slightly elevated risk.

Cohort studies on stomach cancer published since the above-mentioned review are listed in Table 2.5 (available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-31-Table2.5.pdf). In case–cohort study in China of workers in a rubber-manufacturing plant, Li & Yu (2002b) reported an increased risk for stomach cancer. Increased risks were also reported by duration of work in inner tyre-tube manufacturing and milling departments. Mundt *et al.* (1999) found excess risks for stomach cancer among German women employed in the rubber-manufacturing industry, which was stronger among workers hired after 1960.

Straif *et al.* (2000a) reported a moderately increased risk for stomach cancer among male workers in the German rubber-manufacturing industry. An exposure-effect association with talc was observed, but no association with nitrosamines. Data appeared to indicate an association with carbon black, but after adjustment for talc- and asbestos-containing dusts, the risk estimate was lower and no longer significant.

On the basis of internal comparisons, Neves *et al.* (2006) found an increasing risk for stomach cancer among workers in the rubber-manufacturing industry employed in small companies in comparison with workers at large companies, with 10-year lagging and control for confounding (RR, 3.47; 95%CI: 2.57–4.67). Company size was used as a surrogate of probability of exposure to carcinogenic substances. De Vocht *et al.* (2009) found a moderate excess risk for stomach cancer, particularly among workers in the maintenance department of a tyre-manufacturing plant, while Dost *et al.* (2007) showed a modest excess of stomach-cancer incidence among male workers in a study of British rubber plants.

2.6.2 Synthesis

The Working Group concluded that there was evidence of an excess of stomach cancer among rubber-manufacturing workers.

2.7 Cancer of the oesophagus

The previous *IARC Monograph* (IARC, 1982) determined that there was *inadequate evidence* for excess occurrence of cancer of the oesophagus among workers in the rubber-manufacturing industry.

2.7.1 Cohort studies

Kogevinas *et al.* (1998) reported an increased risk for oesophageal cancer in four cohorts (Delzell & Monson, 1985b, in reclaim-department workers; Sorahan *et al.*, 1989; Szeszenia-Dabrowska *et al.*, 1991, Weiland *et al.*, 1996). Other cohorts studies showed no effect.

Straif *et al.* (2000b) reported a significantly increasing trend for oesophageal cancer with increasing exposure to nitrosamines (see Table 2.5, on-line). Tests for trend and associations were also significant for cancers of the lip and oral cavity. In Poland, Szymczak *et al.* (2003) reported a significant excess risk among rubber-footwear workers.

2.7.2 Synthesis

The Working Group concluded that there was some evidence for an excess risk for cancer of the oesophagus among workers in the

rubber-manufacturing industry. [The Working Group noted that in none of the studies adjustments were made for tobacco or alcohol use.]

2.8 Cancer of the prostate

The previous *IARC Monograph* (IARC, 1982) concluded that the evidence of excess risk for prostate cancer was *limited* and that the evidence for a causal association with occupational exposures was inadequate.

2.8.1 Cohort studies

Kogevinas *et al.* (1998) reported excess risks for prostate cancer in five studies (Norseth *et al.*, 1983; Delzell & Monson 1984a, in the industrial-products department; Bernardinelli *et al.*, 1987; Solionova & Smulevich, 1993; Weiland *et al.*, 1996). Other studies did not report any excess (Delzell & Monson, 1984b, 1985b; in the aerospace-products and re-claim departments; Gustavsson *et al.*, 1986; Sorahan *et al.*, 1989; Szeszenia-Dabrowska *et al.*, 1991).

Since then, only one case–cohort study that investigated the association between prostate cancer and work in the rubber-manufacturing industry has been published (Zeegers *et al.*, 2004). In this study a non-statistically significant increased risk for prostate cancer was found.

2.8.2 Synthesis

The Working Group concluded that there is weak evidence of excess risk for prostate cancer among workers in the rubber-manufacturing industry.

2.9 Other cancers

The previous *IARC Monograph* (IARC, 1982) determined that for cancers of the brain, thyroid and pancreas, the evidence was *inadequate* for an excess in occurrence of these cancers and for a causal association with occupational exposures.

2.9.1 Cohort studies

Kogevinas *et al.* (1998) reported that findings for other cancer sites were not consistent between studies, or were derived from too few studies. Since this review, studies on workers in the rubber-manufacturing industry with excess cancers of the brain, pancreas, gallbladder, cervix and liver have been reported (see Table 2.6 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-31-Table2.6.pdf).

2.9.2 Synthesis

The Working Group concluded that there is little evidence of excess risks for cancers at sites other than those mentioned above, being associated with work in the rubber-manufacturing industry. [Excess risks found in single studies may be related to specific exposure circumstances occurring in particular rubber-manufacturing plants. One problem in evaluating findings for other cancer sites is that reporting may have been incomplete in cohort and case–control studies, with possibly preferential reporting of positive findings.]

3. Cancer in Experimental Animals

No data were available to the Working Group.

4. Other Relevant Data

The rubber-manufacturing industry has used and still uses a wide variety of substances that belong to many different chemical categories, e.g. carbon black, aromatic amines, PAH, *N*-nitrosamines, mineral oils, other volatile organic compounds from curing fumes, trace amounts of monomers from synthetic rubber like 1,3-butadiene, acetonitrile, styrene, vinyl chloride, ethylene oxide, etc. (See Section 1). For this reason, it has been difficult to relate the observed

Table 4.1 Biomonitoring studies and cytogenetic assays among workers in the rubber-manufacturing industry

Reference	Description of exposed and controls	Exposure levels	Cytogenetic/genotoxic end-point	Response in exposed	Response in controls	Comments
Degrassi *et al.* (1984) Italy	Exposed: Vulcanizers (n = 34) in a rubber plant Controls: Workers (n = 16) in the same plant and living in the same geographic area	Airborne particulate matter ranged from 0.5 to 3.4, with an average (± SD) of 1.1 (± 1.1) mg/m^3. Exposure duration (± SE) was 8.2 ± 0.8 yr	Chromosomal aberrations (per 100 cells) SCE (per cell)	1.9 ± 1.4 (excl. gaps) 5.2 ± 1.3	2.1 ± 1.5 (excl gaps) 5.2 ± 0.7	NS Cigarette smoking was associated with increased SCE in exposed and controls. Chromosomal aberrations were not correlated
Hema Prasad *et al.* (1986) India	Exposed: Workers (n = 35) employed for 3–12 yr in a rubber factory. There were 20 unexposed controls (not specified)	NR	Chromosomal aberrations (per 100 cells)	Ranged from 1.57 to 2.75, increased with longer time at work	0.6 per 100 cells	$P < 0.05$ No information is given about smoking.
Sasiadek (1992) Poland	Exposed: Vulcanizers (14 women, 7 men; 14 were smokers) in a rubber plant. Controls: Non-exposed women (n = 7) and men (n = 7), of whom 5 were smokers	Exposure duration was 14.2 ± 9.7 yr (range 2–35 yr)	Chromosomal aberrations (per 100 cells) SCE (per cell)	2.2 ± 1.06 (incl. gaps) 16.1 ± 3.5	0.9 ± 1.0 (incl. gaps) 10.0 ± 1.5	$P < 0.01$ $P < 0.001$
Sasiadek (1993) Poland	Exposed: Vulcanizers (19 women, 7 men; 10 were smokers) in a rubber plant. Controls: Non-exposed women (n = 15) and men (n = 10), of whom 10 were smokers	Exposure duration was 0.5–30 yr (mean 15.6 ± 9.5 yr).	SCE (per cell)	13.2 ± 2.9 (range 9–20)	9.8 ± 1.8 (range 7–14)	$P < 0.001$

Table 4.1 (continued)

Reference	Description of exposed and controls	Exposure levels	Cytogenetic/genotoxic end-point	Response in exposed	Response in controls	Comments
Ward *et al.* (1996) USA	Workers in a butadiene-production plant (10 high-exposed, 10 low-exposed) in Texas, USA. Non-exposed controls from elsewhere (n = 9). All 29 were non-smokers. Second study: follow-up after 8 mo. Ongoing study among workers in a styrene-butadiene rubber plant in the same area. Data are presented on 16 high-exposed (5 smokers) and 9 low-exposed (3 smokers) subjects	Exposure survey by the company: mean level 3.5 ± 7.25 ppm From 8-h personal breathing zone air samples: 0.30 ± 0.59, 0.21 ± 0.21, and 0.12 ± 0.27 ppm for high-, intermediate- and low-exposure areas Passive dosimeters worn during the 8-h shift: of 40 samples, 20 were > 0.25 ppm, 11 were > 1 ppm	a) *HPRT* mutants, lymphocytes b) butadiene metabolite in urine (see comments)	3.99 ± 2.81 (high) and 1.20 ± 0.51 (low) *HPRT* mutants/10^{-6} cells 5.33 ± 3.76* (high) 2.27 ± 0.99 (medium), 2.14 ± 0.97 (low) mutants/10^{-6} cells *Non-smokers:* 7.47 ± 5.69 (high)** 1.68 ± 0.85 (low) *Smokers:* 6.24 ± 4.37 (high)** 3.42 ± 1.57 (low)	1.03 ± 0.12 *HPRT* mutants per 10^{-6} cells	$P < 0.02$ *$P < 0.02$ ** $P < 0.01$ *Comment:* dihydroxybutane mercapturate, 1,2-dihydroxy-4(*N*-acetyl-cysteinyl) butane, was measured in urine by GC/MS. The high-exposure groups (butadiene-monomer plant only) had significantly higher levels.
Moretti *et al.* (1996) Italy	Workers at 4 rubber plants (n = 19; 9 smokers) and 20 age-matched (± 5 yr) blood donors as controls (8 of whom were smokers)	NR	a) mutagenicity in urine b) urinary excretion of thioethers	a), b): no differences between exposed and controls		
			c) DNA damage in lymphocytes	median migration distance in Comet assay: 37.99 µm	median migration distance: 33.81 µm	$P > 0.05$
			d) SCE	5.51 ± 0.82 / metaphase	6.06 ± 1.15	$P > 0.05$
			e) MN formation	22.84 ± 15.82 MN per 1000 binucleated cells	13.74 ± 4.42	$P < 0.05$

Table 4.1 (continued)

Reference	Description of exposed and controls	Exposure levels	Cytogenetic/genotoxic end-point	Response in exposed	Response in controls	Comments
Major *et al.* (1999) Hungary	Subjects (n = 29, among whom 24 were smokers; 23 men, 6 women) with mixed industrial exposure during 3–20 yr in the rubber-manufacturing industry. Controls were living and/or working in the vicinity of chemical plants, but had no occupational exposure to chemicals (industrial controls)	Exposures included aromatic solvents, dust, tar, lubricating oil. No quantitative data given		*Exposed*	*Industrial controls*	
			a) chromosomal aberrations per 2900 metaphases scored	3.38 ± 0.26	1.60 ± 0.62	$P < 0.01$
			b) PCD: - mitoses with ≤ 3 chromosomes	11.45 ± 1.43	1.57 ± 0.44	$P < 0.01$
			- mitoses with > 3 chromosomes	6.00 ± 1.18	0.32 ± 0.10	$P < 0.01$
			c) aneuploidy	5.64 ± 0.44	6.20 ± 0.43	NS
Somorovská *et al.* (1999) Slovak Republic	Workers (27 men, 2 women; 18 smokers, 11 non-smokers) in a rubber tyre factory. The industrial controls comprised 22 clerks (8 men, 14 women; 14 smokers, 8 non-smokers) from the same factory. A second control group comprised 17 men and 5 women (7 smokers, 15 non-smokers) who worked in a laboratory in Bratislava	Air sampling was followed by analysis of styrene, toluene, butadiene, PAHs, alkanes, and alkenes	a) DNA breakage (Comet assay) b) chromosomal aberrations c) MN assay	*Sample 1* (1996): 33% DNA in tail *Sample 2* (1997): 45% DNA in tail	*Factory controls:* 13% DNA in tail *Laboratory controls:* 22% DNA in tail	$P < 0.00001$
				1 aberration/100 cells	*Factory controls:* 0.4 aberr./100 cells *Laboratory controls:* 0.2 aberr./100 cells	$P < 0.00001$
				6.5 MN/2000 cells	*Factory controls:* 2.1 MN/2000 cells *Laboratory controls:* 1.5 MN/2000 cells	$P < 0.00001$

Table 4.1 (continued)

Reference	Description of exposed and controls	Exposure levels	Cytogenetic/genotoxic end-point	Response in exposed	Response in controls	Comments
Zhu *et al.* (2000) Guangzhou, China	Workers [197 men (130 smokers) and 174 women (6 smokers)] at a factory that produced tyres, pads and other products. Among these, 281 were in rubber-processing jobs, and 90 controls were in management. There were 318 drinkers and 53 non-drinkers	Environmental monitoring of dust, toluene, xylene, gasoline, H_2S, SO_2	DNA breakage (Comet assay; results given as tail moment)	*All rubber workers:* 1.77 (1.64–1.90)* μm *Finishing:* 1.81 (1.48–2.21) μm *Calendering:* 1.77 (1.54–2.03) μm *Vulcanizing:* 1.64 (1.46–1.83) μm *Mixing:* 2.54 (1.95–3.31)** μm	*Managerial workers:* 1.52 (1.36–1.71) μm	* $P = 0.04$ *Comment*: Non-drinking, non-smoking mixers also had higher tail moment than comparable managers: 2.25 (1.66–3.03) vs 1.39 (1.18–1.63) μm ($P = 0.049$) ** $P = 0.002$
Ma *et al.* (2000) Texas, USA	Male non-smoking workers at a styrene-butadiene polymer plant. Controls were employees at the University of Texas Medical Branch	Breathing-zone air sampling with personal monitors	Analysis of *HPRT* variants and mutants, and of exon deletions in the *HPRT* gene in lymphocytes, with a multiplex PCR assay	*HPRT* variants per 10^{-6} cells: 6.86 ± 3.25 ($n = 12$) *HPRT* mutants per 10^{-6} cells: 17.63 ± 5.05 ($n = 10$)	2.36 ± 1.04 ($n = 8$) 8.47 ± 2.88 ($n = 11$)	$P < 0.05$ $P < 0.05$
Ward *et al.* (2001) Texas, USA (study conducted in 1998)	Workers in a BD rubber plant: 22 in a high-exposure and 15 in a low-exposure group, with levels of 1.71 ± 0.54 (SE) and 0.07 ± 0.03 (SE) ppm butadiene, respectively	Exposure to 1,3-BD was monitored with organic vapour monitors and varied from 4.04 ± 3.45 ppm (tank farm) to 0.29 ± 0.33 (laboratory). Low areas* had 0.05 ± 0.06 ppm *packaging, baling, warehouse, shipping	*HPRT* mutant analysis in lymphocytes	*High-exposure group:* All ($n = 22$)–10.67 ± 1.51 (SE) Non-smokers ($n = 12$)–8.64 ± 1.60 Smokers ($n = 10$)–13.10 ± 2.57	*Low-exposure group:* All ($n = 15$)–3.54 ± 0.61 Non-smokers ($n = 14$)–3.46 ± 0.65 Smokers–4.61	$P = 0.001$ $P = 0.011$ *Comment*: increases in *HPRT* variant frequency of about threefold are seen at average BD exposure levels of 1–3 ppm

Table 4.1 (continued)

Reference	Description of exposed and controls	Exposure levels	Cytogenetic/genotoxic end-point	Response in exposed	Response in controls	Comments
Ammenheuser *et al.* (2001) Texas, USA	Workers (n = 24) in the reactor, recovery, tank farm and laboratory area of a BD rubber plant represented a high-exposure group. Workers (n = 25) in blending, coagulation, baling, shipping, the control room and utility areas were a low-exposure group	Workers were asked to wear an organic vapour monitor during one 8-h work-shift, to measure exposure to butadiene/styrene. Lower detection limit: 0.25 ppm BD	*HPRT* mutant analysis in lymphocytes	*High-exposure group:* Non-smokers (n = 19)– 6.8 ± 1.2* (SE) Smokers (n = 5)– 6.1 ± 2.0	*Low-exposure group:* Non-smokers (n = 20)– 1.8 ± 0.2 Smokers (n = 5)–3.3 ± 0.5	* $P < 0.0005$
Vermeulen *et al.* (2002) the Netherlands	Workers in the rubber-manufacturing industry (n = 52; all non-smokers)	Mutagenicity on likely skin-contact surfaces (high, ≥ 25 revertants/cm^2; low, < 25 rev/cm^2) and in ambient air (high, ≥ 210 rev/m^3 low, < 210 rev/m^3) tested in YG1041 of *S. typhimurium*	DNA-adduct analysis in exfoliated bladder cells collected from 24-h urine, by ^{32}P-postlabelling. Samples from 32 slow and 20 fast acetylators (based on *NAT2* analysis)	Of 52 urine samples, 46 gave reliable data for the presence of three main adducts: 1 in 41 samples, 2 in 13 samples, 3 in 29 samples	NR	The 'slow *NAT2*' subjects had lower levels of adducts 1–3 than the fast acetylators. ($P < 0.04$; $P = 0.32$; $P = 0.15$, resp) No information is given on the identity of the adducts
Laffon *et al.* (2006) Portugal	Exposed male workers (n = 32) and non-exposed male controls (n = 32) in a rubber tyre factory in Oporto, of whom 39% were smokers	NR	a) thio-ethers in post-shift urine	0.41 ± 0.05 mM	0.24 ± 0.02 mM	$P < 0.01$
			b) micronucleus test (MN per 1000 cells)	2.34 ± 0.33	1.84 ± 0.29	NS
			c) SCE/cell	4.35 ± 0.20	4.38 ± 0.17	NS
			d) DNA-breakage (Comet assay) (tail length, µm)	44.72 ± 0.66	48.25 ± 0.71	$P < 0.01$

Table 4.1 (continued)

Reference	Description of exposed and controls	Exposure levels	Cytogenetic/genotoxic end-point	Response in exposed	Response in controls	Comments
Peters *et al.* (2008) the Netherlands	Workers (n = 116; 45 smokers, 71 non-smokers) in the Dutch rubber-manufacturing industry, selected on the basis of their function in the production process. Urine and blood were collected	NR		*Weekday samples:*	*Sunday samples:*	
			a) Hydroxypyrene in urine (result for non-smokers)	0.15–0.19 µmol/mol creatinine	0.12 µmol/mol creatinine	$P < 0.0001$
			b) Mutagenic activity in urine (revertants/g creatinine) of workers in compounding and mixing	10 511	6522	$P < 0.05$
			c) DNA adducts in urothelial cells and in peripheral blood monocytes	Increased compared with control		
Musak *et al.* (2008) Czech Republic	Workers in a tyre plant (n = 177; 69 smokers) and 172 controls (49 smokers)	Personal samplers worn in breathing zone. Average BD level in the mixing department was 2.6 ± 0.2 mg/m^3	Chromosomal aberrations (per 100 metaphases)	2.5 ± 1.8	1.7 ± 1.2	$P = 0.055$
Wickliffe *et al.* (2009) Texas, USA	Workers in a BD rubber plant (see Ward *et al.*, 2001 above)	Current exposures: mean 93.5 ppb, median 2.5 ppb	*HPRT* mutant analysis in lymphocytes	Current, low, exposures to butadiene in this plant do not seem to increase the *HPRT* mutant frequency. However, older workers showed increased *HPRT* mutant frequencies, likely due to previous chronic exposure to higher levels of butadiene.		

BD, styrene-butadiene; h, hour or hours; *HPRT,* hypoxanthine-guanine phosphoribosyltransferase; mo, month or months; MN, micronucleus; NR, not reported; NS, not significant; PCD, premature chromosome condensation; SCE: Sister-chromatid exchange; SD standard deviation; SE standard error; vs, versus; yr, year or years

cancer hazards in the rubber-manufacturing industry to exposure to specific chemicals.

Table 4.1 presents a list of bio-monitoring studies and cytogenetic assays among workers in the rubber-manufacturing industry in various countries and at different times. These studies have focused on analysis of chromosomal aberrations, sister-chromatid exchange, micronucleus formation, premature chromosome condensation, DNA breakage, DNA-adduct formation, mutagenicity in urine, and mutation in the *HPRT* gene. For each of these endpoints, in most studies a positive response has been observed in exposed workers compared with non-exposed controls. It is noted that the studies listed in Table 4.1 span a period of approximately 25 years.

The multiple genetic and cytogenetic effects observed among workers employed in the rubber-manufacturing industry provide strong evidence to support genotoxicity as one mechanism for the observed increase in cancer risk. However, due to the complexity and changing nature of the exposure mixture and the potential interactions between exposures in this industry, other mechanisms are also likely to play a role.

While it is clear that exposures to some agents in the rubber-manufacturing industry have been reduced over time, the outcome of recent cytogenetic studies continues to raise concerns about cancer risks.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of occupational exposures in the rubber-manufacturing industry. Occupational exposures in the rubber-manufacturing industry cause leukaemia, lymphoma, and cancers of the urinary bladder, lung, and stomach.

lso, a positive association has been observed between occupational exposures in the rubber-manufacturing industry and cancers of the prostate, oesophagus, and larynx.

No data in experimental animals with relevance to the rubber-manufacturing industry were available to the Working Group.

The multiple genetic and cytogenetic effects observed among workers employed in the rubber-manufacturing industry provide strong evidence to support genotoxicity as one mechanism for the observed increase in cancer risks. However, due to the complexity and changing nature of the exposure mixture and the potential interactions between exposures in the rubber-manufacturing industry, other mechanisms are also likely to play a role. While it is clear that exposure to some agents in the rubber-manufacturing industry has been reduced over time, the results of recent cytogenetic studies continue to raise concerns about cancer risks.

Occupational exposures in the rubber-manufacturing industry are *carcinogenic to humans (Group 1).*

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