



National Institute for Public Health
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An overview of the available data on the mutagenicity and carcinogenicity of **rubber dust** and **rubber fumes**

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mutagenicity and carcinogenicity of rubber dust
and rubber fumes**

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Colophon

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Synopsis

An overview of the available data on the mutagenicity and carcinogenicity of rubber dust and rubber fumes

Rubber is used in many different products, such as tyres, rain boots and gloves. Manufacturing and processing can result in the release of rubber dust and fumes.

A key question is whether the dust and fumes are carcinogenic or capable of causing DNA damage (mutagenic effects) in exposed workers. The Health Council of the Netherlands asked RIVM to summarise the results of studies on these two properties in scientific literature. The summary covers a total of 18 studies involving human subjects.

The Health Council will use the overview to assess whether the properties are applicable to rubber dust and fumes. The Health Council is providing this advice at the request of the Minister of Social Affairs and Employment.

Keywords: rubber dust, rubber fumes, mutagenicity, carcinogenicity, hazardous properties, hazard classification

Publiekssamenvatting

Een overzicht van de beschikbare informatie over mutageniteit en carcinogeniteit van rubberstof en rubberdamp

Rubber wordt in veel verschillende producten gebruikt, zoals banden, regenlaarzen en handschoenen. Bij de productie en verwerking van rubber kunnen rubberstof en rubberdamp vrijkomen.

De vraag is of rubberstof en rubberdamp kankerverwekkend zijn (carcinogeen) en het DNA kunnen schaden (mutageen) bij mensen die werken met rubber. De Gezondheidsraad heeft het RIVM gevraagd om studies in de wetenschappelijke literatuur over deze twee eigenschappen samen te vatten. In totaal zijn hierover 18 studies samengevat die bij mensen zijn uitgevoerd.

De Gezondheidsraad gebruikt het overzicht om te beoordelen of rubber stof en rubber damp de twee eigenschappen hebben. De minister van Sociale Zaken en Werkgelegenheid (SZW) heeft de Gezondheidsraad om dit advies gevraagd.

Kernwoorden: rubberstof, rubberdamp, mutageniteit, carcinogeniteit, gevaarlijke eigenschappen, gevarenclassificatie

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1 Introduction

The aim of this review is to identify and summarize the available data on carcinogenicity and mutagenicity associated with (occupational exposure to) rubber dust and rubber fumes. The main focus of this review is on potential mutagenic and carcinogenic properties in relation to occupational exposure in the rubber industry.

At the request of the Dutch Minister of Social Affairs and Employment, the Health Council of the Netherlands will use this review to assess the mutagenic and carcinogenic properties and to provide a recommendation for its classification. The assessment will be performed by the Health Council's Subcommittee on Classifying Carcinogenic Substances. This subcommittee falls under the Dutch Expert Committee on Occupational Safety which focuses on health risks associated with occupational exposure of workers to chemicals.

This RIVM report provides a summary of relevant literature and does not include an assessment of the reported carcinogenic toxic properties of rubber dust, nor does it provide a recommendation for classification based on the CLP-criteria (Regulation EC No 1272/2008).

The literature search strategy, which is the basis of the current literature overview, is presented in Chapter 2. Chapter 3 describes the substance identification. In Chapter 4 classifications are described. Available information on measurements and analysis of workplace exposure is provided in Chapter 5, and information on occupational exposure is given in Chapter 6. Chapter 7 provides an overview of data on genotoxicity and mutagenicity. Chapter 8 presents an overview of the data on carcinogenicity.

2 Literature search strategy

The Health Council of the Netherlands has performed a literature search using PubMed, Embase, and Scopus. These databases were searched for scientific publications on the composition of rubber dust and fumes, carcinogenicity and mutagenicity reported in exposed human (worker) populations and the toxic endpoints reported in in vitro or in vivo animal experiments. The search covered publications from 2009 onwards, as studies up to 2009 were identified and evaluated by were reviewed by IARC (1). Records were screened and included if they were considered relevant based on their title and abstract. Additionally, relevant publications cited in selected publications that were not identified by the primary search, were also included.

The review included literature relevant to the classification of mutagenicity and carcinogenicity, focusing on studies that directly address these endpoints. Studies were excluded if there was no exposure to rubber dust or fume, if they involved irrelevant (micro)organisms, or if they primarily used machine learning or AI models. Additionally, case reports, general reviews, and book chapters that did not address carcinogenicity or genotoxicity were omitted. Publications in languages other than English or Dutch were also excluded.

Relevant in vitro, in vivo and epidemiological studies were selected for an extensive summary by the Health Council. Eighteen epidemiological studies were selected for an extensive summary. Sixteen epidemiological studies investigated cancer as an endpoint (12 cohort studies and one case-control study, two meta-analysis studies and one methodological study that estimated the amount of cancer cases that could be attributed to occupational exposure in the rubber industry). Two biomonitoring studies investigated mutagenicity as an endpoint.

The search strategy used for the identification of relevant literature on the carcinogenic and mutagenic effects of rubber dust and rubber fumes are described in Appendix 1.

3 Substance identification

3.1 Composition of rubber

The term rubber is used to describe a wide variety of polymers with elastic properties. Natural rubber (polyisoprene), also called latex, is obtained from the latex tree. Synthetic rubber can be synthesized using approximately 20 different polymers. The main generic rubber types are displayed in Appendix 2 (2).

Rubber is a complex compounded material referred to as a "compound" and usually contains a large number of chemicals to derive the right properties. As many as 15 to 20 different substances can be used in a single rubber compound (2). Generally, rubber compound can consist of (1):

- Natural and synthetic elastomers
- Fillers (mainly carbon black and precipitated amorphous silica; also calcium carbonate, clays, talc, mica etc.)
- Vulcanising agents (e.g. elemental sulphur, sulphur donors such as organic disulphides and higher sulphides, peroxides, urethane cross-linking agents)
- Vulcanisation accelerators (e.g. sulphenamides, thiazoles, guanidines, thiurams, dithiocarbamates, dithiophosphates, zinc isopropyl xanthate, ethylene thiourea)
- Vulcanisation activators (e.g. zinc oxide, magnesium oxide, lead oxide)
- Retarders and inhibitors of vulcanisation (e.g. benzoic acid, salicylic acid, phthalic anhydride, N-nitrosodiphenylamine (NDPA), N-(cyclohexylthio)phthalimide)
- Antidegradants and antioxidants (e.g. phenolics, phosphites, thioesters, amines, quinone-diimines, 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, vegetable oils and fats)
- Other ingredients such as pigments and peptising, blowing and bonding agents

3.2 Definition of rubber dust and rubber fumes

Rubber dust is defined as dust arising in the stages of rubber manufacture where ingredients are handled, weighed, added to or mixed with uncured material or synthetic elastomers (3). This definition does not include dusts arising from the mechanical damage of cured rubber. Rubber fumes are defined as fume evolved in the mixing, milling and blending of natural rubber and synthetic polymers combined with chemicals, and in the processes which convert the resultant blends into

finished products or parts thereof, and including any inspection procedures where fume continues to be evolved (3). The ISO definition for rubber fumes is as follows: "A variety of substances emitted from rubber compounds into a workplace atmosphere as a result of industrial processing, the composition of which depends on the formulation of the compounds concerned, the process technology in use and the associated process parameters (4).

3.3 Rubber manufacturing

Workers in the rubber-manufacturing industry are exposed to dusts and fumes from the rubber-making and production processes. Exposure to rubber dust and fumes occurs during multiple steps in the manufacturing process.

Rubber manufacturing generally comprises the following operations (2):

- Weighing and mixing: To produce the rubber compound, the base rubbers (polymers) have to be extended with a variety of different ingredients. For mixing, internal batch mixers, mixing mills, continuous internal mixers and mixing extruders are being used.
- Shaping operations: This may include milling to form moulding blanks, extruding to form profile shapes, calendaring to produce rubber sheets and eventually component assembly.
- Vulcanisation (curing): The rubbery molecules are converted to stable 3D networks by crosslinking, for example by adding sulfur compounds, which is the main process used. Rubber can sometimes be vulcanised by using peroxide-based systems or metal oxides. Vulcanisation can be performed by a variety of processes where the compound is heated and pressurized.
- Post-vulcanisation: Other processes to achieve the final form, such as grinding or trimming.

A detailed description of the exposure during production processes can be found in overviews of IARC 1982 and IARC 2012 (1, 5). Briefly, the first production step is handling of the raw materials, i.e. the raw polymer and additives. This step includes weighing and mixing. The extensive range of chemicals required and the volume of raw material handled can give rise to substantial quantities of airborne dust. From the mixer, the uncured rubber passes through milling machines where the compound is blended. Heat is generated in this process and the mill operator is exposed to fumes arising from the heated compound. Then, extruders force the rubber through a mould after which strips of softened rubber compound are fed into multiple-roll milling machines (calenders) to form rubber sheeting. Again, fumes are often generated. From the rubber sheets, products can be assembled. This frequently requires the use of solvents where there is possibility of inhalation or dermal exposure to these solvents. In order to cure or vulcanize the rubber product, heat is applied in a mould or autoclave. Operators in this area are exposed to fumes from the heated rubber products. Lastly inspection and finishing of the cured rubber products may also involve exposure to fumes and rubber dust, for example during grinding or trimming. Exposure to vapours may also occur during storage of rubber goods.

3.3.1 *Composition of rubber fumes*

The composition of rubber fumes depends firstly on the type of rubber compound and the chemicals used, but also varies during the different phases of rubber manufacturing depending on process temperatures. As a consequence of heating the compound degradation reactions, stabilization reactions and reactions associated with vulcanisation can occur (2).

Rubber fumes may contain volatile ingredients, reaction and breakdown products (e.g. antioxidants and plasticizers) but also volatile impurities in ingredients (e.g. monomers). In general, the range of chemical species that are present in rubber fumes may include (1, 2):

- Straight chain and cyclic aliphatic hydrocarbons
- Aromatic hydrocarbons (e.g. benzene, toluene, xylenes, ethylbenzene, dimethylbenzenes, diisopropylbenzenes)
- Polyaromatic hydrocarbons, halogenated hydrocarbons (e.g. tetrachloroethylene)
- Isothiocyanates
- Ketones
- Amines and N-nitrosoamines (e.g., N-nitrosodimethylamine (NDMA), N-nitrosodiethylamine (NDEA), N-nitrosodibutyldiamine (NDBA) and N-nitrosomorpholine (NMor))
- Thiazoles
- Aldehydes (formaldehyde, acrolein, acetaldehyde, butyraldehyde and benzaldehyde) and alcohols
- Esters (phthalate and adipate esters) and ethers
- Sulphur compounds (including carbon disulphide).

Concerns related to N-nitrosoamine levels in rubber fumes have resulted in changes in curing systems and raw materials, and measurements between 1980 and 2000 show a 2-5-fold reduction in N-nitrosamine exposure over this period (1).

4 International classifications

4.1 European Commission

According to SCOEL, there is clear evidence of an increased cancer risk in the rubber manufacturing industry. Therefore, exposure to any known carcinogens released during rubber manufacturing processes should be minimized to the lowest levels that are technically and practically achievable. However, it is not possible to quantify the associated cancer risk for classification purposes, or to recommend a specific limit value for rubber dusts or fumes, due to several uncertainties (6). These include the variable composition of rubber dusts and fumes, the absence of a suitable exposure proxy that correlates with cancer risk, and a lack of recent data (post-2010) on their composition.

4.2 The Health Council

No classification has been established yet.

4.3 IARC

The International Agency for Research on Cancer (IARC) has concluded that there is sufficient evidence to classify occupational exposures in the rubber manufacturing industry as carcinogenic to humans (IARC Group 1) (1). According to IARC, these exposures are known to cause leukaemia, lymphoma, and cancers of the urinary bladder, lung, and stomach. There was also a positive association observed between occupational exposures in the rubber industry and other types of cancer, such as prostate, oesophagus, and larynx. With the exception of bladder cancer risk, which was associated with elevated exposure to beta-naphthylamine, and haematological cancer risks, which were associated with exposure to specifically benzene, IARC was unable to clearly identify specific processes, products, exposures, or compounds responsible for the other cancer types, as these factors did vary significantly between individual factories in the studies evaluated by IARC.

4.4 Other countries

No relevant classifications for rubber were found in the legislation or advisory reports of other countries.

5 Measurements and analysis of workplace exposure

5.1 Personal and stationary exposure monitoring of rubber dust and fumes

The *quantitative* measurement of occupational exposure to rubber dust and fumes follows established industrial hygiene protocols. Personal monitoring assesses an individual worker's actual exposure to hazards in their breathing zone, ensuring compliance with legal exposure limits. Stationary (area) monitoring measures general workplace conditions. Together, they form a comprehensive exposure assessment strategy.

Sampling of rubber dust should be carried out as described in the UK's Health and Safety Method MDHS14/4 for inhalable dusts. A pump is used to pull a measured volume of air through a collection substrate such as a filter mounted in a sampler, and the mass of dust collected is determined by weighing the substrate before and after sampling (mg/m³). Recommended inhalable dust samplers are the Institute of Occupational Medicine (IOM) sampler, the conical inhalable sampler (CIS) and the multi-orifice (or seven hole) sampler (7).

Rubber fume (measured as a cyclohexane-soluble material) in the air can be determined using the UK's Health and Safety Method MDHS method 47/3. A measured volume of air is drawn by a pump through a pre-weighed, pre-extracted filter. Sampling should be carried out as described in MDHS14/4 for inhalable dusts (see above). It is recommended that a minimum of six blank filters should be submitted with each set of samples to obtain with reasonable certainty the detection limit of the method. The filter is re-weighed to obtain a value for the total mass of inhalable dust deposited on the filter. Next, the filter is soxhlet extracted with cyclohexane, then re-weighed. The quantity of cyclohexane-soluble material, rubber fume, is obtained from the mass loss of the filter during the extraction. For quantification of rubber fume, a minimum sampling volume of 500 litres is recommended and the procedure is therefore not recommended for short-term (15 min) sampling (8).

Volatile components of rubber fumes can *qualitatively* be identified by thermodesorption- gas chromatography-mass spectrometry (TD-GD-MS), after trapping on a solid sorbent based on 2,6-diphenylphenylene-oxide polymer resin. It is applicable to a screening of emissions from the processing of rubber compounds in the ambient workplace and storage environment (9).

More recently, methods to quantify components of rubber, not commonly listed as components of rubber fumes or dusts, have been developed. This includes methods to quantify p-phenylenediamines (PPDs) and their quinone derivatives (PPD-Qs) in settled dust from tire and seal factories (10) and airborne microplastics that has been found in the production area of rubber manufacturing facilities (11).

5.2 Biological exposure monitoring

There are no biological exposure monitoring (BEM) methods for occupational exposure to rubber dust and fumes as a single entity.

However, since workers in the rubber industry are exposed to a broad spectrum of compounds with alkylating activity it is possible to analyse N-acetyl-l-cysteine S-conjugate metabolites or mercapturic acids (MAs) in the urine. MAs are formed from electrophile-glutathione S-conjugates through sequential transformation, including hydrolysis followed by N-acetylation in the kidney to form MAs, which are excreted in the urine (12, 13). Exposure to alkylating agents is also possible by analysis of hemoglobin adducts in blood. Chemicals or their reactive metabolites bind covalently to specific amino acid residues (most commonly N-terminal valine or cysteine) on the hemoglobin molecule. These bound chemicals serve as surrogate markers for how much of the reactive agent reached critical cellular targets, including DNA (14, 15).

There are BEM methods in the rubber manufacturing industry that are compound-specific. The wide array of substances involved in rubber manufacturing or contained in emissions from the different processes, mean that there are myriad protocols and methods for assessing these exposures. A summary of these is outside the scope of this report.

6 Exposure

Workers are exposed to rubber fumes and rubber dusts which, as previously noted, have complex compositions.

Recent quantitative data on exposure to rubber fumes and dusts is scarce. Furthermore, most exposure data comes from short-term task-based sampling, rather than full-shift time-weighted averages (TWAs), which are more relevant for chronic disease risk assessment. The most comprehensive data resource is the Improved Exposure Assessment for Prospective Cohort Studies and Exposure Control in the Rubber-Manufacturing Industry (EXASRUB) database that holds measurement data from the United Kingdom, Germany, the Netherlands, Poland, and Sweden (1, 16).

6.1 Occupational exposure

Routes of occupational exposure are inhalation and dermal contact. Inhalation is considered to be the main route of exposure.

Occupational exposure to rubber dust and fumes was extensively measured between 1970 and 2003. Data were collected in the EU-EXASRUB database containing 13 380 inhalable and 5657 cyclohexane soluble fraction (CSF) measurements (16, 17). These measurements represent complex and heterogeneous mixtures of rubber particles and process-related fumes.

6.1.1 Occupational exposure to rubber dust and rubber fumes

Reported concentration ranges provide a general sense of exposure levels across countries, although direct comparisons are hampered by methodological differences between difference in sources of data. Average geometric mean personal inhalable rubber dust exposure levels have ranged from 0.72 mg/m³ in the Netherlands to 1.97 mg/m³ in Germany, see also Table 1. (1, 17).

Table 1 Geometric means and standard deviations of inhalable dust measurements measured between 1969 and 2003 (17).

Country	Inhalable dust (mg/m ³), GM (GSD)
Netherlands	0.72 (2.94)
Germany	1.97 (4.80)
United Kingdom	1.00 (3.70)
Poland	1.79 (3.49)
Sweden	1.82 (3.87)

GM: geometric mean; GSD, geometric standard deviation

An overview of exposure in the Netherlands to inhalable rubber dust by production function is based on data from 1997 and is presented in Table 2. The highest median exposure levels were found in the compounding/mixing department (1.47 mg/m³), followed by engineering (0.94 mg/m³) and pre-treating (0.85 mg/m³) (18).

Table 2 Median exposure to inhalable particulates per production function in the Netherlands in 1997 (18).

Production function	N	Median (mg/m³)
Compounding/mixing	6	1.47
Pre-treating	5	0.85
Moulding	6	0.50
Curing	7	0.56
Finishing	5	0.54
Engineering	7	0.94
Laboratory	1	0.22
Shipping	2	0.56

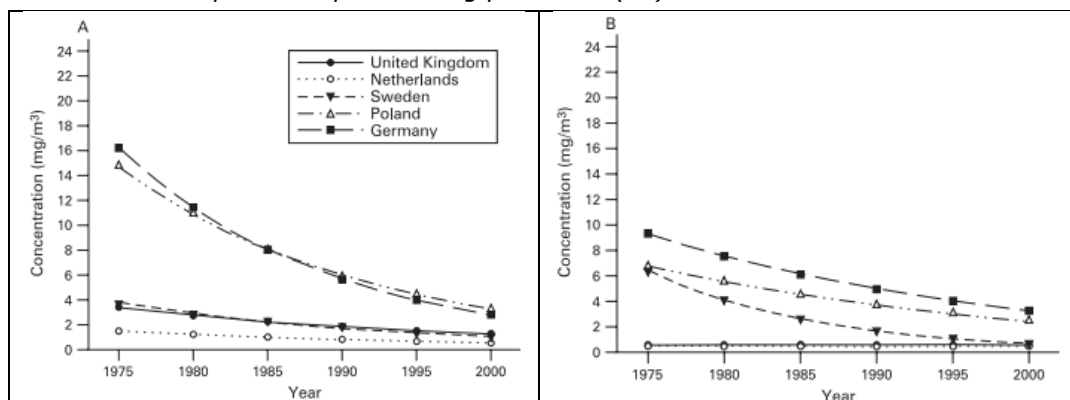
Median inhalable dust concentrations in the general rubber goods sector were also measured in an industry-wide study in the UK (19). Highest median exposures were found in the weighing department (4,2 mg/m³), followed by mixing (1.2 mg/m³), milling (0.8 mg/m³) and extrusion (0.8 mg/m³).

Reported levels can occasionally surpass occupational exposure limits (OELs). These vary between jurisdictions. The ACGIH have set a Threshold Limit Value (TLV) of 3 mg/m³ for respirable rubber dust while under the UK's Control of Substances Hazardous to Health (COSHH) regulations, an 8-hour TWA of 6 mg/m³ has been set for rubber process dust (20). However, in 2023, the Dutch Expert Committee on Occupational Safety (DECOS), in agreement with EC's Scientific Committee on Occupational Exposure Limits (SCOEL), concluded that it was not possible to derive a health-based recommended occupational exposure limit (HBR-OEL) for rubber dusts or rubber fumes based on the scientific data available (21).

6.1.2 *Occupational exposure trends for rubber dust*

In general, workers' exposure to rubber dust in Western Europe has decreased over the years based on the EXASRUB database (22). This is due to improved industrial hygiene practices and regulatory pressure (23). The downward trend in occupational exposure levels is reflected in all five participating countries – United Kingdom, the Netherlands, Poland, Germany and Sweden (1). In the Netherlands, the decrease in exposure from 1998 over the immediate nine years that followed, was about 5.7% per annum for exposure to inhalable particulate matter, with, on average, median concentrations going from 1 mg/m³ to 0.59 mg/m³ (1). Behind these overall trends, relative concentrations (low, medium, high) between departments were largely unchanged across timeframes and highest exposure levels were consistently seen in the compounding and mixing departments (18). This was reflected 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). The downward trends in personal inhalable dust exposures is presented in figure 1 for 'compounding and mixing processes' and 'pre-treating processes' (17).

Figure 1 (A) Estimated time trends in personal inhalable dust exposure in compounding and mixing processes. (B) Estimated time trends in personal inhalable dust exposure in pre-treating processes (17).



6.1.3 Occupational exposure to rubber fumes

The cyclohexane-soluble fraction (CSF) of total particulate matter is used as a proxy for contamination of areas with CSF rubber fumes. Average geometric mean personal rubber fume concentrations between 1977 and 2003, based on inhalable dust sampling, have ranged from less than 0.1 mg/m³ in the Netherlands to over 1.1 mg/m³ in Poland, see also table 3 (17).

Table 3 Geometric means and standard deviations of cyclohexane soluble fraction (CSF) measurements measured between 1977 and 2003 (17). GM: geometric mean GSD, geometric standard deviation

Country	CSF (mg/m³), GM (GSD)
Netherlands	0.0977 (2.55)
Germany	-
United Kingdom	0.366 (3.60)
Poland	1.130 (3.84)
Sweden	0.410 (2.75)

In an industry-wide study in the UK (19), CSF concentrations were highest in the general rubber goods companies (0.40 mg/m³), followed by re-treading plants (0.32 mg/m³) and manufacturers of new tyres (0.22 mg/m³).

- In general rubber goods companies process-specific CSF concentrations were highest in moulding (0.4 mg/m³), followed by extrusion (0.33 mg/m³) and milling (0.18 mg/m³).
- For re-treading CSF concentrations were highest for pressing (0.32 mg/m³), followed by extruding (0.19 mg/m³) and autoclaving (0.10 mg/m³).

Reported levels can occasionally surpass occupational exposure limits (OELs). These vary between jurisdictions. The UK's Control of Substances Hazardous to Health (COSHH) regulations set an 8-hour TWA of 0.6 mg/m³ for rubber process fume (20). However, in 2023, the Dutch Expert Committee on Occupational Safety (DECOS), in agreement with EC's Scientific Committee on Occupational Exposure Limits

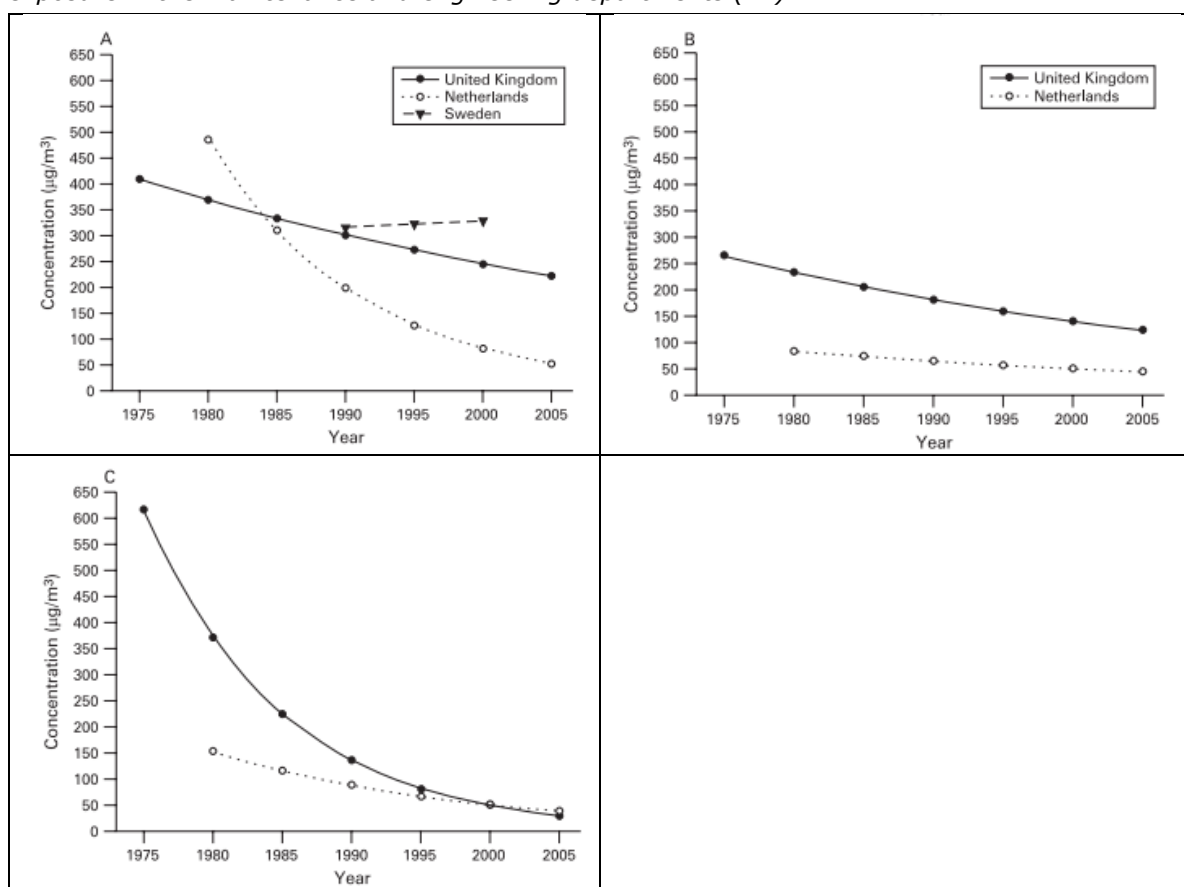
(SCOEL), concluded that it was not possible to derive a health-based recommended occupational exposure limit (HBR-OEL) for rubber dusts or rubber fumes based on the scientific data available (21).

6.1.4 *Trend of occupational exposure to rubber fumes*

Just as with rubber dust, exposure to rubber fumes has also decreased over the years as a result of occupational health and safety measures implemented (22, 23).

There has been a 3% (range –8.6% to 0%) annual decrease in concentration between 1977 and 2003 based on 5657 records in the EXASRUB database. The steepest declines were seen in curing (–8.6% per year) and maintenance and engineering departments (–5.4% per year) (17). See also figure 2.

Figure 2 (A) Estimated time trends in personal cyclohexane soluble fraction (CSF) exposure in the curing departments during compression, transfer or injection curing processes. (B) Estimated time trends in personal CSF exposure in the post-treating departments. (C) Estimated time trends in personal CSF exposure in the maintenance and engineering departments (17).



6.1.5 *Other information*

Marant Micallef et al. (2021) developed a methodology to estimate the lifetime prevalence of exposure to carcinogenic occupational circumstances of national populations, with France as case study (24). Using their method they calculated the population-level lifetime

prevalence of ever having worked in the rubber manufacturing industry in France (0.2% for men and 0.1% for women). RRs derived from a review by Marant Micallef et al. (2018) were used to estimate attributable cancer cases (25). 42 cancer cases (28 men and 14 women) were attributed to occupational exposure in the rubber industry. A limitation of this study was the lack of data on the duration of jobs and thus exposure, resulting in an estimation of lifetime prevalence of exposure based on "over-exposure".

7 Genotoxicity and mutagenicity

No in vitro mutagenicity and cytogenetic and in vivo animal mutagenicity studies were identified in the current literature search.

7.1 **Summary of human data on mutagenicity**

Data on human mutagenicity studies are presented in Table 4, followed by a summary in text. In general, only statistically significant results are reported.

Table 4 Summary table of mutagenic studies

Study design and population	Exposure assessment	Health assessment	Data analysis	Results	Bias/confounding factors	Remarks
<i>Reference:</i> Cavallo et al. (2014) (26) <i>Study design:</i> Cross sectional <i>Study setting:</i> Industry-based <i>Country:</i> Italy <i>Study population:</i> 159 ex-rubber workers employed between 1962-1980 (divided into 5 risk classes based on estimated level of exposure) and 97 unexposed healthy subjects both aged 30-83 years <i>Observation period:</i> 2 days	<i>Type of exposure:</i> Exposure to rubber dust and fumes in workplace air measured in urine using biomonitoring divided into 5 risk classes: 1: preparation and weighing of raw materials (highest expected exposure) 2: mixing raw materials 3: assembly 4: vulcanization 5: checking, storage, and transportation of the finished product (lowest expected exposure) <i>Sampling:</i> personal <i>Number of measurements:</i> Urine	<i>Type of mutagenic effects:</i> DNA damage measured by comet assay, telomerase activity measured by TRAP (telomeric repeat amplification protocol), chromosomal changes measured by FISH, cellular atypia assessed by urine cytology (as early detection for bladder cancer) <i>Type of health data:</i> biological samples (urine)	<i>Type of statistical analysis performed:</i> SPSS, Mann-Whitney U, chi square, Kruskal-Wallis post hoc Bonferroni test, Fisher test, Pearson's correlation coefficients Comparisons were made between the different risk classes and between the risk classes and controls	<i>Type of health effects observed:</i> DNA damage, change in telomerase activity, chromosomal changes Statistically significant higher tail moment found in subjects of the highest risk class compared to other risk classes and to controls ($p < 0.05$) <i>Tail moment:</i> Significant increase in tail moment values in the comet assay observed in highest class of risk (20.39 ± 15.96) compared to all classes of risk (16.81 ± 13.23) and controls (14.11 ± 7.18), $p < 0.05$	<i>Confounding factors included in analysis:</i> age, smoking habits, alcohol intake, drug assumptions, diagnostic radiation exposure and dietary habit. Statistically significant differences were found for age ($p < 0.005$), alcohol intake and dietary habit ($p < 0.001$) between the exposed group and the controls Potential biases: Selection bias; significant difference for age between exposed and	The authors did not mention bias as such in the text. Concordance between positive FISH and TRAP results was observed in 14/19 workers (74%). Standard urine cytology showed dysplasia or UBS in 5/11 workers with positive FISH, TRAP, and/or comet assay

Study design and population	Exposure assessment	Health assessment	Data analysis	Results	Bias/confounding factors	Remarks
	was collected freshly in the morning of the first two days of the week and divided in three aliquots <i>Type of job history data:</i> not known <i>Information on job and exposure history:</i> matrix job/exposure considering: department, task, duration of employment, year of beginning and end			Statistically significant association between exposure and DNA damage ($p < 0.05$) <i>TRAP:</i> Class with highest risk has higher TRAP positive levels (69.3%) compared to all classes of risk (16%) and controls (15%), not significant.	controls, whereas age is a risk factor for bladder cancer Information bias; a JEM was used to estimate exposure	
<i>Reference:</i> Germitha et al. (2013) (27) <i>Study design:</i> Cross sectional <i>Study setting:</i> Industrial-based	<i>Type of exposure:</i> Exposure to rubber dust and fumes in workplace air measured in buccal cells using biomonitoring Subgroups: Both workers and controls	<i>Type of mutagenic effect:</i> Cytogenetic damage in buccal cells measured by micro nuclei assay	<i>Type of statistical analyses performed:</i> Student's t-test, ANOVA Subgroup analyses:	<i>Type of health effects observed:</i> Genetic damage in buccal cells Significant increased induction of MN in buccal cells in all subgroups rubber	<i>Confounding factors included in analysis:</i> smoking and alcohol intake No remarks were made about bias by the authors.	The authors state that a larger sample size is needed to draw definitive conclusions

Study design and population	Exposure assessment	Health assessment	Data analysis	Results	Bias/confounding factors	Remarks
<i>Country:</i> Rural areas of South India <i>Study population:</i> 35 occupational exposed rubber workers and 30 controls <i>Observation period:</i> 1 cheek scrape after the end of a shift	were divided into four subgroups; smokers, non-smokers, alcoholics, non-alcoholics <i>Sampling:</i> personal <i>Number of Measurements:</i> 1 <i>Type of job history data:</i> enquired from the workers <i>Information on job and exposure history:</i> enquired from the workers	<i>Type of health data:</i> Biological samples (buccal cells) and self-reported information on lifestyle <i>Type of medical examinations:</i> MN assay in buccal cells, questionnaires for lifestyle and medical history, one investigator analysed the samples	-all workers were compared to all controls -the workers' subgroups were compared to the same controls' subgroups	workers vs. matched controls ($p < 0.05$). Subgroups: -Smokers: Increased induction of MN in rubber workers (2.55 ± 1.04 vs 1.31 ± 0.67 in controls) -Non-smokers: Increased induction of MN in rubber workers (2.0 ± 0.93 vs 1.18 ± 0.75 in controls) -Alcoholics: Increased induction of MN in rubber workers (1.90 ± 0.64 vs 0.93 ± 0.57 in controls) -Non-alcoholics: Increased induction of MN in rubber workers (1.53 ± 0.83 vs 0.57 ± 0.64 in controls)		

7.1.1 *Mutagenic studies overview*

Cavallo et al. (2014)

In a cross-sectional biomonitoring study, Cavallo et al. (2014) (26) examined non-invasive biomarkers in urine for early diagnosis of bladder lesions in 159 ex-workers from the rubber tyre industry, employed between 1962 and 2006. Exposure was estimated using a JEM and information about the type and duration of the job. Based on the estimated level of exposure workers were divided into five risk classes: (1) preparation and weighing of raw materials; (2) mixing of raw materials; (3) assembly; (4) vulcanization; and (5) checking, storage, and transportation of the finished product. A comet assay, TRAP assay and FISH analysis were used to assess DNA damage, telomerase activity and chromosomal alterations. Workers in the highest risk class (e.g. with the highest estimated exposure) (n=74) had a significantly higher tail moment compared to other classes and controls ($p<0.05$). A significant association was observed between exposure and DNA damage in the highest risk class compared to other risk classes and when all exposed ex-workers were compared with controls ($p<0.05$).

Germitha et al. (2013)

Germitha et al. (2013) (27) performed a cross-sectional biomonitoring study towards cytogenetic damage in buccal cells of rubber workers using a micro nuclei assay. Workers and controls were divided in four subgroups of non-smokers, smokers, non-alcoholics and alcoholics. All workers were compared to controls and subgroup analyses was performed for the four different groups. A significant increase in cytogenetic damage was observed in all workers subgroups compared to their matched control group ($p<0.05$).

8 Carcinogenicity

No studies with animal data on carcinogenicity were identified in the current literature search.

8.1 **Summary of observations in humans**

The carcinogenic effects as observed in cohort studies are summarized in Table 5. The case control studies are summarized in Table 6. The meta-analyses are summarized in Table 7. All tables are followed by a summary in text.

Table 5 Cohort studies

Study design and population	Exposure assessment	Health assessment	Data analysis	Results	Bias/confounding	Remarks
Reference: Boniol et al. (2016) (28) <i>Study design:</i> Multinational retrospective cohort study <i>Location:</i> Germany, Italy, Sweden, UK, Poland <i>Time period:</i> 1975-2013. Average follow-up 26 years (18.7-29.4) <i>Censoring:</i> Follow-up ended at death, emigration, loss to follow-up or study end. In Germany, years with missing data were excluded, and from 2001, correction factors for immigration and mortality were applied to adjust person-years. <i>Study population:</i> 38,457 individuals (77.4% male) who worked in the rubber industry ≥ 1975 <i>Reference population:</i> National and regional general	<i>Specificity of agent:</i> Non-specific, rubber workers exposed to rubber dust and fumes <i>Method:</i> Exposure assessment was conducted using an industry-specific JEM <i>Type of job history data:</i> company records	<i>Studied endpoint:</i> cancer mortality <i>Health data collection:</i> Active linkage to national and regional mortality registries, determining cause of death and vital status. Completeness was high. Only Germany had some missing data <i>Diagnosis and/or classification of health effects:</i> ICD-9 codes <i>Vital status of cohort members:</i> Alive, deceased or lost to follow-up <i>Type of health data:</i> cancer	<i>Epidemiological measure:</i> Standardized mortality ratios (SMRs) <i>Statistical analysis:</i> Poisson regression for duration of employment analysis. Heterogeneity was determined using forest plot, I² and Cochran's Q statistic. Sensitivity and stratified analysis. <i>Covariates included in the analysis:</i> The Poisson model included age-and gender-specific function of duration of employment.	<i>Type of health effects observed:</i> Bladder and lung cancer (primary); all cancers combined, stomach cancer, leukaemia, multiple myeloma and non-Hodgkin's lymphoma (secondary); all other cancer types (exploratory) <i>Data on risk estimates:</i> All industries and participants combined: bladder cancer SMR: 0.80 (95% CI: 0.46-1.38) (not sign), lung cancer SMR: 0.81 (95% CI: 0.70-0.94), all cancers combined SMR: 0.81 (95% CI: 0.76-0.87) <i>Sub analysis:</i> stratified analysis for gender: Decreased risk of death for (p<0.05) lung cancer (m), all cancers (m, f) <i>Sub analysis:</i> stratified analysis for type of industry and gender: Decreased risk of death (p<0.05) for	<i>Potential biases:</i> Healthy worker effect Survivor bias; longer employment duration may reflect survivor bias, as healthier workers are more likely to remain employed Incomplete follow-up data; For Germany there was incomplete follow-up and mortality data <i>Confounding:</i> not discussed in the text. Potential confounding factors such as smoking, socioeconomic status and lifestyle could not be controlled for, since data on these variables were not available	

Study design and population	Exposure assessment	Health assessment	Data analysis	Results	Bias/confounding	Remarks
populations, using gender, age and period specific mortality <i>Type of industry:</i> Tyre industry, General rubber goods industry, other rubber industry <i>Inclusion criteria:</i> workers who 1) were at least 1 year employed in one of the cohorts; 2) had a first employment in the rubber industry after 1 January 1975 <i>Study size:</i> all 38,457 people were exposed (949,370 person years)		registries and mortality registries		Tyre industry: men lung cancer and all cancers, women all cancers, men and women combined lung cancer and all cancers Mixed industries: men all cancers, men and women combined all cancers All industries combined: men lung cancer, all cancers, all causes of death, cardiovascular diseases and colorectal cancer; women all cancers, all causes of death; men and women combined lung cancer, all cancers and colorectal cancer. Increased risk of death ($p < 0.05$) for: General rubber goods: men stomach cancer and multiple myeloma, men and women combined stomach cancer and multiple myeloma Stratified analysis to commencement of employment: workers who started in the rubber industry after 1985 had a lower risk of		

Study design and population	Exposure assessment	Health assessment	Data analysis	Results	Bias/confounding	Remarks
				total cancer mortality (not sign)		
Reference: Boniol et al. (2017,b) (29) Study design: Multinational retrospective cohort study Location: UK and Sweden Time period: 1 Januari 1975 until 31 December 2011 Censoring: Follow-up started after 1 year of employment and ended at death, emigration, loss to follow-up or study end. Study population: 16,026 individuals (77.6% male) who worked in the rubber industry ≥ 1975 (N Sweden= 7424, N UK= 8602) Reference population: national gender-, age- and period-specific incidence rates from Sweden, England/Wales and Scotland.	Specificity of agent: Non-specific, rubber workers exposed to rubber dust and fumes Method: Exposure assessment was conducted using industry-specific JEM Type of job history data: company records	Studied endpoints: Cancer incidence Health data collection: Cancer diagnoses were confirmed by linkage to national cancer registries in Sweden and the UK. Completeness was high Diagnoses and/or classification of health effects: ICD-7 and 8 in Sweden and ICD-9 and 10 in UK. Diagnoses were pathologically confirmed. Vital status of cohort members: alive deceased, or lost to follow-up	Epidemiological measure: Standardized incidence ratio (SIR) Statistical analyses: SIRs with 95% CI, random-effects models, heterogeneity was calculated using I² statistics and Cochran's Q-test, sensitivity analysis, Poisson and cubic natural splines for duration of employment. Covariates included: age-, gender- and period-specific covariates	Type of health effects: cancer of the bladder and lung (primary) stomach, leukaemia, non-Hodgkin's lymphoma and multiple myeloma (secondary) brain, colon, kidney, larynx, melanoma, oesophagus, oral cavity and pharynx, pancreas, prostate, testis, breast, endometrial and ovary (exploratory) Data on risk estimates: Combined cohorts Decreased cancer risk for lung (SIR: 0.74; 95% CI 0.59-0.93), all cancers combined (SIR: 0.83; 95% CI 0.74-0.92), non-Hodgkin's lymphoma (SIR: 0.67; 95% CI 0.45-1.00) and prostate (SIR: 0.77; 95% CI 0.64-0.92) Sweden Decreased risk for all cancers combined and leukaemia (p<0.05)	Potential biases: Possible registration bias and overdiagnosis may have influenced melanoma incidence in Swedish women Confounding: no confounding factors included (smoking, socio-economic status)	Information on loss to follow-up: patients were censored at loss to follow-up or emigration References of earlier publications on the same cohort: Boniol et al. (2016)(28)

Study design and population	Exposure assessment	Health assessment	Data analysis	Results	Bias/confounding	Remarks
<i>Inclusion criteria:</i> workers who 1) were at least 1 year employed in one of the cohorts; 2) had a first employment in the rubber industry after 1 January 1975 <i>Study size:</i> 16,026 workers (all exposed)		<i>Type of health data:</i> National cancer registries and national population registries		UK Decreased cancer risk for lung, all cancers combined, colon, melanoma and prostate ($p < 0.05$) Significant heterogeneity between the two countries for all cancers combined, colon cancer and melanoma ($p < 0.05$) Stratified analysis Men UK: decreased cancer risk for lung, all cancers combined, colon, melanoma and prostate ($p < 0.05$) No sign. results for Sweden Combined cohorts: decreased cancer risk for lung, all cancers combined and prostate ($p < 0.05$) Significant heterogeneity between countries for all cancers combined and colon ($p < 0.05$)		

Study design and population	Exposure assessment	Health assessment	Data analysis	Results	Bias/confounding	Remarks
				Women Sweden: decreased risk for all cancers combined ($p < 0.05$) increased risk for melanoma ($p < 0.05$) no sign. results for UK Combined cohorts: decreased risk for all cancers combined ($p < 0.05$) increased risk for melanoma ($p < 0.05$) No sign. heterogeneity between the two countries Analysis performed with 10-years induction-latency period Sweden: decreased risk for all cancers combined and leukaemia ($p < 0.05$) UK: decreased cancer risk for bladder, lung, all cancers combined, colon, melanoma and prostate ($p < 0.05$) Combined cohorts: decreased cancer risk for lung, all		

Study design and population	Exposure assessment	Health assessment	Data analysis	Results	Bias/confounding	Remarks
				cancers combined and prostate ($p < 0.05$) Significant heterogeneity between the countries for all cancers combined, colon cancer and melanoma ($p < 0.05$)		
Reference: DeBono (2020) (30) <i>Study design:</i> retrospective cohort study <i>Location:</i> Ontario (Canada) <i>Time period:</i> 1983-2016 <i>Censoring:</i> Follow-up started at their first compensation claim in the rubber industry. Follow-up ended at the occurrence of a primary cancer of interest, death, emigration from Ontario, reaching 85 years of age or the end of the study. <i>Study population:</i> rubber manufacturing workers from	<i>Specificity of agent:</i> Non-specific, rubber manufacturing workers exposed to rubber dust and fumes <i>Method:</i> Exposure was assessed using administrative records from workers' compensation claims, based on coded occupation and industry at the time of the compensated injury or disease <i>Type of job history data:</i> administrative data from WSIB	<i>Studied endpoints:</i> Cancer incidence <i>Health data collection:</i> Cancer diagnoses were confirmed through active record linkage with the Ontario Cancer Registry. Completeness was high <i>Diagnoses and/or classification of health effects:</i> population based on accepted compensation claims in the ODSS. Cancer diagnoses via the	<i>Epidemiological measure:</i> Hazard ratio (HR) <i>Type of statistical analyses performed:</i> Cox proportional hazard regression model and a sensitivity analysis <i>Covariates included in the analysis:</i> age at the start of follow-up, birth year and sex	<i>Type of health effects:</i> cancer in the lung and bronchus, oesophageal, stomach, liver, pancreas, kidney, bladder, brain and nervous system, breast and prostate and leukaemia and non-Hodgkin lymphoma <i>Data on risk estimates:</i> Decreased risk of leukaemia (HR: 0.69; 95% CI 0.47-0.99) <i>Stratified analysis by sex:</i> Women Increased risk for lung cancer (HR: 1.39; 95% CI 1.07-1.81) Men No significant changes in risk observed	<i>Potential biases:</i> Potential selection bias, since only workers with an accepted claim are included Non-differential misclassification from exposure was likely common, since job history was only determined based on the job in the claim Potential healthy worker bias, although reduced by the use of diagnostic endpoints rather than mortality.	<i>Remarks related to the quality of the study:</i> the reference population are workers from other hazardous occupations, so they might also be exposed to carcinogens <i>Information on loss-to follow-up:</i> 1.9% loss to follow-up. Same in exposed and reference population

Study design and population	Exposure assessment	Health assessment	Data analysis	Results	Bias/confounding	Remarks
the Occupational Disease Surveillance System (ODSS) <i>Reference population:</i> all other workers in the ODSS <i>Inclusion criteria:</i> rubber workers with an accepted claim at the Ontario Workplace Safety and Insurance Board (WSIB) <i>Study size:</i> 13,030 exposed, around 2.1 million non-exposed		Ontario Cancer Registry <i>Vital status of cohort members:</i> alive, deceased or lost to follow-up <i>Type of health data:</i> records of cancer diagnosis from the Ontario Cancer registry			<i>Confounding:</i> Similar occupational exposures in the reference group may lead to underestimation of cancer in the rubber workers Lifestyle factors like smoking were not included as covariates Sex-specific confounding may occur because men in the reference group more often have industrial jobs and related exposures, potentially masking cancer risks in male rubber workers	
<i>Reference:</i> De Vocht et al. (2009) (31) <i>Study design:</i>	<i>Specificity of agent:</i> Job-exposure matrix (JEM) for occupational exposure to	<i>Studied endpoints:</i> Cancer mortality <i>Health data collection:</i> Vital	<i>Epidemiological measure:</i> Risk ratio	<i>Type of health effect(s) observed:</i> Urinary bladder cancer associated with aromatic amine exposure:	<i>Potential biases:</i> Historic exposure to b-naphthylamine, exposure to rubber fumes, n-	Loss to follow-up 3.2% for men and 2.7% for women.

Study design and population	Exposure assessment	Health assessment	Data analysis	Results	Bias/confounding	Remarks
Retrospective industrial based cohort <i>Location:</i> Poland <i>Time period:</i> 1950-1995, follow up until 2002 <i>Study population:</i> Workers in a Polish tyre manufacturing plant <i>Inclusion and exclusion criteria:</i> Inclusion: employed at least three months between 1950 and 1995 <i>Study size:</i> 11,582 men 6,054 women	aromatic amines, inhalable aerosols and rubber fumes, based on data in EU-EXASRUB database; based on geometric mean concentrations for these chemicals in different departments in the factory per year between 1981 and 1996. <i>Type of job history data:</i> Company records	status: Personal records at the HR department (16%), local municipal sources or the Polish Electronic System of Population Evidence (84%). Cause of death: local civil registration office records or hospitals. Coded according to ICD-9.	<i>Type of statistical analyses performed:</i> Pearson correlations for cumulative exposure estimates, Cox proportional hazard models for exposure-response associations.	0.09-1.64 year mg/m³: RR: 7.32 (95% CI: 1.05-50.98) 1.64-8.19 year mg/m³: RR: 8.27 (95% CI: 1.03-66.27) Trends for associations between inhalable aerosol exposure and increased liver and intrahepatic bile ducts (p=0.04) and decreased respiratory and intrathoracic organs (p=0.03), larynx (p=0.03), and colon (p=0.05). men: Prostate cancer associated with aromatic amine exposure: 0.03-0.99 year mg/m³: RR: 5.86 (95% CI: 1.04-33.09) Women: All malignant neoplasms associated with aromatic amine exposure: 0.98-4.42 year mg/m³: RR: 2.50 (95% CI: 1.40-4.47) Digestive organs and peritoneum neoplasms	nitrosamines and solvents. Healthy worker effect minimised by using internal comparisons, exposure misclassification bias (exposure based on department level instead of task), selection bias (JEM based on 51-58% of person-years) <i>Confounding factors:</i> Limited exposure data (exposure levels at department level), no information on smoking, occupational exposure at other companies or other non-occupational exposure available.	<i>References of earlier publications on the same cohort:</i> Wilczynska et al. (2001)(32) Szadkowska-Stanczyk et al. (2001)(33) De Vocht et al. (2005)(16) De Vocht et al. (2008)(17) Additional follow-up of 7 years in this study.

Study design and population	Exposure assessment	Health assessment	Data analysis	Results	Bias/confounding	Remarks
				associated with aromatic amine exposure: 0.98-4.42 year mg/m ³ : RR: 4.54 (95% CI: 1.37-15.06) Trends for associations between aromatic amine exposure and increased breast neoplasms (p=0.01).		
Reference: Dutheil et al. (2017) (34) Study design: Prospective industrial based cohort Location: France Time period: 1993-2013 Study population: Rubber manufacturing workers Inclusion and exclusion criteria: Exclusion: women, current smokers at the time of study Study size:	Specificity of agent: Non-specific, tire workers exposed to rubber dust and solvents Type of job history data: Occupational sector as reported by occupational physician.	Studied endpoints: High dysplasia and malignancy cytology Health data collection: Urine samples	Epidemiological measure: Odds ratio Type of statistical analyses performed: Strata v13: Univariate analysis to examine the relationships between suspicious/malignant cytology and variables using the χ^2 trend test. Multivariate analysis using logistic regression.	Type of health effect(s) observed: Working in rubber manufacturing risk of high dysplasia or malignant cytology: OR: 1.32 (95% CI: 1.05-1.65, p=0.02) Relationship between duration of employment and suspicious and malignant cytology (p=0.005): Duration of exposure multivariate OR: 1.03 (95% CI: 1.01 – 1.04; p<0.001) 1–10 years: 4.3% reference 11–20 years: 7.5% OR: 1.79 (95% CI: 1.09-2.93, p=0.02) 21–30 years: 9.1%,	Potential biases: No follow-up through retirement, healthy worker effect, selection bias (only non-smoking men is not representative for all workers), information bias (urine cytology used as only screening tool without reference test) Confounding factors: Smokers excluded but other urothelial cancer risk factors not assessed.	Final diagnosis status not known.

Study design and population	Exposure assessment	Health assessment	Data analysis	Results	Bias/confounding	Remarks
606 rubber manufacturing workers				OR: 2.24 (95% CI: 1.39-3.59, p=0.001) >30 years: 7.6% OR: 1.99 (95% CI: 1.11-3.57, p=0.02) More recent years of exposure OR: 0.97 (95% CI: 0.94-0.99, p=0.02) 1993–1997 reference 2003–2007 OR:0.62 (95% CI: 0.40 to 0.97, p=0.04)		
Reference: Hidajat et al. (2019) (35) Study design: Prospective industrial based cohort Location: Great Britain Time period: 1967-2015 Study population: Cohort: rubber industry workers Control: Population estimates for males in England and	Specificity of agent: Modelled cumulative exposure from EU-EX-ASRUB database for rubber dust, rubber fumes and N-nitrosamines, divided into four quartiles Type of job history data: Survey by predecessor to UK Health and Safety Executive: job health at the time of recruitment into study.	Studied endpoints: Cancer mortality Health data collection: Unknown	Epidemiological measure: Subdistribution hazard ratio Type of statistical analyses performed: Competing risk survival analysis (Fine & Gray, stcrreg in Stata V.15) Exposure analysis in quartiles and continuous metric.	Type of health effect(s) observed: Cancer mortality also described in McElvenny (2018)(36) Rubber dust: Trends (p<0.01) for exposure and SHR for all malignant neoplasms, lung, leukaemia, brain, unknown Rubber fumes: Trends (p<0.01) for exposure and SHR for all malignant neoplasms, lung, leukaemia, and (p<0.05) for multiple myeloma, oesophagus, prostate, pancreas	Potential biases: Healthy worker effect not observed (increased mortality rate). Selection bias (workers age >35), information bias (use of JEM, no information of work duration before 1967). Confounding factors: No information on smoking or other risk factors available.	References of earlier publications on the same cohort: Baxter et al. (1980)(37) McElvenny et al. (2018)(36)

Study design and population	Exposure assessment	Health assessment	Data analysis	Results	Bias/confounding	Remarks
Wales obtained from Office for National Statistics <i>Inclusion and exclusion criteria:</i> Inclusion: men aged over 35 employed more than 1 year in rubber industry Exclusion: women, men under 35 years, cancellation of registration with GP or emigration <i>Study size:</i> 36,441 males (89.2% of original cohort)	Job groups based on British Rubber Manufacturing Association classification					
<i>Reference:</i> McElvenny et al. (2018) (36) <i>Study design:</i> Prospective industrial based cohort <i>Location:</i> Great Britain <i>Time period:</i> 1967-2015 <i>Study population:</i>	<i>Specificity of agent:</i> Non-specific, tire workers exposed to rubber dust and solvents <i>Type of job history data:</i> Survey by predecessor to UK Health and Safety Executive: job health at the time of recruitment into study.	<i>Studied endpoints:</i> Cancer mortality <i>Health data collection:</i> Unknown	<i>Epidemiological measure:</i> Standardized mortality ratios <i>Type of statistical analyses performed:</i> Strata: strate and smrby	<i>Type of health effect(s) observed:</i> Cancer mortality All-cause mortality: SMR: 1.11 (95% CI: 1.10-1.12) All cancer cases: SMR: 1.14 (95% CI: 1.12-1.16) Stomach cancer: SMR: 1.26 (95% CI: 1.18-1.36)	<i>Potential biases:</i> Healthy worker effect unlikely (increased mortality rate observed), information bias (complete work history or exposure unknown), multiple testing bias (increased risk of false positive findings) <i>Confounding factors:</i>	<i>References of earlier publications on the same cohort:</i> Baxter et al. (1980)(37)

Study design and population	Exposure assessment	Health assessment	Data analysis	Results	Bias/confounding	Remarks
Cohort: rubber industry workers Control: Population estimates for males in England and Wales obtained from Office for National Statistics <i>Inclusion and exclusion criteria:</i> Inclusion: men aged over 35 employed more than 1 year in rubber industry Exclusion: women, men under 35 years, cancellation of registration with GP or emigration <i>Study size:</i> 36,442 males (89.2% of original cohort)	Job groups based on British Rubber Manufacturing Association classification			Rectum and rectosigmoid junction cancer: SMR: 1.22 (95% CI: 1.10-1.34) Trachea, bronchus and lung cancer: SMR: 1.25 (95% CI: 1.21-1.29) Bladder cancer: SMR:1.16 (95% CI:1.05-1.28) <i>Sub analysis:</i> Decade of employment start: statistically heterogeneity trends for all causes ($p<0.001$), all neoplasms ($p=0.017$), trachea, bronchus, lung cancer ($p<0.001$) and for bladder cancer ($p=0.015$), bladder cancer only significant in employees that started before 1930. Tyre vs non-tyre sector of rubber industry: Stomach cancer elevated in both sectors but significantly higher in tire sector ($p=0.042$) Job group:	No information on smoking or other risk factors available.	

Study design and population	Exposure assessment	Health assessment	Data analysis	Results	Bias/confounding	Remarks
				Significant heterogeneity for all causes ($p < 0.001$), all malignant neoplasms ($p < 0.001$), trachea, bronchus and lung cancer ($p < 0.001$); highest in "crude materials"		
Reference: Mirabelli et al. (2012) (38) Study design: Retrospective industrial based cohort Location: Italy, Cuneo, Piedmont Time period: 1962 to 2004 for mortality; 1988 to 2003 for bladder cancer incidence Study population: Cohort: tire manufacturing workers Control: Regional, s. ex, age and calendar period specific mortality rates for Death, population of Turin for bladder cancer	Specificity of agent: Non-specific, tire workers exposed to rubber dust and solvents (exposure to beta-naphthylamine excluded) Type of job history data: Company records	Studied endpoints: Mortality, bladder cancer incidence Health data collection: Death certificates from Local Health Authorities, ICD-9 Bladder cancer cases from hospitals in Cuneo province	Epidemiological measure: Standardized mortality ratios, standardized incidence ratios Type of statistical analyses performed: Mortality: OCMAP 3.10, Poisson test to assess monotonic increases by category (men only). Bladder cancer: multivariable Poisson regression using STATA 9.2	Type of health effect(s) observed: Cancer mortality, bladder cancer incidence Men: Increased cancer of nasal cavities: SMR: 4.93 (95% CI: 1.02-14.4) Decreased all causes mortality: SMR: 0.93 (95% CI: 0.86-0.99) Decreased all cancer SMR: 0.81 (95% CI: 0.72-0.91) Decreased Lip, oral cavity and pharynx cancer SMR: 0.48 (95% CI: 0.21-0.95) Decreased lung cancer SMR 0.74 (95% CI: 0.59-0.92) No trends for increased cancer mortality incidence observed for duration of employment or time since first employment,	Potential biases: Healthy worker bias, significantly lower SMR for all cause deaths in men Whole cohort analysed, no stratification by exposure groups Comparison bias from initial workforce selection Bladder cancer mortality in Turin (used as reference population) higher than residents of the Cuneo province Previous employment unknown: wooden	Lost to follow-up: 0.9% Only men included for mortality calculations, as not enough deaths observed in women (32).

Study design and population	Exposure assessment	Health assessment	Data analysis	Results	Bias/confounding	Remarks
<i>Inclusion and exclusion criteria:</i> Inclusion: workers hired between 1962 and 2000 <i>Study size:</i> 9,501 (of which 815 women)				trend for decreased lung cancer mortality mortality incidence for lung cancer observed for duration of employment or time since first employment Bladder cancer mortality in men: No statistically significant difference in rate ratios, but an increasing trend with time since first employment was observed ($p < 0.02$) Bladder cancer incidence: No statistically significant results observed	furniture production common in the province <i>Confounding factors:</i> Smoking and other lifestyle information not collected	
<i>Reference:</i> Rubin et al. (2011) (39) <i>Study design:</i> Retrospective industrial based cohort <i>Location:</i> North America, Wisconsin <i>Time period:</i>	<i>Specificity of agent:</i> Non-specific, tire workers exposed to rubber dust and solvents <i>Type of job history data:</i> Company records received from	<i>Studied endpoints:</i> Cancer mortality <i>Health data collection:</i> Information from the Wisconsin Department of Health, Vital Record Office;	<i>Epidemiological measure:</i> Standardized proportional mortality ratio and standardized proportional cancer mortality ratio	<i>Type of health effect(s) observed:</i> Cancer mortality Total cancer mortality: Male: PMR: 1.53 (95% CI: 1.29-1.81) Female: 2.33 (95% CI: 1.31-3.85)	<i>Confounding factors:</i> Smoking and other lifestyle information not collected <i>Potential biases:</i> Healthy worker bias, data obtained from lawsuit, exposure misclassification,	Focus of this study is on benzene Small number of cancer deaths: 15 total female cancer deaths identified, 144 males

Study design and population	Exposure assessment	Health assessment	Data analysis	Results	Bias/confounding	Remarks
1932-1992 (plant closure) <i>Study population:</i> Cohort: tire manufacturing workers Control: reference population (CDC WONDER) for Wisconsin <i>Inclusion and exclusion criteria:</i> Inclusion: union workers <i>Study size:</i> 2,924 (433 deaths identified)	plaintiff's attorney in lawsuit	coded to ICD-9 and ICD-10)	<i>Type of statistical analyses performed:</i> Breslow and Day or Fisher's exact method.	Cancer mortality male 75-84 years: PMR: 1.54 (95% CI: 1.10-2.09) Cause specific PCMRs for females: significant ($p < 0.05$) for reproductive organs (17.3, 95% CI 4.37-96.07) and lymphoma (5.81, 95% CI 1.58-14.84) Sub analysis based on seniority date: 1932-1950: Brain cancer in males: PCMR: 8.67 (1.77-25.1) Blood cancer in males: PCMR: 42.3 (1.06 - 234.1) Vulva cancer in females: PCMR: 363.1 (9.04 - 1998.99) 1951-1992: Colon cancer in males: PCMR: 3.28 (1.20-7.14) Esophagus cancer in males: PCMR: 4.39 (1.42 - 10.2) Lymphoma in females: PCMR: 27.7 (5.62 - 79.7) 1932-1970:	denominator dilution bias	

Study design and population	Exposure assessment	Health assessment	Data analysis	Results	Bias/confounding	Remarks
				Colon cancer in males: PCMR: 2.55 (1.10-5.04) Brain cancer in males: PCMR: 6.05 (1.96-14.1) Myeloma in males: PCMR: 4.93 (1.35-12.6) Vulva cancer in females: PCMR: 219.6 (5.56-1222.6) Lymphoma in females: PCMR: 22.5 (4.64 - 65.8) 1971-1992 No significant PCMR		
Reference: Sathiakumar et al. (2009) (40) Study design: Retrospective industrial based cohort Location: North America and Canada Time period: 1943 to 2002 for women and 1944 to 1998 for men Study population: Cohort: Men and women working at plants	Specificity of agent: Cumulative exposure estimates to 1,3-butadiene and styrene based on work history and work area/job specific exposure estimates Type of job history data: Company records	Studied endpoints: Lung cancer cases Health data collection: Link with national databases at the end of the study period.	Epidemiological measure: Rate ratio Type of statistical analyses performed: Cox regression with age as time scale, exposure trend analysis: continuous, natural logarithm, deciles Confounders included in model: Year of birth, race, time-dependent	Type of health effect(s) observed: Lung cancer Women exposed vs non-exposed: Butadiene exposure RR lung cancer: 1.99 (95% CI: 1.28 to 3.10) Styrene exposure RR lung cancer: 1.64 95% CI: 1.02 to 2.65 Men: not significant No exposure-response trend in men or women	Confounding factors: Smoking, other exposures in rubber industry (PAHs) Potential biases: Detecting bias	Focus of this study is on 1,3-butadiene and styrene exposure References of earlier publications on the same cohort: Macaluso et al. (1996)(41) Macaluso et al. (2004)(42) Delzell et al. (2006)(43) Sathiakumar et al. (2005)(44)

Study design and population	Exposure assessment	Health assessment	Data analysis	Results	Bias/confounding	Remarks
manufacturing styrene-butadiene rubber exposed to styrene and/or butadiene Control: Unexposed workers in the same plants <i>Inclusion and exclusion criteria:</i> Exclusion: two of the eight plants originally studied, due to lack of detailed work histories <i>Study size:</i> 4,101 women 15,958 men			years since hire, plant and pay status, gender			Sathiakumar et al. (2007)(45) Sathiakumar et al. (2009)(46)
Reference: Sathiakumar et al. (2019) (47) <i>Study design:</i> Retrospective industrial based cohort <i>Location:</i> North America and Canada <i>Time period:</i> 1943 to 2009 for women and 1944 to 2009 <i>Study population:</i>	<i>Specificity of agent:</i> Cumulative exposure estimates to 1,3-butadiene and styrene based on work history and work area/job specific exposure estimates <i>Type of job history data:</i> Company records	<i>Studied endpoints:</i> Cancer mortality <i>Health data collection:</i> Link with national databases at the end of the study period. - US: death certificates and ICD codes from NDI - Canada: CMDB	<i>Epidemiological measure:</i> Standardised mortality ratio <i>Type of statistical analyses performed:</i> Occupational Mortality Analysis Program to compute SMR and 95% CI. Cox regression	<i>Type of health effect(s) observed:</i> Cancer mortality Hourly workers (men and women combined, worked <10 years): Decreased buccal cavity and pharynx cancer SMR: 0.51 (95% CI: 0.26-0.92) Hourly workers (men and women combined, worked >10 years):	<i>Confounding factors:</i> Smoking and other lifestyle factors <i>Potential biases:</i> Healthy worker bias (general mortality SMR: 0.87 (95% CI: 0.85-0.89), misclassification bias	Focus of this study is on 1,3-butadiene and styrene exposure Loss to follow up: 158 men, 128 women. <i>References of earlier publications on the same cohort:</i> Macaluso et al. (1996)(41)

Study design and population	Exposure assessment	Health assessment	Data analysis	Results	Bias/confounding	Remarks
Cohort: Men and women working at plants manufacturing styrene-butadiene rubber Control: general population in states where plants were located <i>Inclusion and exclusion criteria:</i> Inclusion: hourly or salary workers <i>Study size:</i> 4,861 women 17,924 men			<i>Confounders included in model:</i> Payroll status, duration of employment, time since hire, history of exposure to butadiene or styrene.	Increased bladder cancer SMR: 1.42 (95% CI: 1.06-1.86) Increased Leukaemia SMR: 1.39 (95% CI: 1.07-1.76) Decreased liver cancer SMR: 0.66 (95% CI: 0.42-0.98) Hourly workers (men and women combined <20 years since hire) Decreased all cancer SMR: 0.66 (95% CI: 0.57-0.76) Decreased buccal cavity and pharynx cancer SMR: 0.33 (95% CI: 0.07-0.95) Decreased pancreas cancer SMR: 0.35 (95% CI: 0.12-0.83) Decreased non-Hodgkin lymphoma SMR: 0.11 (95% CI: 0.00-0.59) Decreased other myeloid cancer SMR: 0.63 (95% CI: 0.41-0.91) Hourly workers (men and women combined >20 years since hire) Increased bladder cancer SMR: 1.31 (95% CI: 1.02-1.66)		Macaluso et al. (2004)(42) Delzell et al. (2006)(43) Sathiakumar et al. (2005)(44) Sathiakumar et al. (2007)(45) Sathiakumar et al. (2009)(40) Sathiakumar et al. (2009)(46)

Study design and population	Exposure assessment	Health assessment	Data analysis	Results	Bias/confounding	Remarks
				Decreased buccal cavity cancer SMR: 0.66 (95% CI: 0.45-0.94) Decreased larynx cancer: SMR 0.57 (95% CI: 0.31-0.95) Hourly workers (men and women combined, worked <10 years, <20 years since hire): Decreased all cancer SMR 0.56 (95% CI: 0.45-0.69) Decreased oesophagus cancer SMR: 0.00 (95% CI: 0.00-0.95) Decreased lung cancer SMR: 0.64 (95% CI: 0.42-0.94) Non-Hodgkin lymphoma: SMR: 0.00 (95% CI: 0.00-0.65) Hourly workers (men and women combined, worked <10 years, >20 years since hire): Increased Lung cancer SMR: 1.19 (95% CI: 1.06-1.33) Hourly workers (men and women combined, worked		

Study design and population	Exposure assessment	Health assessment	Data analysis	Results	Bias/confounding	Remarks
				>10 years, <20 years since hire): Decreased all cancer SMR: 0.80 (95% CI: 0.65-0.98) Decreased Pancreas cancer SMR: 0.16 (95% CI: 0.00-0.88) Hourly workers (men and women combined, worked >10 years, >20 years since hire): Increased bladder cancer SMR: 1.48 (95% CI: 1.10-1.95) Increased non-Hodgkin lymphoma SMR: 1.36 (95% CI: 1.02-1.77) Increased leukaemia SMR: 1.39 (95% CI: 1.06-1.79) Butadiene: Lung cancer in exposed women: SMR: 2.02 (95% CI: 1.52-2.64); RR vs unexposed women: 1.97 (95% CI: 1.33-2.90); Trend not significant Exposure-response trend for bladder cancer ($p < 0.001$) (both men and women), total		

Study design and population	Exposure assessment	Health assessment	Data analysis	Results	Bias/confounding	Remarks
				leukaemia ($p < 0.05$) and lymphoid cancer ($p < 0.01$) Styrene: Lung cancer in exposed women: SMR: 1.79 (95% CI: 1.35-2.33); RR vs unexposed women: 1.55 (95% CI: 1.01-2.37); Trend not significant Lung cancer in exposed men: SMR: 0.90 (95% CI: 0.83-0.97). RR and trend not significant. Exposure-response trend for lymphoid cancer ($p < 0.05$) and bladder cancer ($p < 0.01$)		
<i>Reference:</i> Vlaanderen et al. (2013) (48) <i>Study design:</i> Retrospective industrial based cohort <i>Location:</i> Germany, five factories in Western Germany producing tires or rubber goods	<i>Specificity of agent:</i> Non-specific (mix of rubber-associated exposures to be expected) <i>Type of job history data:</i> Company records	<i>Studied endpoints:</i> Cancer mortality (prevalence) <i>Health data collection:</i> Health insurance files and death certificates ICD coded by nosologist.	<i>Epidemiological measure:</i> Standard mortality ratio <i>Type of statistical analyses performed:</i> SMRs calculated in SAS v. 9.2 using stratify macro. Heterogeneity	<i>Type of health effect(s) observed:</i> Death: men 4.571 (39%), women 344 (18%) Cancer mortality: men 1.282; women 117 Men: Increased SMR trachea, bronchus or lung cancer: 1.23 (420/341.4) 95% CI: 1.12 to 1.35	<i>Potential biases</i> Healthy worker survivor effect for workers with longer employment <i>Confounding</i> No data on smoking habits or other lifestyle factors available (inherent to SMR	Exposure to mixtures of compounds Cause of death unknown for 7% of deceased men and 10% of deceased women <i>References of earlier</i>

Study design and population	Exposure assessment	Health assessment	Data analysis	Results	Bias/confounding	Remarks
<i>Time period:</i> From 1981 to 2000 (cohort followed until death, or age 85, end of follow-up or loss of follow-up) <i>Study population:</i> Cohort: Men: blue collar rubber industry workers active or retired on January 1st 1981 Women: blue collar rubber industry workers active on January 1st 1981. Reference population: national expected rates (general Western German population) <i>Inclusion and exclusion criteria</i> Inclusion: Actively employed for at least 1 year on January 1st 1981 Exclusion: retired women <i>Study size:</i> Number of exposed: 11,632 men and 1,863 women			across work areas using test suggested by Brewslow and Day (1987) <i>Covariates included in the analysis</i> Duration of employment, year of hire, work area. Not adjusted for smoking.	Increased SMR pleura cancer: 2.57 (21/8.2) 95% CI: 1.59 to 3.93 Decreased SMR liver or gallbladder cancer: 0.70 (33/47.3) 95% CI: 0.48-0.98) Women: Increased SMR trachea, bronchus or lung cancer: 1.81 (19/10.5) 95% CI: 1.09 to 2.82 Increased SMR oral cavity cancer: 5.75 (3/0.5) 95% CI: 1.19 to 16.82 Increased SMR lip, oral cavity or pharynx: 4.26 (5/1.2) 95% CI: 1.38-9.95 Subanalyses of work areas: Heterogeneity observed for lung cancer ($p < 0.0001$) and leukaemia ($p = 0.0145$). No trends observed for years of employment.	approach)	<i>publications on the same cohort:</i> Weiland et al. (1996)(49) Weiland et al. (1998)(50) Straif et al. (1998)(51) Straif et al. (1999)(52) Straif et al. (1999)(53) Straif et al. (1999)(54) Mundt et al. (1999)(55) Straif et al. (2000)(56) Straif et al. (2000)(57)

8.1.1 Cohort studies: overview

Boniol et al. (2016)

In a multinational retrospective cohort study performed by Boniol et al. (2016) (28), 38457 rubber workers from Germany, Italy, Sweden, the UK and Poland were pooled to evaluate the risk of cancer in workers exposed to rubber dust. Eligible participants were workers who had worked at least 1 year in the rubber industry and started after 1 January 1975. Mortality in the cohort was compared to national, regional and WHO mortality databases using SMRs.

Overall bladder cancer mortality was neither elevated nor decreased in rubber industry workers (SMR: 0.80; 95% CI: 0.46-1.38). Lung cancer mortality was decreased in rubber industry workers (SMR: 0.81; 95% CI: 0.70-0.94), as well as mortality from all cancers combined (SMR: 0.81; 95% CI: 0.76-0.87). Stratified analysis showed a significant decreased lung, colorectal and combined cancer mortality risk in several groups of the tyre industry, the mixed industry and all industries combined. Also, a significant increase in multiple myeloma and stomach cancer mortality risk was observed in several groups of the general rubbers goods industry. This study noted healthy worker bias. Furthermore, the study was limited by lack of potential confounding data, a potential for survivor bias and incomplete follow-up data for one country.

Boniol et al. (2017,b)

In a multinational retrospective cohort study performed by Boniol et al. (2017,b) (29), data from 16,026 rubber workers employed for at least one year from Sweden and the UK were pooled to examine cancer incidence compared to the general population. Standardised incidence ratio's (SIRs) were analysed for all cancer types. Stratified analyses were performed for gender and separate analyses was conducted for a 10-years induction-latency period. Heterogeneity between countries was evaluated using Cochrane Q and Higgins I² statistics.

A statistically significant increase in melanoma incidence was observed in Swedish women SIR: 1.75 (CI: 1.07-2.71). Furthermore, no statistically significant increases in cancer incidence were found. When all data was combined, statistically significant decreased incidences were observed for lung cancer SIR: 0.74 (CI: 0.59-0.93), all cancers combined SIR: 0.83 (CI: 0.74-0.92), non-Hodgkin's lymphoma SIR: 0.67 (CI: 0.45-1.00) and prostate cancer SIR: 0.77 (CI: 0.64-0.92). Heterogeneity was observed between the two countries for all cancers combined, colon cancer and melanoma with all data considered ($p < 0.05$).

DeBono et al. (2020)

In a large retrospective cohort study by DeBono et al. (2020) (30), cancer incidence was examined among 13,030 rubber manufacturing workers in Ontario, Canada, using data from the Occupational Disease Surveillance System (ODSS). Workers with accepted compensation claims were followed from 1983 to 2016, and cancer diagnoses were ascertained through linkage with the Ontario Cancer Registry. Cox proportional hazard regression models were used to estimate hazard

ratios (HRs) for site-specific cancers, with adjustments for age, birth year, and sex. Stratified analyses were performed by gender.

A statistically significant decreased risk was found for leukaemia HR: 0.69 (CI: 0.47-0.99). A statistically significant increased risk for lung cancer among female rubber workers was observed HR: 1.39 (CI: 1.07-1.81), while no significant changes in risk were observed in men. Possible confounding due to occupational exposures to other carcinogens and similar lifestyle factors (e.g. smoking) in the reference group was noted. Misclassification of outcomes and healthy workers bias cannot be excluded, although both are likely reduced by the use of diagnostic endpoints rather than mortality data.

De Vocht et al. (2009)

De Vocht et al. (2009) (31) conducted a retrospective industrial cohort study in Poland, evaluating cancer mortality among 11,582 men and 6,054 women employed for at least three months at a Polish tire manufacturing plant between 1950 and 1995, with follow-up until 2002. Occupational exposures were estimated for aromatic amines, inhalable aerosols, and rubber fumes. Risk ratios (RR) for cancer outcomes were estimated for different exposure levels.

Results showed an association between aromatic amine exposure and urinary bladder cancer in both men and women (highest RR: 8.27, 95% CI: 1.03-66.27), and an increased risk of prostate cancer in men (RR: 5.86, 95% CI: 1.04-33.09). Among women, all malignant neoplasms (RR: 2.50, 95% CI: 1.40-4.47) and digestive organ neoplasms (RR: 4.54, 95% CI: 1.37-15.06) were associated with second quartile aromatic amine exposure. Significant trends were observed for increased breast cancer risk in women ($p=0.01$), and for liver/intrahepatic bile duct cancer with inhalable aerosol exposure in both men and women ($p=0.04$). Conversely, inverse associations were found for respiratory, laryngeal, and colon cancers. Potential biases included historic exposures to other carcinogens, healthy worker effect, and lack of data on smoking or exposures outside the plant. This study included an additional seven years of follow-up compared to earlier reports from the same cohort.

Dutheil et al. (2017)

Dutheil et al. (2017) (34) conducted a prospective industrial cohort study in France to assess the risk of cytological abnormalities among 606 male rubber manufacturing workers employed between 1993 and 2013. Eligible participants were male tire workers, women and current smokers were excluded. Occupational history was reported by an occupational physician, and urine samples were collected for cytological analysis. The primary endpoints dysplasia and malignant cytology, with odds ratios calculated.

The study found that employment in rubber manufacturing was associated with an increased risk of dysplasia or malignant cytology (OR: 1.32, 95% CI: 1.05-1.65, $p=0.02$). Risk increased with longer duration of employment. More recent years of exposure were associated with a lower risk (OR: 0.97, 95% CI: 0.94-0.99, $p=0.02$). Potential biases included the healthy worker effect and lack of follow-up after

retirement. Although smokers were excluded, other urothelial cancer risk factors were not assessed. The study also noted limitations of urine cytology and the absence of reference diagnostic tests, with final cancer status unknown.

Hidajat et al. (2019)

Hidajat et al. (2019) (35) carried out a prospective, industry-based cohort study of 36,441 male rubber workers in Great Britain, followed from 1967 to 2015, to investigate associations between occupational exposures and cancer mortality. Eligible workers were men over 35 years of age with more than one year of employment in the rubber industry, men who deregistered with a GP or emigrated were excluded. Mortality in the cohort was compared with that of the male population of England and Wales, using national statistics as the reference. Cumulative exposures to rubber dust, rubber fumes, and N-nitrosamines were modelled using the EU-EX-ASRUB job-exposure database and analysed in quartiles as well as continuously and subdistribution hazard ratios (SHRs) were estimated.

Significant exposure-response trends were observed. For rubber dust, increasing cumulative exposure was associated with higher SHRs for all malignant neoplasms, lung cancer, leukaemia, brain cancer, and cancers of unknown origin. For rubber fumes, significant trends were identified for all malignant neoplasms, lung cancer, leukaemia, multiple myeloma, and cancers of the oesophagus, prostate, and pancreas. Cancer mortality outcomes were reported in McElvenny et al. (2018), which describes the cohort's overall cancer incidence. A healthy worker effect was not apparent, as mortality was elevated relative to population expectations. The study was limited by the absence of information on smoking and other lifestyle confounders. This analysis forms part of a series of investigations on the same cohort, which has been previously reported in Baxter et al. (1980) and updated by McElvenny et al. (2018) (36, 37).

McElvenny et al. (2018)

McElvenny et al. (2018) (36) conducted a prospective cohort study of 36,442 male rubber industry workers in Great Britain, followed from 1967 to 2015, to assess cancer mortality. Eligible participants were men aged over 35 years who had worked for more than one year in the industry, with population mortality rates for England and Wales serving as the reference. Cancer mortality was compared with national population rates using SMRs.

Overall mortality was elevated in rubber industry workers (SMR: 1.11; 95% CI: 1.10-1.12), as was cancer mortality (SMR: 1.14; 95% CI: 1.12-1.16). Significant excesses were found for stomach (SMR: 1.26), rectal (SMR: 1.22), lung (SMR: 1.25), and bladder (SMR: 1.16) cancers. Sub-analyses showed increasing temporal trends for all-cause and lung cancer mortality, but a decreasing trend for bladder cancer, which was only elevated among those employed before 1930 in this cohort. Furthermore, stomach cancer mortality was higher in the tire sector compared with other rubber sectors ($p=0.042$). Notably, a healthy worker effect was not observed, as mortality rates exceeded national averages. However, there was a lack of smoking and lifestyle data. This

study updated earlier analyses of the same cohort reported by Baxter et al. (1980).

Mirabelli et al. (2012)

Mirabelli et al. (2012) (38) conducted a retrospective cohort study among 9,501 tire manufacturing workers in Cuneo, Piedmont (Italy) to study cancer mortality (between 1962 and 2004) and bladder cancer incidence (between 1988 and 2003). Workers hired between 1962 and 2000 were included, with exposure considered non-specific to rubber dust and solvents (but excluding β -naphthylamine). Mortality and incidence rates were compared with regional and population references using SMRs.

Results showed a significantly increase in nasal cavity cancer in men working in tire manufacturing plants (SMR: 4.93; 95% CI: 1.02-14.4), while no consistent trends were observed for overall cancer mortality or incidence by employment duration or latency. Bladder cancer mortality in men showed no significant differences but exhibited an increasing trend with time since first employment ($p < 0.02$), whereas bladder cancer incidence was not increased. This study noted potential healthy worker bias, absence of exposure stratification, and possible confounding by smoking and prior employment (especially wooden furniture industry).

Rubin et al. (2011)

Rubin et al. (2011) (39) conducted a retrospective industrial cohort study in Wisconsin, USA, examining cancer mortality among 2,924 tire manufacturing workers employed between 1932 and 1992. Eligible participants were unionized workers, and cancer mortality rates were compared with those of the general Wisconsin population. Mortality information was obtained from the Wisconsin Department of Health and coded according to ICD-9/10. The primary endpoints were PMRs and PCMRs.

Total cancer mortality was elevated in both men (PMR: 1.53; 95% CI: 1.29-1.81) and women (PMR: 2.33; 95% CI: 1.31-3.85) working in tire manufacturing plants. Stratified analyses showed particularly high PCMRs among early workers (1932-1970), including brain, colon, myeloma, and blood cancers in men and vulvar and lymphoid cancers in women. No significant excesses were observed for those employed after 1971. The study was limited by small numbers of cancer deaths, lack of smoking and lifestyle data, and potential healthy worker bias.

Sathiakumar et al. (2009)

Sathiakumar et al. (2009) (40) conducted a retrospective industrial cohort study in North America and Canada among workers at styrene-butadiene rubber manufacturing plants, covering employment from 1943 to 2002(women)/1944 to 1988(men). The study included 4,101 women and 15,958 men, with cumulative exposures to 1,3-butadiene and styrene estimated from company work records. The primary endpoint was lung cancer incidence (RR), comparing exposed and unexposed workers within the same plants.

Results showed a significant increase in lung cancer risk among exposed women for butadiene (RR: 1.99; 95% CI: 1.28-3.10) and styrene (RR: 1.64; 95% CI: 1.02-2.65), while associations among men were not significant. No clear exposure-response trends were observed in either gender. Potential limitations included lack of smoking data, possible co-exposures to PAHs, and detection bias. Earlier analyses of the same cohort were reported (Macaluso et al., 1996, 2004; Delzell et al., 2006; Sathiakumar et al., 2005, 2007, 2009) (41-46).

Sathiakumar et al. (2019)

Sathiakumar et al. (2019) (47) conducted a retrospective industrial cohort study in North America and Canada among workers at styrene-butadiene rubber manufacturing plants, covering employment from 1943 (women)/1944 (men) to 2009. The cohort included 4,861 women and 17,924 men, with exposure estimates to 1,3-butadiene and styrene based on company records and job-specific exposure data. Cancer mortality was compared with state population rates using SMRs.

Results indicated elevated risks of bladder cancer (SMR: 1.42; 95% CI: 1.06-1.86) and leukaemia (SMR: 1.39; 95% CI: 1.07-1.76) among hourly workers (male and female combined, >10 years employed). Long-term workers (male and female combined, >10 years employed and >20 years since hire) also showed increased mortality from bladder cancer, non-Hodgkin lymphoma, and leukaemia.

Among exposed women, lung cancer risks were elevated for both butadiene (SMR: 2.02) and styrene (SMR: 1.79) exposure, though exposure-response trends were non-significant. Exposure response trends were however significant for bladder cancer and leukaemia (butadiene) and lymphoid cancers (styrene). Potential limitations included lack of smoking data and a healthy worker effect. Earlier analyses of the same cohort were reported (Macaluso et al., 1996, 2004; Delzell et al., 2006; Sathiakumar et al., 2005, 2007, 2009, 2009)(40-46).

Vlaanderen et al. (2013)

Vlaanderen et al. (2013) (48) conducted a retrospective cohort study of rubber industry workers from five factories in Western Germany, covering employment between 1981 and 2000. The cohort included 11,632 men and 1,863 women employed for at least one year as of January 1, 1981. Cancer mortality was compared to national rates for Western Germany using SMRs. Health data were obtained from insurance files and death certificates coded by nosologists.

Among men in the rubber industry, statistically significant excess mortality was observed for lung cancer (SMR: 1.23; 95% CI: 1.12-1.35) and pleural cancer (SMR: 2.57; 95% CI: 1.59-3.93), while among women, increased risks were found for lung cancer (SMR: 1.81; 95% CI: 1.09-2.82) and oral cavity cancer (SMR: 5.75; 95% CI: 1.19-16.82). Heterogeneity across work areas was significant for lung cancer and leukaemia, but no trends were observed by employment duration. Potential biases included a healthy worker survivor effect, and lack of smoking data. Earlier analyses of the same population were reported (Weiland et al., 1996, 1998; Straif et al., 1998, 1999, 1999, 1999, 2000, 2000; Mundt et al., 1999) (49-57).

Table 6 Case-control studies

Study design and population	Exposure assessment	Health assessment	Data analysis	Results	Bias/confounding	Remarks
<i>Reference:</i> Oddone et al. (2013) (58) <i>Study design:</i> Population-based <i>Location:</i> Italy (Lombardy) <i>Time period:</i> 2002-2009 <i>Study population:</i> Women residing in Lombardy, Italy. All female breast cancer incident cases, and controls randomly sampled from the same population <i>Inclusion and exclusion criteria:</i> Inclusion: aged between 35 and 69 years, "blue collar" workers as defined by INPS database Exclusion: diagnosis of breast cancer in 1999-2001, women working in public sector, women who have never	<i>Specificity of agent:</i> Not specific, at least 1 year of employment in rubber industry was considered "exposed" <i>Type of job history data:</i> Record linkage of databases (INPS), available from 1974: Rubber industry (ATECO 81 (Italian statistical classification of economic activities) code: 341, 481, 482)	<i>Case definition:</i> Hospital discharge records (incident cases) ICD IX rev.: 174	<i>Epidemiological measure:</i> Odds Ratio <i>Type of statistical analyses performed:</i> Unconditional logistic regression analysis Adjusted for multiple regression according to the Benjamini-Hochberg method <i>Covariates included in the analysis:</i> Age, province of residency, latency. No information available on other confounders (e.g., smoking).	Non-significant increase in breast cancer cases working in rubber industries: OR: 1.26 90% CI: 1.03-1.54 p-value: 0.062 q-value: 0.394 (adjusted for multiple regression) <i>Subanalyses by duration of employment compared to 0-4 years exposure:</i> 5-9 years: OR: 2.81 90% CI: 1.23-6.39 p-value: 0.039 q-value: 0.634 (adjusted for multiple regression) 10-19 years: OR: 2.22 90% CI: 1.03-4.78 p-value: 0.089 q-value: 0.650 (adjusted for multiple regression) 20+ years OR: 2.71 90% CI: 1.25-5.87 p-value: 0.034	<i>Potential biases:</i> Information bias: occupational exposure identification may be insufficiently detailed Occupational data only available from 1974, resulting in exclusion of women aged over 69 and a loss of years of exposure. Selection bias: not all relevant groups included and potential elevated risk in control group <i>Potential confounding factors:</i> Unknown socioeconomic status, dietary habits, alcohol, medication use, genetic factors,	Exposure to organic solvents or other chemical compounds in rubber sector likely <i>Earlier publication on the same study population:</i> Crosignani (2006)

Study design and population	Exposure assessment	Health assessment	Data analysis	Results	Bias/confounding	Remarks
worked, and white collar workers. <i>Study size:</i> Cases: 11,188 Controls 25,329				q-value:0.634 (adjusted for multiple regression) Trend not significant	reproductive history or physical activity of exposed and controls.	

8.1.2 *Case control studies: overview*

Oddone et al. (2013)

Oddone et al. (2013) (58) conducted a population-based case-control study in Lombardy, Italy (2002–2009), to assess breast cancer risk among women employed in the rubber industry. The study included 11,188 incident breast cancer cases and 25,329 controls, all blue-collar workers aged 35–69 years. Employment history was obtained through INPS records (available from 1974), with at least one year in the rubber industry considered as exposure. Logistic regression analyses adjusted for age, province, and latency showed a non-significant increase in breast cancer risk (OR: 1.26; 90% CI: 1.03–1.54).

Subanalyses by duration of employment suggested a higher risk for women employed 5–9 years (OR: 2.81), 10–19 years (OR: 2.22), and ≥ 20 years (OR: 2.71), though none remained statistically significant after correction for multiple testing. Limitations included potential information bias from insufficiently detailed occupational exposure data, and incomplete employment histories before 1974. An earlier analysis of the same population was published by Crosignani (2006).

Table 7 Meta-analysis studies

Selected studies	Study selection criteria	Health effects / epidemiological measures	Data analyses	Results / pooled estimates	Heterogeneity	Remarks
Reference: Boniol et al. (2017,a) (59) Study design: meta-analysis Number of individual studies included: observational studies (46 cohorts and 59 case-control) from North- and South America, Europe, Asia, New-Zealand Total number of participants/cases: 527,143/55,221	Search period: Studies up to April 2016 in PubMed and references from two previous systematic reviews by Alder et al. (2006) and Kogevinas et al. (1998) Keyword's themes: Study design (case-control/cohort), carcinogens (neoplasm/tumour/malignancy), rubber/tyre industry/workers Search medium: PubMed Exclusion criteria: proportionate mortality ratio approach, non-English written studies Flow chart: Included and non-selected studies described in	Type of health Effects: Cancer incidence and mortality (32 types/organs; most studied: bladder, lung, colorectum, stomach and leukaemia) Stratified analyses: gender, study design, outcome (incidence or mortality), type of industry, type of cancer, workers employed after 1960 and after 1970, workers with the longest duration of employment Unadjusted and adjusted data: RR, OR, SMR, SIR and 95% CI were	Epidemiological measure: Standardized rate ratio (SRR) Statistical analyses performed: heterogeneity assessed with Cochrane Q and Higgins' I^2, publication bias evaluated with Macaskill, Begg, Egger tests and funnel plots, leave-one-out sensitivity analysis conducted	Results: Organ cancer: Overall increased carcinogenic risk for bladder (SRR: 1.36; 95% CI 1.18, 1.57), leukaemia (SRR: 1.29; 95% CI 1.11, 1.52), lymphatic and haematopoietic systems (SRR: 1.16; 95% CI 1.01, 1.31), larynx (SRR: 1.46; 95% CI 1.10, 1.94) No significant increased carcinogenic risk for stomach (SRR: 1.06; 95% CI 0.95, 1.17) and lung (SRR: 1.08; 95% CI 0.99, 1.17) Stratified analysis: Increased risk for cancer mortality and incidence for bladder and leukaemia ($p < 0.05$, bladder I^2: 53-56%, leukaemia mortality I^2: 37% incidence I^2: 4%)	Results of heterogeneity tests: statistically significant heterogeneity for all studies combined, bladder, lung, leukaemia, gallbladder, head and neck, oesophagus, larynx, pleura and body of uterus cancer (no p value reported) Degree of heterogeneity: pleura I^2: 83% lung I^2: 71% bladder I^2: 67% larynx I^2: 50% leukaemia I^2: 35% stomach I^2: 25% thyroid I^2: 0%	Publication bias was suspected for lung cancer, bladder cancer and leukaemia. After applying trim-and-fill, the risk for these cancers did not change

Selected studies	Study selection criteria	Health effects / epidemiological measures	Data analyses	Results / pooled estimates	Heterogeneity	Remarks
	supplementary material <i>Type of quality assessment of individual studies:</i> No formal quality assessment performed. Data extraction was double checked to minimize errors. <i>Type of meta-analyses performed:</i> Random effect meta-analysis including stratified analyses	extracted from the studies		Increased risk for cancer incidence in lung and larynx ($p < 0.05$, lung I^2: 16%, larynx I^2: 29%) Larynx: increase in larynx cancer risk in people working in the general rubber goods industry ($p < 0.05$, I^2: 45%) . For tyre industry no significant increase. Men: increased risk of cancer for larynx, bladder and leukaemia ($p < 0.05$, I^2 34-43%) Women: increased risk of cancer for bladder ($p < 0.05$, $I^2 = 0\%$)		
Reference: Cumberbatch et al. (2017) (60) <i>Study design:</i> Meta-analysis <i>Number of individual studies included:</i> 8 studies about rubber workers (cohort and case control) from the UK.	Search period: Until March 2016 <i>Keyword's themes:</i> Terms for occupation, industry, bladder cancer or urothelial/transitional carcinoma	<i>Type of health effects:</i> Bladder cancer risk and disease specific mortality (DSM) <i>Subgroup analyses:</i> 111 different	<i>Epidemiological measure:</i> Relative risk (RR) <i>Statistical analyses performed:</i> Heterogeneity assessed with I^2,	<i>Results:</i> Bladder cancer risk: Significant elevated bladder cancer incidence for rubber workers (RR: 1.82; 95% CI 1.40-2.38) Bladder cancer mortality: Elevated DSM for rubber	<i>Heterogeneity results:</i> Significant heterogeneity for bladder cancer incidence (I^2: 75.5%; $p < 0.01$) and DSM (I^2: 78.8%; $p < 0.05$)	Publication bias was not significant Potential confounder: confounding by region; many exposed in West

Selected studies	Study selection criteria	Health effects / epidemiological measures	Data analyses	Results / pooled estimates	Heterogeneity	Remarks
<i>Total number of Participants/cases:</i> 5,783.6/609	<i>Search medium:</i> PubMed, Medline, Embase, Web of Science <i>Inclusion criteria:</i> original data reported on occupational bladder cancer risk in adults working in the UK. Sufficient data to calculate CIs. No time or language limits. <i>Flow chart:</i> Included with reasons for exclusion. <i>Type of meta-analyses performed:</i> Random effect meta-analyses including subgroup analyses.	occupational classes for bladder cancer incidence and 43 for DSM. One of these classes is rubber workers. <i>Unadjusted and adjusted data:</i> RR, OR, SMR, SIR and 95% CI were extracted from the studies	publication bias evaluated with Begg's rank correlation test, Egger's linear regression and funnel plots	workers (RR: 1.28; 95% CI 0.57-1.28) (not sign.)		Midlands which has one of the lowest smoking rates in UK

8.1.3 *Meta-analysis studies: overview*

Boniol et al. (2017,a)

In a meta-analysis performed by Boniol et al. (2016) (59), data from 46 cohorts and 59 case-control studies worldwide were pooled to examine cancer risk in 32 organs among workers in the rubber industry. The analysis included 55,221 cancer cases and 471,922 controls. Summary risk estimates were extracted from the individual studies. A random effects model was used to pool the results. Stratified analyses were performed for gender, study design, cancer outcome, type of industry, cancer site and employment duration. Heterogeneity between studies was evaluated using Cochrane Q and Higgins I^2 statistics.

A significant increase in cancer risk was found for bladder cancer SRR: 1.36 (CI: 1.18, 1.57), leukaemia SRR: 1.29 (CI: 1.11, 1.52), lymphatic and haematopoietic systems SRR: 1.16 (CI: 1.01, 1.31) and the larynx SRR: 1.46 (CI: 1.10, 1.94). No increased cancer risk was found for stomach cancer SRR: 1.06 (CI: 0.95, 1.17) and lung cancer SRR= 1.08 (0.99, 1.17). Heterogeneity for all studies combined was statistically significant.

Cumberbatch et al. (2017)

Cumberbatch et al. (2017) (60) studied the association between occupational exposure to rubber dust and the risk of bladder cancer and disease specific mortality (DSM) in a meta-analysis from the UK. Data from 609 bladder cancer cases and 5,174.6 controls from 8 studies were analyzed for bladder cancer risk and data from 53 cases and 0 controls from 2 studies were analyzed for DSM. A random effects model was used to pool the data. Subgroup analyses were performed, where rubber workers were one subgroup. Heterogeneity was evaluated using I^2 statistics.

Rubber workers had a significant increase in bladder cancer risk with RR: 1.82 (CI: 1.40-2.38). The DSM was elevated but not significant with RR: 1.28 (CI: 0.57-1.28). A significant heterogeneity was observed for bladder cancer risk I^2 : 75.5% ($p < 0.01$) and DSM I^2 : 78.8% ($p < 0.05$).

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Appendix 1 Search terms for literature search

Substance name or group	Synonyms
General - proces	
Rubber manufacture/manufacturing	
Rubber mixing	
Rubber vulcanisation	
Rubber weighing	
Rubber mix(ing)	
General - compounds	
Rubber dust	
Rubber damp	
Rubber fume(s)	
Rubber vapo(u)r	
Rubber gases	
Rubber aerosols	
Natural rubber	
Natural rubber latex	
Latex	
Synthetic rubber	
Generic rubber types (ISO, 2017)	
Polyisoprene	Synthetic NR; IR
Polybutadiene	BR
Styrene butadiene	SBR
Acrylonitrile butadiene rubber	Nitrile; NBR
Hydrogenated nitrile rubber	HNBR
Polychloroprene	CR
Butyl rubber	IIR
Halogenated butyl rubber	BIIR; CIIR
Ethylene propylene rubber	EP; EPDM
Epichlorohydrin rubbers	CO; ECO; ETER
Chlorinated polyethylene	CPE; CM
Chlorosulfonated polyethylene	CSM; CSPE
Polyacrylate rubbers	ACM
Ethylene-acrylic rubber	EACM; AEM
Ethylene-vinyl acetate	EVA; EAM
Silicone rubbers	MQ; VMQ; FVMQ; PVMQ
Fluorocarbon rubbers	FPM; FKM
Polyurethane	AU; EU; PU
Polysulfide rubber	OT; EOT

Substance name or group	Synonyms
Special case compounds	
Aromatic amines	
N-nitrosamines	N-nitrosodimethylamine, N-nitrosomorpholine, N-nitrosodibutylamine, N-nitrosodiethylamine, N-nitrosopiperidine; NDMA; NDEA; NDBA; NMor
2-mercapto-benzothiazole	MBT
Benzene	
Styrene	
Dimethyldithiocarbamat	DMDTC
Straight chain and cyclic aliphatic hydrocarbons	
Aromatic hydrocarbons	e.g. benzene, toluene, xylenes, ethylbenzene, dimethylbenzenes, diisopropylbenzenes
Polycyclic aromatic hydrocarbons	halogenated hydrocarbons; e.g. tetrachloroethylene
Isothiocyanates	
Ketones	
Thiazoles	
Aldehydes and alcohols	e.g. formaldehyde, acrolein, acetaldehyde, butyraldehyde and benzaldehyde
Esters and ethers	e.g. phthalate and adipate esters
Sulphur compounds	including carbon disulphide

General terms:

Carcinogenicity
 Carcinogenic
 Mutagenicity
 Mutagenic
 Tumour/tumor
 Cancer
 Carcinogenesis
 Malignan*
 Oncogenic
 Tumorigenic
 Toxic*

Toxicology studies:

Mutagens
Oncogens
Cell transformation
Genotoxicity
Experimental animal studies
Genetic damage
Neoplasms
Animals
Mice
Rats
DNA damage
Unscheduled DNA synthesis
DNA adducts
Genetic process
Strand break
Genetic toxicology
Clastogen
Chromosom*

Epidemiology studies:

Human epidemiology
Occupational exposure
Epidemiology
Epidemiologic studies
Epidemiolog*
Workers
Cohort
Biomonitoring
Occupational disease

Appendix 2 Main generic rubber types

- Natural rubber and natural rubber latex (NR)
- Polyisoprene (synthetic NR) (IR)
- Polybutadiene (BR)
- Styrene butadiene (SBR)
- Acrylonitrile butadiene rubber (also known as nitrile or NBR)
- Hydrogenated nitrile rubber (HNBR)
- Polychloroprene (CR)
- Butyl rubber (IIR)
- Halogenated butyl rubber (BIIR/CIIR)
- Ethylene propylene rubber (EP/EPDM)
- Epichlorohydrin rubbers (CO/ECO/ETER)
- Chlorinated polyethylene (CPE, CM)
- Chlorosulfonated polyethylene (CSM/CSPE)
- Polyacrylate rubbers (ACM)
- Ethylene-acrylic rubber (EACM, AEM)
- Ethylene-vinyl acetate (EVA, EAM)
- Silicone rubbers (MQ, VMQ, FVMQ, PVMQ)
- Fluorocarbon rubbers (FPM, FKM)
- Polyurethane (AU, EU, PU)
- Polysulfide rubber (OT, EOT)

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