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Rubber fumes and dusts

Opinion from the
Scientific Committee on Occupational Exposure Limits

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OPINION FROM THE SCIENTIFIC COMMITTEE ON OCCUPATIONAL EXPOSURE LIMITS FOR RUBBER DUSTS AND FUMES

8-hour TWA:	not applicable
STEL:	not applicable
BLV:	not applicable
Additional categorisation:	No conclusion on cancer category can be made
Notation:	not applicable

The present Opinion was adopted by SCOEL on 2016-09-12.

OPINION EXECUTIVE SUMMARY

Key background documents used for the preparation of this opinion include Scoping Study on behalf of DG EMPL on Occupational exposures and related health effects in the rubber manufacturing industry (JRC, 2014) and IARC monograph 100F on occupational exposure in the rubber-manufacturing industry (IARC, 2012) supplemented by the data published thereafter.

1. DEFINTION:

UK Health and Safety Executive (HSE) has defined "rubber process dust" as "dust arising in the stages of rubber manufacture where ingredients are handled, weighed, added to or mixed with uncured material or synthetic elastomers" which "does not include dusts arising from the abrasion of cured rubber" (HSE 2005). Rubber process dust is determined gravimetrically as the mass of inhalable particles in the workplace air. The composition of the dust varies widely, depending on the raw materials applied. Abrasion products of cured rubber are regarded by HSE as general inhalable/respirable dust and are determined gravimetrically.

HSE defines "Rubber fumes" as "fume evolved in the mixing, milling and blending of natural rubber or synthetic elastomers, or 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" (HSE, 2005). The above definition is related to HSE method for the determination of rubber fumes in air. It includes the cyclohexane soluble fraction of inhalable particles, and does not address vapours themselves for which the individual species limits apply.

ISO definition (ISO, 2014) for Rubber Process 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".

2. COMPOSITION

There are a wide-range of rubber products varying from tyres and tyre products, which account for the majority of the produced rubber, to e.g. rubber hoses, gloves, rubber footwear and clothes. There are more than 20 different base rubbers (either natural or synthetic) each with a unique chemical structure and each of them including a number of different grades available. To achieve this, a wide variety of chemicals are applied in the rubber manufacturing process, depending on the type and desired properties of the final product (IARC 2012).

The composition of the rubber dust formed during handling, weighting and mixing are affected by the raw materials applied. After mixing, the materials are incorporated into the elastomer matrix and will no longer be released as dust, but fumes might be released as a result of increasing temperatures during the mixing. In addition to natural and synthetic elastomers, the applied raw materials include (Datta & Ingham 2001; JRC, 2014):

- 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); and
- other ingredients such as pigments and peptising, blowing and bonding agents.

Rubber fumes can be formed especially during vulcanisation, but also during mixing, moulding and post curing phases of rubber product manufacturing (oven postcuring and e.g. storage of rubber products)). Raw materials affect the composition of rubber fumes. In addition, production processes and process parameters vary, which have an impact on the composition of fumes formed. Composition of rubber fumes varies also during the different phases of rubber manufacturing process depending on process temperatures. Below 100^{o}C volatile raw materials are found in the air whereas reaction and breakdown products are expected at higher temperatures (Forrest 2015). In addition to volatile ingredients, reaction and breakdown products, also volatile impurities in

ingredients affect the final composition of rubber fumes. In general, the range of chemical species that are present in rubber fumes may include: 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), esters (phthalate and adipate esters) and ethers, sulphur compounds (including carbon disulphide) (Gromiec et al. 2002; Forrest 2015; Jönsson et al. 2007). The composition of rubber fumes has also changed over the years. For example, concerns related to PAH- and N-nitrosoamine levels in rubber fumes have resulted in changes in used raw materials decreasing the levels of these compounds in rubber fumes.

In general, workers' exposure to rubber dusts and fumes in Western Europe has also decreased over the years: based on about 14.000 rubber dusts and 6.000 rubber fumes measurements collected within the framework of the European Union Concerted Action EXASRUB, historical exposure trends were estimated between 1970 and 2003 (Agostini et al., 2010, de Vocht et al 2008). Hierarchical mixed effects models taking into account between-factory, between-worker/location and day-to-day variability in exposure concentrations revealed that exposure to rubber dusts and fumes decreased overall on average by 4% and 3% per year, respectively. Significant reductions in rubber dust concentrations were found in all involved countries (DE, NL, PL, UK, SE) for handling of crude materials and mixing and milling (-7% to -4% per year), as well as for miscellaneous workers (-11% to -5% per year), while significant rubber fumes exposure (measured as the cyclohexane soluble fraction of inhalable aerosols) reductions were found in curing (-9% per year) and maintenance and engineering departments (-5% per year). On average exposure levels of rubber dusts and fumes have steadily declined in the

European rubber manufacturing industry during the last three decades of the last century. In addition to differences in exposure reductions and levels among various stages of the production process, large differences between and even within countries however were noted.

3. CHEMICAL AGENT AND SCOPE OF LEGISLATION

Rubber dusts and fumes are not a single chemical entity but rather a highly variable mixture of a variety of different substances. Chemical composition of both rubber dusts and fumes varies significantly depending on compounding, manufacturing process (curing method) and type of manufactured rubber items. Although epidemiological studies have provided scientific evidence for increased cancer risks related to occupational exposures in the rubber manufacturing industry, it has been only in few cases possible to identify specific causative agents or specific processes related to these cancers in the rubber manufacturing industry (bladder cancers caused by beta-naphthylamine and haematological cancers caused by benzene). Moreover, it is not clear whether these risks are still present given the elimination of agents like beta-naphthylamine and benzene, and the current composition and reduced levels of exposure to rubber process dusts and fumes in Europe. Therefore, it is not possible to address rubber dusts and fumes *per se* or related subprocesses as process generated substances under Chemical Agents Directive (CAD) or under Carcinogen and Mutagen Directive (CMD). However, rubber dusts and fumes may contain several specific chemicals, some of which fulfill the criteria of carcinogenic and mutagenic chemical agents in accordance with CMD (e.g. certain PAHs and n-nitrosoamines).

4. HEALTH EFFECTS

Carcinogenicity

IARC (2012) have concluded that there is sufficient evidence in humans for the carcinogenicity of occupational exposures in the rubber manufacturing industry (IARC group 1). According to IARC, occupational exposures in the rubber-manufacturing industry cause leukaemia,

lymphoma, and cancers of the urinary bladder, lung, and stomach. Evidence on other cancers is more limited. It is noted that with exception of bladder cancers caused by beta-naphthylamine and haematological cancers caused by benzene, IARC could not clearly identify specific processes, productions, exposures or compounds, which vary between individual factories, as possible causative agents.

Evidence for increased lung cancer risk comes from several cohort studies especially from the UK, Germany, Poland and China (Dost et al., 2007; deVocht et al., 2009; Mundt et al., 1999; Straif et al., 2000; Szymczak et al., 2003; Pronk et al., 2009) and from the relatively recent case-control studies suggesting an increased lung cancer risk among non-smoking female workers in rubber manufacturing industry (Pohlabeln et al., 2000; Zeka et al., 2006). Exposure to asbestos may have contributed to the excess lung cancer risk in the older cohorts (Straif et al., 2000). In the more recent cohorts, however, no exposure to asbestos is expected.

In older cohorts, urinary cancer risk was clearly associated with exposure to 2-naphthylamine, but in newer cohorts also exposure to other agents (e.g. o-toluidine) may have contributed to the cancer risk (IARC, 2012). Leukemia in older cohorts has been attributed to exposure to benzene (IARC, 2012). Increased risk for lymphatic cancers, including multiple myeloma, has been observed e.g. in German and UK cohorts (Mundt et al., 1999; Dost et al., 2007). In a German cohort (Mundt et al, 1999; Streif et al., 2000) also excess risk for stomach cancers was observed. Similarly, increased risks for stomach cancers were observed also in Chinese, Brasilian, Polish and UK cohorts (Li and Yu, 2002; Neves et al., 2006; deVocht et al., 2009; Dost et al. 2007). No clear association between stomach cancer and N-nitrosoamine exposure were however observed.

After the IARC evaluation two Italian cohort studies have been published (Pira et al. 2012, Mirabelli et al. 2012) and an extended follow-up from a German cohort (Vlaanderen et al. 2013). No statistically significant excess for cancer cases were observed in the two Italian cohorts. In the study of

Vlaanderen et al. (2013), statistically increased risk was found for cancers of the lung and pleura, and non-statistically increased risk for cancers of the stomach, esophagus, larynx, bladder, oral cavity, and leukaemia. None of these risks showed relation with duration of exposure. Also a non-statistically decreased risk for prostate cancer and cancers of the lymphatic system was observed. In a study by Boniol et al (2016) anonymized data from cohorts of rubber workers first employed since 1975 for at least 1 year in 64 factories from Germany, Italy, Poland, Sweden, and the UK were pooled. No increased cancer mortality was noted. The authors of this study suggested that general hygienic improvements and changes in the composition of the rubber dusts and fumes might have had a beneficial effect. However, it is noted that the duration of the follow-up and the latencies in this study are still somewhat limited.

Genotoxicity

A recent systematic review of the genotoxic risk in the rubber manufacturing industry has been published (Bolognesi and Moretto, 2014). It has been concluded that there are substantial differences between the companies and control measures, due to the composition of the exposure mixture and the processing which differ between the type of rubber goods being manufactured (e.g: tires vs general rubber goods), and even between different types of the same rubber good (e.g.: car vs truck tires).

Studies have been conducted *in vitro* with airborne particulates and fumes collected by either ambient or personal sampling using common (e.g. TA98, TA100) and specific (YG1021, YG1024, YG1041) *S. typhimurium* strains (Fracasso et al., 1999; Monarca et al. 2001; Vermeulen et al, 2000a,b; Vermeulen et al., 2001). Some evidence of mutagenicity was observed, but the identification of any classes of chemicals or industrial processes specifically associated with the mutagenic activity of environmental samples was not possible. The specific “company” appears

to be the main determinant for mutagenicity, likely because of specific chemicals, and industrial processes and practices.

A number of biomonitoring studies have been conducted assessing different transient and permanent genotoxic responses that include urinary mutagenicity (marker of exposure), DNA adducts in different surrogate tissues (peripheral lymphocytes and urothelial exfoliated cells, considered a measure of the dose at the target), DNA single strand breaks determined by Comet assay in peripheral lymphocytes (considered markers of early effect), chromosomal alterations, SCE and micronuclei frequency (marker of chromosomal damage), and frequency of *hprt* mutants in peripheral lymphocytes (as marker of expressed genetic damage). Most of these studies suffered from low statistical power due to small sample sizes.

Six studies report on urinary mutagenicity (*S. Typhimurium* and *E. Coli*) (Vermeulen et al., 2000a; 2000b; 2003; Peters et al., 2008; Falk et al., 1980; Moretti et al., 1996). Mixed results have been obtained in studies on tyre factories, while studies in rubber factories in the Netherlands showed increased urinary mutagenicity during the work week (Vermeulen et al, 2000a; 2000b; Vermeulen et al 2003; Peters et al 2008). A significant confounding by lifestyle factors, namely environmental and mainstream tobacco smoke has been observed.

Levels of DNA adducts in urothelial cells and peripheral blood lymphocytes, showing mixed results and lack of correlation between bladder and blood cell adducts (Talaska et al., 2002; Schoket et al., 1999; Vermeulen et al, 2002; Peters et al, 2008).

DNA damage in workers from different factories in various countries was assessed using different protocols and parameters, thus preventing study comparisons. Mixed results have been obtained in these studies (Somorovska et al., 1999; Moretti et al., 1996; Laffon et al., 2006; Cemeli et al., 2009; Zhu et al., 2000).

Chromosomal damage (chromosomal aberrations, micronuclei frequency or SCE) was investigated in 10 studies, 6 of which reported positive results. However, the only statistically powerful study (Musak et al., 2008) showed a borderline increase in chromosomal aberrations in tire plant workers, with high interindividual variability. The other studies have low potency, showed both positive and negative results and are dated before year 2000 (for review see Bolognesi and Moretto, 2014). Most recently Li et al. (2011) report a reduction in telomere length in workers in a Swedish rubber manufacturing industry but a number of issues prevents a clear interpretation of the data.

Gene mutations (*HPRT* mutant lymphocyte assay) have been observed, in the past, in a plant using polymerized butadiene and styrene-butadiene copolymers (Abdel-Rahman et al., 2001), but not recently with improved exposure control (Wickliffe et al., 2009).

In conclusion, companies and the industrial processes differ and the latter also changed over time. This may explain the mixed results obtained testing airborne particulates and fumes, or during biomonitoring of workers. The available data on biomonitoring in exposed workers suggest a genotoxic hazard in certain plants, possibly in the past, but they are inadequate to estimate the genotoxic risk associated with the exposure in different manufacturing processes, and do not allow the identification of the specific causative agent. As such, these data do not provide clear indication on the mechanism and the causative agent of the increased cancer risk observed in rubber industry.

Non-cancer health effects

Regarding non-cancer effects in humans, there are few studies, which associate work in the rubber industry, especially exposure to rubber dusts and fumes with decreased pulmonary function and increase in self-reported respiratory symptoms, such as chronic cough (Attarchi et al., 2013; Zuskin et al., 1996; Jönsson et al., 2007, 2008; Meijer et al.,

1998). The levels of respirable particles in the workplace air has been high (≥5 mg/m3) in those studies showing clearest effects on lung function (Attarchi et al., 2013, Zuskin et al., 1996). The available epidemiological studies in the rubber industry do not provide clear indication on the increased mortality to non-cancer respiratory or cardiovascular diseases or to other non-cancer diseases (Pira et al., 2012, Mirabelli et al., 2012, Dost et al., 2007, Wingren et al., 2006; Gustavsson et al, 1986; Ke and Shungzhang et al., 2002; Ietri et al., 1997). Reproductive health in the rubber industry has been investigated to a minor extent. The only large study is a Swedish Population Registry and Medical Birth Register linkage study among 18,518 rubber factory employees from 12 locations in Sweden involving 17,918 children. It found an altered sex ratio, increased risk for multiple births and reduced birth weight when both mother and father worked in the rubber industry (Jakobsson and Mikocky, 2009). When only mothers were exposed, these effects became less or non-significant. The significance of these findings is unclear, and needs support from further studies.

Natural rubber (latex) is a well-known skin sensitizer causing protein urticaria. Latex has caused also cases of occupational asthma and rhinoconjunctivitis in the use and manufacturing of rubber products e.g. gloves (Fish, 2002). In addition, different chemicals used in the manufacturing of rubber products have caused skin sensitization in humans mostly in the use of rubber products (e.g. gloves). These include some accelerators, e.g. thiuram-, dithiocarbamate-, benzothiazole- and thiourea compounds and p-phenylenediamine -derivatives used as an antioxidants in black rubber products (Warburton et al., 2015ab, Buttazzo et al., 2016).

Conclusions

In conclusion, carcinogenic and genotoxic risks have been observed in workers employed in the rubber manufacturing industry. Identified carcinogens, which may be (or have been) released in the process include for example aromatic amines (o-toluidine), N-nitrosamines, aromatic

solvents (benzene) and certain polycyclic aromatic hydrocarbons (PAHs). Also, small amounts of 1,3-butadiene may be released in processing of styrene-butadiene-rubber. In the past, also exposure to known human carcinogens such as 2-naphthylamine, asbestos and benzene has occurred in the industry, which needs to be taken into account when interpreting the epidemiological data.

There is no agreement on an overall suitable proxy of the complex mixture of exposures correlating with cancer risk in the rubber manufacturing industry. Therefore, it is not possible to identify an exposure-response for cancer risk in the rubber manufacturing industry. In addition, the composition of the rubber dusts and fumes varies depending on raw materials, production processes, process parameters, and depending on the exact phase (handling and weighting, mixing, moulding, vulcanisation and post curing phase) of the rubber manufacturing process. It has only partially been possible to identify specific processes, productions, exposures or compounds, as possible causative agents for bladder cancer, leukaemia and lymphoma, but not for other increased cancer risks. There have also been major changes in the exposures within the European rubber manufacturing industry over the recent decades and many chemicals, known or suspected to be carcinogenic or causing other diseases, have been replaced by other compounds. Thus, it is unclear whether the current (post-2010) exposures in the rubber manufacturing industry still pose genotoxic and carcinogenic risks. Because of the highly variable nature of rubber dusts and fumes, general limit values for rubber dusts or fumes may not effectively target carcinogenic and genotoxic compounds present in rubber industry and may have limited impact on cancer risk. Future emphasis should be in the identification of relevant exposure proxies, which might be better predictors of health risks in rubber industry. These may include, among others, N-nitrosamines, PAHs, aromatic amines or combinations of these compounds. Development of these exposure proxies requires new exposure data regarding the current exposures in the rubber

manufacturing industry and future epidemiological studies with documentation on exposures and an effort to determine exposure-response relationships for specific chemical agents and/or biologically relevant exposure proxies.

Due to the variable composition, lack of suitable exposure proxy correlating with cancer risk and lack of recent (post-2010) data on the composition of the rubber dusts and fumes, it is not possible to give a recommendation for a limit value for rubber dusts or fumes, or quantitate the cancer risk related to the exposure to rubber dusts or fumes. Given the clear evidence of an increased cancer risk in the rubber manufacturing industry, the exposure to any known carcinogens (listed in the beginning of this chapter) released during the processes shall be minimized to as low levels as technically and practically possible.

Dusts released during handling, weighting and mixing are composed of the constituents of the raw materials applied and therefore, substance-specific exposure limits may be applied to each individual component or group of components, where appropriate.

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