Public Draft

Gezondheidsraad

Occupational exposure during iron and steel founding

Evaluation of the carcinogenicity and genotoxicity

Subcommittee on the Classification of Carcinogenic Substances of the Dutch Expert Committee on Occupational Safety, a committee of the Health Council of the Netherlands

Comments before April 6, 2019

Preferentially by E-mail

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All comments received and the response of the Committee will be publicly available (www.gezondheidsraad.nl) from the moment of presentation of the final report.

Contents

Samenvatting

Op verzoek van de Minister van Sociale Zaken en Werkgelegenheid heeft de Gezondheidsraad beoordeeld of beroepsmatige blootstelling tijdens het ijzer- en staalgieten een genotoxisch effect heeft en tot kanker kan leiden. Het advies is opgesteld door de Subcommissie Classificatie kankerverwekkende stoffen - hierna aangeduid als de commissie –, een subcommissie van de vaste commissie Gezondheid en beroepsmatige blootstelling aan stoffen. De Gezondheidsraad heeft een vaste rol bij de bescherming van werknemers tegen mogelijke schadelijke effecten van stoffen waar zij tijdens hun werk mee in aanraking kunnen komen. Meer informatie over die rol staat op www.gezondheidsraad.nl.

Het gieten van ijzer en staal

In dit advies wordt de beroepsmatige blootstelling tijdens het ijzer- en staalgietproces als geheel in ogenschouw genomen. Individuele stoffen die in de emissie tijdens het ijzer- en staalgietproces kunnen voorkomen worden niet afzonderlijk beoordeeld. Het ijzer- en staalgietproces omvat het maken van mallen, het smelten en behandelen van de basismaterialen, het gieten in mallen, het laten afkoelen van het gegoten materiaal en het verwijderen van de mallen. De ijzer- en staalproducten die hieruit voorkomen kennen een brede toepassing in onder meer de auto- en scheepvaartindustrie, constructie-industrie en verpakkingsindustrie.

Beoordeling kankerverwekkende en mutagene eigenschappen

De commissie beoordeelt aan de hand van de beschikbare wetenschappelijk literatuur of er aanwijzingen zijn dat een stof genotoxisch en kankerverwekkend is en hoe groot de bewijskracht daarvoor is. Genotoxische stoffen met mutagene eigenschappen kunnen het erfelijk materiaal in de cel blijvend veranderen (mutatie of genafwijking). Hierdoor kunnen zij kankerverwekkend zijn. Aan de hand van de bewijskracht doet de commissie vervolgens voorstellen om de stof te classificeren in gevarencategorieën: één die aangeeft hoe groot de bewijskracht is dat de stof mutageen is in geslachtscellen, en één die aangeeft hoe groot de bewijskracht is dat de stof tot kanker kan leiden. De categorieën zijn gebaseerd op EU-verordening (EG) 1272/2008 over de classificatie van stoffen. Op basis van de voorstellen van de commissie kan de minister besluiten om de stof al dan niet als mutageen in geslachtscellen en/of als kankerverwekkend aan te merken.

Advies aan de minister

Op basis van de beschikbare gegevens beveelt de commissie aan om beroepsmatige blootstelling tijdens het ijzer- en staalgieten te classificeren als mutageen in geslachtscellen in categorie 2 ("*stof die reden geeft tot bezorgdheid voor de mens omdat zij mogelijk erfelijke mutaties in de geslachtscellen van mensen veroorzaakt*"). De mutageniteit wordt veroorzaakt door een stochastisch genotoxisch werkingsmechanisme.

De commissie concludeert dat beroepsmatige blootstelling aan de uitstoot van stoffen tijdens het ijzer- en staalgieten kankerverwekkend is voor de mens, en beveelt aan deze blootstelling in categorie 1A ("*stof is kankerverwekkend voor de mens*") te classificeren.

Executive summary

At request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands assessed whether occupational exposure during iron and steel founding may induce genotoxic effects and may cause cancer (annex A). The assessment is performed by the Subcommittee on Classifying carcinogenic substances - hereafter called the committee - of the Dutch Expert Committee on Occupational Safety of the Health Council. The Health Council has a permanent task in the protection of employees to harmful health effects of substances to which they may be exposed during work. More information on this task can be found on the website www.gezondheidsraad.nl.

Iron and steel founding

In the present advisory report, the evaluation accounts for the occupational exposure during the iron and steel founding process as a whole. Evaluation of individual substances that can be found in the emission of iron and steel founding are not considered. Iron and steel founding comprises creating a mould, melting and treating the basic material, pouring in moulds, cooling down the metal, and removing the mould. Iron and steel products are widely used, such as in the car and shipping industry, construction industry and the packaging industry.

Assessment of genotoxicity and carcinogenicity

Based on the available scientific literature, the committee assesses the potential genotoxic and carcinogenic properties of the substance in question. If there are indications for such properties, it recommends classifying the substance in two hazard categories, which represent the grade of evidence that the substance is mutagenic in germ cells (a measure for genotoxicity), and that the substance is carcinogenic. The categories are based on the hazard categories set by the European Commission (EU-guideline (EG) 1272/2008). The recommendation can be used by the Minister to decide whether the substance should be listed as mutagenic in germ cells and/or carcinogenic.

Recommendation

Based on the available data, the Committee recommends classifying occupational exposure during iron and steel founding as a germ cell mutagen in category 2 (“*Substances which cause concern for humans owing to the possibility that they may*

induce heritable mutations in the germ cells of humans"). The mutagenicity is caused by a stochastic genotoxic mechanism.

The committee concludes that exposure during iron and steel founding is carcinogenic to humans, and recommends classifying the exposure in category 1A ("*known to have carcinogenic potential for humans*").

1 Scope

1.1 Background

In the Netherlands a special policy is in force with respect to occupational use and exposure to carcinogenic substances. Regarding this policy, the Minister of Social Affairs and Employment has asked the Health Council of the Netherlands to evaluate the carcinogenic properties of substances, and to propose a classification. In addition to classifying substances as carcinogenic, the Health Council also assesses the genotoxic properties of the substance in question, and proposes a classification on germ cell mutagenicity. Both classifications are based on the criteria set by the European Parliament (EU Regulation No. 1272/2008), and expressed in the form of standard sentences (see Annex G and H for mutagenicity and carcinogenicity, respectively).

This report contains the evaluation of the mutagenicity and carcinogenicity of occupational exposure during iron and steel founding. The evaluation accounts for the occupational exposure during the iron and steel founding process as a whole. Evaluation of individual substances that can be found in the emission of iron and steel founding are not considered.

1.2 Committee and procedure

The evaluation is performed by the subcommittee on Classifying Carcinogenic Substances of the Dutch Expert Committee on Occupational Safety of the Health Council, hereafter called the committee. The members of the committee, including the consulted experts, are listed on the last page of this report.

In 2018, the President of the Health Council released a draft of the report for public review. The committee has taken these comments into account in deciding on the final version of the report. The comments, and the replies by the committee, can be found on the website of the Health Council.

1.3 Data

The evaluation and recommendation of the committee is standardly based on scientific data, which are publicly available. The starting points of the committees' reports are, if possible, the monographs of the International Agency for Research on Cancer (IARC). This means that the original sources of the studies, which are mentioned in the IARC-monograph, are reviewed only by the committee when these are considered most

relevant in assessing the carcinogenicity and genotoxicity of the substance in question. In the case of exposure during iron and steel founding, such an IARC-monograph is available, of which the summary and conclusion is inserted in Annex A.

More recently published data were retrieved from the online databases Medline, Toxline, Chemical Abstracts, and RTECS. The last updated online search was in October 2018. The literature search was based on the following key words: foundry or foundries, iron foundry/foundries, steel foundry/foundries, occupational exposure, cancer, carcinog*, mutag*, genotox*.

2 Identity of the substance

The information in this chapter is abstracted from IARC Monographs.[1-3]

2.1 Name and other identifications

The present evaluation relates to occupational exposure to the emission of iron and steel founding. It concerns exposure to the whole emission; individual components that can be present in the emission are not evaluated separately.

2.2 Composition of emission formed during iron and steel founding

The iron and steel foundry industry is very diverse in materials and processes, resulting in occupational exposure to a wide variety of substances (gases, aerosols and particles). Substances found in the emission of iron and steel founding are for instance respirable (metal) dust and quartz, carbon monoxide and carbon dioxide, aliphatic hydrocarbons (*e.g.*, benzene), and organic binder materials (*e.g.*, isocyanates, phenol, formaldehyde, various amines). In airborne pyrolysis products (coal tar pitch) substantial quantities of polycyclic aromatic compounds can be found, such as pyrene and benzo(a)pyrene. A list of all the main substances to which workers are likely exposed during iron and steel founding is given by IARC (1984).[1]

2.3 Physicochemical properties

Since the emission of iron and steel founding is a complex mixture of gases, aerosols and particles, no physicochemical properties are specified.

3 International classification

3.1 European Commission

Not evaluated.

3.2 IARC

In 2012 IARC concluded that there is sufficient evidence in humans for the carcinogenicity of occupational exposures during iron and steel founding.[3] Occupational exposures during iron and steel founding cause cancer of the lung. No data on the carcinogenicity to experimental animals of mixtures present in iron and steel founding were available to the Working Group. Occupational exposures during iron and steel founding are carcinogenic to humans (Group 1). A summary of the evaluation and conclusion by IARC is given in Annex A.

3.3 The Health Council of the Netherlands

Not evaluated.

4 Monitoring

4.1 Environmental exposure monitoring

Exposure during iron and steel founding implies exposure to a complex mixture, suggesting that varying markers may be applied for the measurement of exposure in workplaces. Overall, in the literature no preference for a certain exposure marker is identified. However, in human studies on the carcinogenic potential of occupational exposure during iron and steel founding, airborne concentrations of respirable dust and quartz, carbon monoxide, binder compounds, polycyclic aromatic hydrocarbons, metals, and refractory ceramic fibers have been used to assess exposure to the emission of iron and steel founding.

4.2 Biological exposure monitoring

No specified.

5 Manufacture and uses

5.1 Manufacture

Iron and steel founding is a process of casting iron and steel products. It starts with creating a mould in which melted iron or steel are poured. The casting is then cooled down until the metal is solidified, after which the mould is removed from the metal core.

Depending on the required iron or steel product, various materials are used as moulds (*e.g.*, sand, ceramics, metals), and as principle material (*e.g.*, iron ores, scrap, steel alloys). Also, different types of furnaces (*e.g.*, cupolas, electric arc, induction, reverberatory and crucible furnaces) are used to heat and melt the material, and different melting temperatures and procedures are followed. The melting process includes melting the principle material, refining the melt to remove deleterious gases and elements to avoid casting defects, adjusting the melt chemistry by adding other materials to get the required composition, and degassing to remove gasses (*e.g.*, hydrogen) in the melted metals.

5.2 Identified uses

Iron and steel products are used in a variety of applications, such as in the car and shipping industry, construction industries, packaging industry, and in machinery. It is estimated that worldwide in 2017 more than 1,630 million tonnes of steel were produced, of which about 624,000 tonnes in the Netherlands.

6 Summary of toxicokinetics

6.1 Absorption, distribution and elimination

Data are available on certain individual substances that can be found in the emission of iron and steel founding, but no such data are available for the emission as a whole. Since in the present report only the emission as a whole is evaluated, this topic is not further discussed.

6.2 Toxicokinetics

Data are available on certain individual substances that can be found in the emission of iron and steel founding, but no such data are available for the emission as a whole. Since in the present report only the emission as a whole is evaluated, this topic is not further discussed.

7 Germ cell mutagenicity

7.1 Summary and relevance of the provided information on (germ cell) mutagenicity

7.1.1 Summary of genotoxicity tests in vitro

Mutagenicity

The results of the mutagenicity tests are shown in Annex B. Overall samples of aerosols and fumes, which are formed during iron and steel founding, and which are obtained from several plants in various countries, induce reverse mutations in *Salmonella typhimurium* strains TA98 and TA100.

Clastogenic and aneugenic effects

Humfrey et al. (1996) tested whether fume extracts from binder system sites in an iron foundry, could induce micronuclei in a human lymphoblastoid cell line.[4] As shown in Table 1, the extracts increased the number of cells with micronuclei in a dose-dependent matter. No other studies are available.

Table 1. Micronuclei formation

Method and reference	**Cell type and conditions**	**Source test substance and doses applied in test system**	**Results**	**Reliability** (Annex I)
Micronucleus test Humfrey et al. (1996)[4]	MCL-5 cells (human lymphoblastoid cell line) 500 binucleated cells per dose applied were scored for micronuclei	Iron foundry fumes sampled from 3 different binder systems (in casting area): - A: green sand binder - B: shellmould binder - C: cold box amine gassed binder Final concentration of fume suspension applied: 0,1, 5, and 10 µg/ml	Statistically significant dose-related increase in number of micronucleated cells/500 binuclear cells reported Significant cytotoxicity observed at highest dose applied (based on cut-off of 20% decrease in viability)	Reliability 2

Unscheduled DNA synthesis

Humfrey et al. (1996) also reported that the fume extracts induced unscheduled DNA synthesis in a dose-dependent matter (see table 2).[4] No other studies are available.

Table 2. Unscheduled DNA synthesis.

Method and reference	**Cell type and conditions**	**Source test substance and doses applied in test system**	**Results**	**Reliability** (Annex I)
Unscheduled DNA synthesis Humfrey et al. (1996)[4]	Primary rabbit tracheal cells and rat hepatocytes	Iron foundry fumes sampled from 3 different binder systems (in casting area): - A: green sand binder - B: shellmould binder - C: cold box amine gassed binder Concentration of fume suspension applied: - Rabbit cells: 0, 100, 500 and 1,000 µg/ml - rat cells: 0, 50, 100, 200 and 500 µg/ml Positive control rabbit cells: 1,6-dinitropyrene Positive control rat cells: 2-acetylaminoflurene	*Rabbit tracheal cells* Statistically significant dose-related increase in net nuclear grains reported *Rat hepatocytes* Statistically significant dose-related increase in net nuclear grains reported Overall, fumes suspensions from various binder systems showed differences in potency, the lowest potency found in binder C. Significant cytotoxicity noted at or above 500 µg/ml in rabbit tracheal cells; no toxicity observed in rat hepatocytes	Well-performed study Reliability 1

Conclusion on genotoxicity

In various in vitro studies, extracts of fumes or aerosols of the emission of iron and steel founding significantly induced gene mutations in bacteria. In addition, extracts of the fumes increased the number of cells with micronuclei in a dose-dependent way. Also increased unscheduled DNA-synthesis is observed, indicating that fumes of iron and steel founding may affect DNA. The committee notes that the number of studies on in vitro genotoxicity (other than mutagenicity tests) is limited, and that the study on unscheduled DNA synthesis does not give prove of genotoxicity, but rather is a marker for exposure that supports the suggestion of genotoxicity. However, it is clear to the

committee that extracts of the emission of iron and steel founding induces gene mutations in vitro.

7.1.2 Summary of human data relevant for germ cell mutagenicity

Data on gene mutations, other genotoxic effects and effects on DNA are summarized in Annex C. A few small studies have been performed with iron and steel foundry workers from which blood samples were taken. In all these studies the concentration of benzo(a)pyrene served as exposure marker. In a single study, no increased HPRT mutations were found in white blood cells with and without adjustment for smoking habits. In another single study, no difference was found in the frequency of micronuclei in white blood cells between workers exposed to high and low concentrations of benzo(a)pyrene (high, 3.1 - 13.7 µg/m^3; low, 0.0 – 0.006 µg/m^3).[5] Two other studies could not be interpreted by the committee due to low quality. In four studies, moderate to clear increases in DNA-adduct formation was observed, in two of these studies reaching statistical significance.

7.1.3 Summary of genotoxicity tests in mammalian somatic or germ cells in vivo

Currently, no animal experiments have been performed on the genotoxic activity of iron and steel founding samples.

7.2 Comparison with the CLP-criteria

According to the criteria in Annex VI of the European regulation No. 1272/2008 (see annex G), classification as a mutagen in category 1 is warranted when positive evidence of *in vivo heritable germ cell* mutagenicity in humans (1A) or mammals (1B) has been reported. For exposure to the emission of iron and steel founding, no data have been found on human or animal germ cell mutagenicity. Therefore, the committee concludes that there is a lack of evidence to classify exposure during iron and steel founding in category 1.

In addition, substances may be categorized in 1B if there are "*positive results from in vivo somatic cell mutagenicity tests in mammals, in combination with some evidence that the substance has potential to cause mutations to germ cells*". The latter may be based on a) "*supporting evidence from mutagenicity or genotoxicity tests in germ cells in vivo*", or b) "*by demonstrating the ability of the substance or its metabolites to interact with the genetic material of germ cells*" (see Annex G). Currently, no in vivo mutagenicity or other genotoxicity tests on germ cells have been performed on samples, which were taken during iron and steel founding.

If substances do not meet the criteria for classification in category 1, they may be classified in category 2 if there is "*positive evidence from experiments in mammals and/or in some cases from in vitro experiments obtained from a) somatic cell mutagenicity tests in vivo, in mammals*", or b) "*other in vivo somatic cell genotoxicity tests, which are supported by positive results from in vitro mutagenicity assays*" (see Annex G). Moreover, "*substances which are positive in in vitro mammalian mutagenicity tests, and which also show chemical structure activity relationship to known germ cell mutagens, shall be considered for classification as category 2 mutagens*". Extracts from the emission of iron and steel founding showed to be mutagenic in vitro. Limited evidence is available on the clastogenic properties in vitro and in vivo. In addition, in the emission of iron and steel founding, substances may be found with known mutagenic properties (*e.g*, coal tar and benzo(a)pyrene). Taking into account these findings, the committee is of the opinion that exposure to the emission of iron and steel founding should be classified in category 2. Most likely the mutagenic activity is caused by a stochastic genotoxic mechanism of action.

7.3 Conclusion on classification and labelling for germ cell mutagenicity

Based on the available data, the Committee recommends classifying exposure during iron and steel founding as a germ cell mutagen in category 2 ("*Substances which cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans*"). In addition, the committee concludes that the mutagenic components which can be formed during iron and steel founding act by a stochastic genotoxic mechanism.

8 Carcinogenicity

8.1 Summary and relevance of the provided information on carcinogenicity

8.1.1 Observations in humans

Available data on cancer development in humans are summarized in Annex D (meta-analyses), E (cohort studies), and F (case-control studies). The publications contain data from several studies of industrial workers worldwide, which are exposed to the emission of iron and steel founding at varying exposure levels.

Meta-analyses

Four meta-analyses have been published on occupational exposure during iron and steel founding. Rota et al. (2014) used data from 13 cohort studies.[7] They associated occupational exposure during iron and steel founding with increased cancer mortality in the lungs (pooled relative risk (RR) 1.31, 95% confidence interval (95%CI) 1.07-1.61), larynx (pooled RR 1.48, 95%CI 1.14-1.91) and bladder (pooled RR 1.38, 95%CI 1.14-1.91).[7] In addition, Bosetti et al. (2006) found positive associations for lung, respiratory and bladder cancer.[8] The pooled RR (95%CI) were 1.40 (1.32-1.49), 1.40 (1.31-1.49) and 1.29 (1.06-1.57), respectively. Alicandro et al. (2016) did not find an association for lymphatic and haematopoietic neoplasms; data on possible neoplasms or cancer at other sites of the body were not analysed.[9] Singh et al. (2018) is difficult to interpret because of the limited reporting.[10]
Uncertainties and limitations. In the meta-analyses by Rota et al. and Bosetti et al., the authors reported the presence of heterogeneity between the studies. This is not surprising to the committee, because the exposure in the iron and steel foundries vary considerably among each other. In addition, the committee noted that in none of the meta-analysis a description was given on how the authors assessed the quality of the studies, and to what degree each study contributed to the pooled relative risk estimates. Furthermore, no sensitivity analyses were performed to account for smoking habits. Regarding the data on iron and steel workers, in most cohort studies data on smoking habits were not collected or reported.

Cohort studies

Several retrospective cohort studies have been performed on cancer mortality among iron and steel workers. The committee noted the variable outcomes, but overall positive associations with statistical significance have been found between occupational

exposure during iron and steel founding and certain types of cancer, such as lung, stomach and bladder cancer.

In some studies data on exposure-response relationships were presented, using years of employment, job title, employment history, or age, as indicators for cumulative exposure. The majority of the studies did not find associations between the cumulative exposure and cancer mortality. Adzersen et al. (2003) found increased lung cancer mortality among workers with more than 30 years since first exposure compared to workers with less than 10 years since exposure (standardized mortality ratio (SMR), 1.36, 95% confidence interval 1.04-1.99).[11] In the small study by Mallin et al. (1998), an association between bladder cancer mortality and heaters was reported, but no associations were found for other job titles.[12] Sitas et al. (1989) found a positive association between lung cancer mortality in workers of 65 years old or older, but not in the younger population.[13] In addition, Westberg et al. (2013) reported a positive association between a latency period of more than 20 years and lung cancer mortality, irrespective of the duration of employment (SMR, 2.35 (95% confidence interval 1.12-4.32; 0 -19 years of employment); SMR, 1.72 (95% confidence interval 1.08-2.61; more than 20 years of employment).[14]

In two studies, the level of PAH exposure was assessed. Tola et al. (1979) found no clear association between current PAH exposure and lung cancer mortality.[15] The committee noted that for accurate exposure levels in relation to cancer development, also historical exposure levels should be taken into account, since working conditions may change over time. In a nested-case control study, Moulin et al. (2000) observed increased trends between estimated PAH exposure and lung cancer mortality (odds ratio 1.42, p=0.06).[16] The estimated PAH exposures were based on exposure levels that might have occurred in the past, and thus may contain a degree of uncertainty.

Uncertainties and limitations. Various factors may have influenced the outcomes of the cohort studies. These include variations in working conditions and thus in exposure levels and composition, uncertainties in historical exposure, not accounting for smoking habits, and lack of data on latency.

Case-control studies

Case-control studies include studies in worker populations and studies in the general population. Overall workers' exposure is assessed by job titles, work areas and duration of employment, rather than by measuring exposure levels. Statistically significant positive associations were found for lung cancer, and in one study also for stomach cancer.[17-21] In all these studies data were adjusted for tobacco smoking. In the study by Becher et al. (1989), a positive association was only found among iron and steel workers with the longest years of employment (more than 30 years),[17] whereas Xu et al. (1996) found positive associations in groups of workers with less than 15 years of employment.[20] In two population-based studies no associations were found for lung cancer or bladder cancer and working in iron and steel foundries.[22,23]

Uncertainties and limitations. No data were reported on historical and current exposure to substances in the emission of iron and steel founding. In addition, possible confounding by the healthy worker effect was not taken into account, indicating that the calculated excess of cancer mortality could be underestimated.

Conclusion on observations in humans

Occupational exposure during iron and steel founding comprises exposure to a complex mixture of substances with variable composition and concentrations, indicating some degree of heterogeneity. In addition, not always potential bias was taken into account, such as smoking habits and the healthy worker effect. Overall, however, the majority of the cohort studies showed a positive association between exposure during iron and steel founding and cancer mortality, in particular lung cancer mortality. The meta-analyses and the case-control studies support the findings from the cohort studies. In most case-control studies data were adjusted for tobacco smoking. In conclusion, the committee is of the opinion that there is sufficient evidence of an association between occupational exposure during iron and steel founding and lung cancer development in humans.

8.1.2 Animal carcinogenicity studies

Humfrey et al. (1996) performed an animal experiment on the carcinogenicity of extracts of aerosols collected from the emission of iron and steel founding.[4] Male and female Wistar rats were exposed to iron foundry fume extracts in pellets by intrabroncheal installation. The committee noted that the chosen exposure route is irrelevant for the human working situation. Furthermore, reporting on tumour development was limited. Therefore, the committee considers this study too limited for a conclusion. So far known, no other animal experiments have been performed.

8.2 Comparison with the CLP-criteria

Several observational studies among workers in the iron and steel foundry industry show a positive association between exposure during iron and steel founding and cancer-related mortality. Types of cancer observed include mainly lung cancer, but also bladder and stomach cancer have been reported. Data on animal carcinogenicity is too limited to draw a conclusion. Based on the observational studies, the committee concludes that there is sufficient evidence of an association between exposure during iron and steel founding and lung cancer development in humans. According to the criteria (see Annex H) the exposure should be considered as "*known to be carcinogenic to humans*", which corresponds to classification in category 1A.

8.3 Conclusion on classification and labelling for carcinogenicity

The committee concludes that exposure during iron and steel founding is carcinogenic to humans, and recommends classifying the exposure in category 1A ("*known to have carcinogenic potential for humans*").

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Annexes

A IARC evaluation and conclusion

Iron and steel founding was considered by IARC Working Groups in 1984, 1987 and in 2012.[1-3] Foundries produce shaped castings from re-melted metal ingots and scrap. The processes in iron and steel founding generally comprise pattern-making, moulding and core-making, melting, pouring and shake-out, and fettling. A detailed description of these production steps can be found in IARC (1984).[1] The iron and steel industry is very diverse in materials and processes, resulting in occupational exposures to a wide variety of substances, including (but not limited to) silica and carbon monoxide, airborne polycyclic aromatic hydrocarbons (PAHs), airborne chromium and nickel compounds, phenol, formaldehyde, isocyanates and various amines. In several studies significant exposure levels of one or more of these substances were demonstrated.

There were 13 cohort studies available on iron and steel founding workers in various parts of the world. A significantly increased risk for lung cancer was observed in almost all cohorts or high-exposed subgroups. In two additional cohorts supportive evidence of an excess of lung cancer in foundry workers was observed, based on proportional mortality. Two population-based case-control studies demonstrated a statistically significant excess of lung cancer in association with foundry work, with adjustment for smoking. Considering the observations in the cohort studies and case-control studies, the epidemiological data clearly support the notion that work in iron and steel foundries is associated with an increased risk for lung cancer. Chance, bias and confounding are not likely to explain the excess risk.

There are no data available on cancer in experimental animals.

Exposures in the iron and steel founding industry are complex and includes a wide variety of known genotoxic and carcinogenic substances including PAHs, metals (e.g. nickel, chromium) and formaldehyde. These agents have been previously reviewed by IARC (1983, 1990, 1995, 2010). In human studies a (significant) correlation was observed between the estimated exposures and DNA-adduct levels in peripheral white blood cells or in leucocytes. Based on this it was concluded that there is moderate evidence that extracts of particles collected from a steel foundry act through a genotoxic mechanism, based on bacterial mutation studies. There is weak evidence of a genotoxic mechanism of action for exposure during iron and steel founding, based on DNA-adduct studies.

Based on the available information, IARC concluded that there is sufficient evidence in human for carcinogenicity of occupational exposures during iron and steel founding. Occupational exposures during iron and steel founding cause cancer of the lung.

No data on the carcinogenicity to experimental animals of mixtures present in iron and steel founding were available to the Working Group.

Occupational exposures during iron and steel founding are *carcinogenic to humans (Group 1)*.

1 # B Genotoxicity: mutagenicity in vitro

Method and reference	**Cell type and conditions**	**Source test substance and doses applied in test system**	**Results**	**Reliability** (Annex I)
Reverse mutation (Ames test) Skyttä et al. (1980)[24]	*Salmonella typhimurium* TA98 and TA100, with (+) and without (-) metabolic activation (S9)	Organic, cyclohexane soluble foundry air contaminants sampled in two iron foundries (A and B). Samples obtained from breathing zone; concentration of B(a)P ranged between 0.6-57.5 µg/m^3 Doses applied: single or two solutions of sample extracts (samples contained 0.1 - 2.7 µg B(a)P)	TA98: positive (+S9) TA100: positive (+S9) (samples contained 0.1-2.7 µg B(a)P per plate) Samples from plant A showed a dose-related correlation between the amount of B(a)P and mutagenicity, when compared to the corresponding dose response correlations of known B(a)P concentrations (correlation coefficients): - TA98: 0.78 - TA100: 0.87 - B(a)P standard: 0.99	Only two strains tested; no data on cytotoxicity; limited statistical analyses; no further details on concentrations applied Reliability 2
Reverse mutation (Ames test) Bryant and McCalla (1982)[25]	*Salmonella typhimurium* TA98 and TA100, with (+) and without (-) metabolic activation (S9) spontaneous mutation rate in TA98 (15-20 revertants/plate) and in TA100 (150 rev/ plate)	Extracts of airborne particulates from breathing zone from workers in two iron foundries (using coal-tar pitch as an additive); no data reported on concentrations of particulate extracts used in test system, but figure 1 in paper shows concentrations of 0,100, 200, 500 and 750 µg particulate.	TA98 Positive in TA98 (+/- S) Positive dose-related response in TA98 with metabolic activation TA100 Negative	Only two strains tested; no data on cytotoxicity; no data on composition of extracts Reliability 2
Reverse mutation (Ames test)	*Salmonella typhimurium* TA98, with (+)	Ferrous foundries; foundry-air particulate was collected and filtered, and	Foundry areas (foundry not specified): positive (+/- S9)	Study design not appropriate

Gibson et al. (1983)[26]	and without (-) metabolic activation (S9)	all mould and core-making materials were tested for mutagenicity; sampling at different sites in foundry (crane, core, mould, finish, etc.) Mean values of PAH in particulates (B[a]P µg/m^3, modified data from literature): Steel foundry: 0.43 Iron foundry: 0.94	+ S9 gave higher mutation rates than -S9 Bulk of total mutagenicity associated with particulates <1.1 µm diameter Moulding materials: negative	Only one strains tested; lack of positive control, no statistical analyses; one dose applied only Reliability 3
Reverse mutation (Ames test) McCalla et al. (1983)[27]	*Salmonella typhimurium* TA98, with (+) and without (-) metabolic activation (S9)	Steel foundry, Canada; collection of different size classes of airborne particulate matter Samples collected 5 successive (size class, µm): <1.1, 1.1-2.0, 2.0-3.3, 3.3-7.0, and >7.0; dose applied on plates: 0.5, 2.0 and 5 mg equivalents of particulates Positive control: 2-acetylaminofluorene	Positive outcome (+S9) - The smaller the particles the higher number of revertants per mg particulate - dose-related increase in revertants per plate No or lower positive scores without metabolic activation.	Study design not appropriate Only one strain tested; no data on spontaneous mutant frequency; no data on positive controls; no data on cytotoxicity; no data on statistical analyses Reliability 3
Reverse mutation (Ames test) Kaiser-Farell et al. (1986)[28]	*Salmonella typhimurium* TA 98, with (+) and without (-) metabolic activation (S9)	Extracts of emissions from binder systems used in Steel Foundry; emission was generated when molten steel was poured into sand molds fabricated with different binder systems (1) shell core, 2) conventional oil-clay-cereal, 3) new green sand, 4) green sand with reclaimed silica sand, 5) green sand with reclaimed	+S9: positive for all binder systems -S9: positive for all binder systems. Mutagenic activity: - varied among binder types - higher in tests +S9 than in tests -S9	Study design not appropriate Only one strain tested; data on controls not shown; no data on statistical analysis; no data on cytotoxicity Reliability 3

		silica sand plus hot topping compound, 6) sodium silicate, 7) furan no-bake, and 8) kold set). For each binder emission samples were taken. Positive controls: 2-acetylamino-fluorene, 1-nitropyrene and 2-nitrofluorene Negative control: ambient background		
Reverse mutation (Ames test) Humfrey et al. (1996)[4]	*Salmonella typhimurium* TA98 and TA100, with (+) and without (-) metabolic activation (S9)	Iron foundry fumes sampled from 3 different binder systems (in casting area): - A: green sand binder - B: shell mould binder - C: cold box amine gassed binder Doses applied: 0, 50, 150, 500, 1,500, and 5,000 µg extract/ml. Test include positive controls	Positive in TA98 and TA100 (+/-S9) for all binders: - A: TA98 (50/20), TA100 (80/50) - B: TA98 (30/60), TA100 (70/80) - C: TA98 (690/130), TA100 (570/170) Significant dose-related increase in number of revertants (A, B and C): C was most potent (description of authors, no data presented) Preliminary study did show cytotoxicity up to 5,000 µg/ml	Only two strains tested; no results presented on positive and negative controls; no data on statistical analysis Reliability 2
Reverse mutation (Ames test) Kaiser et al. (1981) (Source: IARC 1984)[1]	*Salmonella typhimurium* TA98 and TA100 with and without metabolic activation (S9)	Steel foundry; air samples collected (breathing zone) on glass-fibre filters and extracted; no data on concentrations in tested samples.	Pouring-floor level: TA98: positive (+/-S9) TA100: negative (+/-S9) Floor level: TA98: positive (+/-S9) TA100: negative (+/-S9)	Secondary source available only Reliability 4
Reverse mutations (Ames assay;	Urinary samples obtained from Canadian steel	Steel foundry No data on exposure or	Result focuses on smoking habits; no results shown for separate groups.	Only one strain tested; lack of detailed

Salmonella typhimurium TA98) Tomkins et al. (1990)[29], Tomkins et al. (1986)[30]	foundry workers (N= 125) Groups: - high-risk (crane operators) - intermediate-risk (molders and finishers) - unexposed controls (office workers from elsewhere in the plant) Groups were matched for age, smoking history and years of exposure	emission levels in foundry	Reverse mutations (smoking status) - never: 1.65- 2.00 rev/ml - current: 3.81-4.09 rev/ml No other data presented.	information on results, such as number of workers among groups, and number of smokers Reliability 4

1

C Genotoxicity in humans

Gene mutation assays

Method and reference	**Cell type and conditions**	**Source test substance and doses applied in test system**	**Results**	**Remarks and reliability** (Annex I)
Somatic gene mutation (*HPRT* locus) Perera et al. (1994)[31]	Peripheral white blood cells from healthy iron male and female foundry workers (N=64; 51 males, 13 females) Average length of employment: 14 years (range 1 to 47 years) One or two samples were taken in November/ december 1990 (year 1) and/or in november/ december 1991 (year 2) 50% current smokers	Finnish iron foundry 8-Hour dust samples taken from stationary and personal air monitoring; B(a)P was extracted from dust samples. Workers were placed in one of the three exposure groups (in concentration of B(a)P): - low: < 5 ng/m^3, N=20 - medium: 5-12 ng/m^3, N=26 - high: >12 ng/m^3, N=18	*HPRT mutations (mutation frequency/10^6 cells; year 1, year 2 and year 1+2)*): - low:1.0±0.2, 1.1±0.5, 1.1±0.5 - medium:1.1±0.2, 1.0±0.6, 1.1±0.5 - high: 1.7±0.9, 0.9±0.0, 1.7±0.9 No statistically significant differences found	Small study Data were adjusted for smoking Variability in exposure levels within groups Reliability 2

Other genotoxicity tests

Method and reference	**Cell type and conditions**	**Source test substance and doses applied in test system**	**Results**	**Quality score** (see Annex I)
Micronuclei	Peripheral	Polish steel foundry	Mean micronuclei	Small study

frequency (Kubiak et al. (1999)[5]	lymphocytes obtained from steel foundry workers (N=91) Samples were taken in 1991, 1993 and 1996 Lymphocytes were cytokinesis-blocked	Ambient PAH levels at the work stand (mean µg B(a)P/m^3, 1991-1993-1996): - coke oven unit workers, high exposure, N=55): 9.69-3.05-13.72 - Reference group (rollers with low exposure, N=10): 0.006-nd*-nd* * not determined Mean 1-hydroxypyrene excretion in urine (µmoles/mol creatinine): - Coke oven workers: 10.78 ± 13.44 (p=0.0008) - Rollers:0.76 ± 0.63	frequency: - Coke oven workers: 12.4 ± 0.77, p=0.84 - Rollers: 11.3 ± 0.59 Difference between groups not statistically significant No relationship between micronuclei frequency and duration of work.	Information on smoking, drinking, protective equipment and current or prior occupational exposures Reliability 2
Chromosome aberrations (CA); Sister chromatid exchange (SCE) Rudek (1990)[32]	Peripheral lymphocytes obtained from male and female inhabitants: - living nearby a steel foundry (N=9+21)* - living in central Kraków (N=8+12)* - living in a small village at 40 km distance from city and foundry (N=8+12)* * Age groups 7-15 yrs: children 50-73 yrs: adults (children+ adults) Blood samples retrieved in the	No data on exposure levels; no data on environmental emission levels from steel foundry; no data on background emission levels	Data shown below concern adults only CA (% gaps, % other aberrations): - Nearby: 1.14, 0.79 - Kraków: 0.59, 0.65 - Village: 0.28, 0.50 ($p<0.05$) SCE range (mean/cell): - Nearby: 10.4±3.0 - Kraków: 7.9±3.0 - Village: 6.0±2.0 ($p<0.01$) Limited data on smoking habits (past and present smokers combined; SCE range (mean/cell)): - Nearby (N=5): 12.6±2.9 - Kraków (N=5): 7.9±3.4 - Village (N=2): 6.1±2.9 No data on never smokers	Population-based study No data on exposure levels; no information on work history; lack of data on workers in steel foundry Data not relevant

	period 1986-1988; CA counted in 150-200 metaphases/ sample, SCE counted in 50 metaphases/ sample			
Chromosome aberrations (CA); Sister chromatid exchange (SCE); micronuclei Tomkins et al. (1990),[29] Tomkins et al. (1986)[30]	Blood samples obtained from Canadian steel foundry workers (N= 125) Groups: - high-risk (crane operators) - intermediate-risk (molders and finishers) - unexposed controls (office workers from elsewhere in the plant) Groups were matched for age, smoking history and years of exposure	Steel foundry No data on exposure or emission levels in foundry	Result focuses on smoking habits; no results shown for separate groups. Smoking status % micronuclei - never: 0.57 - current: 0.57 No. of micronuclei/1,000 cells: - never: 5.98 - current: 6.03 % cells with CA - never: 9.01 - current: 11.31 Mean SCE per cell - never: 14.80 - current:16.22 No other data presented.	Lack of detailed information on results, such as number of workers in groups, and number of smokers Reliability 4

DNA-adduct formation

Method and reference	**Cell type and conditions**	**Source test substance and doses applied in test system**	**Results**	**Quality score** (see Annex I)
Aromatic DNA adducts (^{32}P-postlabelling assay)	Peripheral white blood cells from healthy iron foundry workers (N=24)	Finnish iron foundry Industrial hygiene measurements for PAH in 1978-1980 (as B(a)P]). Workers divided into three	Mean no. of adducts/10^8 nucleotides (range)): - low: 0.06 (0 – 0.6) - high/medium: 1.8 (0 – 10.0) - controls: 0.2 (0 -1.9)	Small study Variability in exposure levels; no data on statistical

Phillips et al. (1988)[33]	Unexposed controls: subjects from different parts of Finland (N=9)	exposure groups; - low (<0.05 µg/m^3), N=16 - medium (0.05-0.2 µg/m^3), N=6 - high (>0.2 µg/m^3), N=2	Large amount of inter-individual variation as well as in samples taken from the same individual, but at different times No effect from smoking observed	analysis Reliability 2
Aromatic DNA adducts (^{32}P-postlabelling assay) Reddy (1991)[34]	Peripheral white blood cells from healthy iron male and female foundry workers (N=61) Unexposed controls: (N=19) DNA adduct expressed as scores (no. of adducts/10^8 nucleotides): 0: <5 1: 5-10 2: 10-20 3: >20	Finnish iron foundry Workers were divided into exposure groups: low (N=24), medium (N=32) and high (N=5) Industrial hygiene measurements for PAH in 1978-1980 (as B(a)P); - low (<0.05 µg/m^3) - medium (0.05-0.2 µg/m^3) - high (>0.2 µg/m^3)	Mean DNA adduct score: - Low: 0.5-1.0 - Medium: 1.4-2.0 - High: 2.0-2.8 - Control: 0.0-0.3 Highly significant correlation between estimated exposure and adduct levels.	Small study No effects observed taking into account for age or smoking habits (57% were smokers) No data on job history Reliability 2
Aromatic DNA adducts (^{32}P-postlabelling assay) Santella et al. (1993)[35]	Peripheral white blood cells from healthy iron male and female foundry workers (N=48; 37 males, 11 females) Employment period ranges from 2 to 46 years (average 13 years)	Finnish iron foundry Personal exposure to PAH (determination of B(a)P) ranged between 2 and 60 ng/m^3): - Low: < 5 ng/m^3 - Medium: 5 – 12 ng/m^3 - High: >12 ng/m^3 Mean 1-hydroxypyrene levels (µmol/mol creatinine) in group: - Low: 2.7±2.2 - Medium: 1.8±1.2	Mean DNA adducts (adducts/10^8 nucleotides, adjusted for smoking habits): - Low: 5.1±4.1 - Medium: 6.1±4.3 - High: 9.6±8.1 Dose-related increase with exposure (r=0.28, p=0.08); exposure groups did not differ significantly from each other No Influence of cigarette smoking on formation of	Small study Large inter-individual variability; study did not include reference group without exposure, lowest exposure group served as reference Reliability 2

		- High: 3.6±2.5	DNA adducts (54% of workers were smokers)	
Aromatic DNA adducts (^{32}P-postlabelling assay) PAH-DNA adducts (competitive ELISA) Somatic gene mutation (*HPRT* locus) Perera et al. (1994)[31]	Peripheral white blood cells from healthy iron male and female foundry workers (N=64; 51 males, 13 females) Average length of employment: 14 years (range 1 to 47 years) One or two samples were taken in 1990 (year 1) and/or in 1991 (year 2) 50% current smokers	Finnish iron foundry Workers were divided into exposure groups (in B(a)P): - low: < 5 ng/m^3, N=20 - medium: 5-12 ng/m^3, N=26 - high: >12 ng/m^3, N=18	*Aromatic DNA adducts (mean no. of adducts/10^8 nucleotides; year 1, 2, 1+2)* - low: 2.2±0.8, 1.3±0.6, 1.9±0.9 - medium: 2.1±1.4, 1.5±1.1, 2.0±1.4 - high: 2.5±1.2, 2.3±2.0, 2.5±1.2 *PAH-DNA adducts (mean no. of adducts/10^8 nucleotides; year 1,year 2 and year 1+2))*: - low: 5.2±4.1, 1.5±1.4, 4.4±3.9 - medium: 6.1±4.3, 2.9±3.1, 5.2±4.2 - high: 9.6±8.1*, 3.9±4.1, 9.6±8.1 * p<0.05 (low versus high exposure)	Small study Adjustments made for smoking Variability in exposure levels within groups; study did not include reference group without exposure, lowest exposure group served as reference Reliability 2

1

D Epidemiology: meta-analyses

Note: heterogeneity p<0.10 is indicative for substantial heterogeneity (variation between studies).

Selected studies and study population	**Study selection criteria**	**Results**	**Remarks and reliability** (Annex J)
Cohort studies on workers employed in industries with potential PAH exposure (N = 3, iron and steel foundries, total of 5,658 subjects)* Singh et al. 2018[10] * Gibson et al. 1977; Moulin et al. 2000; Koskela et al. 1997. Details of the individual studies are shown in Annex E (indicated as [A])	*Search period*: 1977- 2017 *Inclusion criteria*: lung cancer/tumours; sufficient data on level of PAH exposure; retrospective, longitudinal and prospective cohorts; one publication per cohort (most informative); cancer cases and deaths (mortality and incidences); publication in English only *Quality assessment individual studies*: not included *Meta-analyses*: standard mortality ratios, pooled relative risks; random-effects models to take into account heterogeneity; fixed effect models *Subgroup analyses*: job title	Outcome: study too limited to draw a conclusion Pooled relative risk (95% confidence interval) *Lung cancer* 1.52 (1.05-2.21), 135 cases (incidence and mortality combined) Authors reported on wide variation in smoking habits and exposure to PAH, but data on PAH exposure levels not reported	Appropriate design Presentation of data is limited; no data on heterogeneity for subgroup 'iron and steel foundries'; no quality assessment of individual studies performed; smoking habits not taken into account, because of limited number of studies with data on smoking Reliability 2
Cohort studies on workers employed in iron and steel foundries with data on lymphatic and haematopoietic neoplasms (N=12)* Alicandro et al. (2016)[9] * Decoufle et al. 1979;	*Search period: up to February 2016* *Inclusion criteria*: workers exposed to PAH; incidence or mortality risk from (non-) Hodgkin lymphomas, multiple myeloma or leukemia, related to PAH exposure; publications	Outcome: no associations found Meta-relative risks (95% confidence interval, number of cases, I-squared (%), p for heterogeneity: Hodgkin lymphoma	Appropriate design and reporting No quality assessment of individual studies performed; smoking habits

Anjelkovisch et al. 1990; Moulin et al. 1990; Sherson et al. 1991; Rotimi et al. 1993; Hansen et al. 1997; Firth et al. 1999; Park et al. 2005; Hoshuyama et al. 2006; Westberg et al. 2013; Yoon and Ahn 2014. Details of the individual studies are shown in Annex E (indicated as [B])	in English, French or Italian; cause specified according to international classification of diseases *Quality assessment individual studies*: not reported *Meta-analyses*: incidence ratios (SIR), Standardized mortality ratios (SMR) and relative risks (RR) with corresponding 95% confidence intervals; analyses on heterogeneity, random effect models; sensitivity analyses performed	1.38 (0.95-2.01), 26 cases, 0%, p=0.53 Non-Hodgkin lymphoma 0.94 (0.73-1.22), 57 cases, 0%, p=0.87 Multiple myeloma 1.00 (0.67-1.51), 23 cases, 0%, p=0.26 Leukaemia 1.13 (0.93-1.39), 103 cases, 4%, p=0.41 No significant between-study heterogeneity was observed; no indications for publication bias	not taken into account Reliability 2
Cohort studies on workers employed in industries with potential PAH exposure (N = 13, iron and steel foundries)* Rota et al. (2014)[7] * Koskela et al. 1976; Gibson et al. 1977; Breslin 1979; Andjelkovich et al. 1990; Hansen 1991; Sherson et al. 1991; Rotimi et al. 1993; Sorahan et al. 1994; Moulin et al. 2000; Adzersen et al. 2003; Park et al. 2005; Hoshuyama et al. 2006; Westberg et al. 2013. Details of the individual studies are shown in Annex E (indicated as [C])	*Search period*: 1958 – 2014 *Inclusion criteria*: cancer/tumours on respiratory and urinary tracts; PAH exposure; retrospective, longitudinal and prospective cohorts; one publication per cohort (most informative); cancer cases and deaths *Quality assessment individual studies*: not included *Meta-analyses*: standard mortality ratios, pooled relative risks; random-effects models to take into account heterogeneity *Heterogeneity:* p<0.10 is indicative for substantial heterogeneity (variation between studies)	Outcome: positive association for certain cancer types Standard mortality ratios (SMR) and pooled relative risk (RR) (95% confidence interval), observed/expected, p value for heterogeneity: *Respiratory tract* - all: SMR 1.05, pooled RR 1.31 (1.08 – 1.59), 2,932//2,784, p<0.0001 - lung cancer: SMR 1.05, pooled RR 1.31 (1.07-1.61), 2,903/2,762, p<0.0001 - larynx: SMR 1.43, pooled RR 1.48 (1.14-1.91), 59/41, p=0.537 *Bladder cancer* SMR 1.18, pooled RR 1.38 (1.00 – 1.91), 151/127, p=0.001	Appropriate design and reporting No quality assessment of individual studies performed; smoking habits not taken into account Authors report that workers may be exposed in the past to various potential carcinogenic substances other than PAH Reliability 2

		Cancer in the kidneys SMR 0.98, pooled RR 1.03 (0.78-1.35), 68/69, p=0.304	
Cohort studies on workers in the iron and steel foundry with potential PAH exposure (N=10)* Bosetti et al. 2006[8] *Koskela et al. (1976), Gibson et al. (1977), Breslin et al. (1979), Decouflé (1979), Andjelkovich et al. (1990), Hansen (1991), Sherson et al. (1991), Rotimi et al. (1993), Sorahan et al. (1994), Moulin et al. (1993). Details of the individual studies are shown in Annex E (indicated as [D])	*Search period*: Up to December 2005 *Inclusion criteria*: workers in industries with high PAH exposure; cohort design; mortality or incidence data on cancer risk (the lungs, the respiratory tract, the bladder, the urinary tract) *Quality assessment individual studies*: not performed or reported *Meta-analysis*: pooled relative risk (RR; calculated as a weighted average of the SMRs, using the inverse of the variance as weight), fixed-effects model, chi-square test for heterogeneity	*Outcome:* positive association for cancer in the lungs, respiratory tract and the bladder; no association for kidney cancer *Order:* standardized mortality ratio (SMR), observed/expected no. of cases, pooled RR (95% confidence intervals), p=value for heterogeneity *Lung cancer (9 cohorts)* SMR, 1.39, 975/703.7, 1.40 (1.32-1.49), p=0.007 *Respiratory tract cancers (10 cohorts)* SMR, 1.38, 1,004/726, 1.40 (1.31-1.49), p=0.012 *Bladder cancer (7 cohorts)* SMR, 1.19, 99/83, 1.29 (1.06-1.57), p<0.001 *Kidney cancer (4 cohorts)* SMR, 1.29, 40/31, 1.30 (0.095-1.77), p=0.91	Appropriate design and reporting No quality assessment of individual studies performed; smoking habits not taken into account Reliability 2

1

E Epidemiology: cohorts studies

Study design and population	Data on exposure and health assessment	Results	Remarks and reliability (annex J)
Prospective cohort studies			
No studies.			
Retrospective cohort studies			
Iron, steel and non-ferrous foundries, N= 22 iron and steel foundries; Finland; follow-up 1950 -1987; N=6,415 workers with at least 3 months of exposure (including former and present workers); reference population, general male population in Finland [A]Koskela et al. (1997)[36] Note: same cohort as described by Koskela et al. (1976)[37]	*Exposure*: exposure levels: low, medium and high depending on physical job demands; data on duration of employment available *Mortality and other data:* cause of death verified by death certificates and Population Information System; cause specified according to international classification of diseases; questionnaires to current and former workers for additional information *Selection of subjects* Basic information from employers' records (history of foundry work); subjects traced from Population Data Register of the Social Insurance Institution	Outcome: positive association for certain cancer types Standardized mortality ratio (95% confidence interval, expected/observed) Cancer development (134,660 person-years): - all types of tumours: 1.29 (1.13-1.47), 184.4/238, p<0.001 - lung cancer: 1.43 (1.17-1.74), 71.3/102, p<0.001 - cancer digestive organs: 1.50 (1.14-1.94), 39.3/59, p<0.01	Appropriate study design No analyses by duration of exposure or job demands presented; no data on common confounding factors, such as smoking habits Reliability 2
Iron, steel and non-ferrous	*Exposure:* duration of	Outcome: no association found	Appropriate study

foundries, N= 20 foundries; Finland; follow-up 1950 -1972; N=3,876 workers with at least 3 months of exposure (including former and present workers); reference population, general male population in Finland [C,D]Koskela et al. (1976)[37] Note: same cohort as described by Koskela et al. (1997)[36]	exposure, type of foundry, category of monoxide and dust exposure *Mortality:* cause of death verified by death certificates and; cause specified according to international classification of diseases; only primary cause of lung cancer included (verified from Finnish Cancer Registry) *Selection of subjects* Basic information from employers' records (history of foundry work); subjects traced from Population Data Register of the Social Insurance Institution	N = 224 deaths recorded; loss in follow-up 1.3% Standardized mortality ratio (SMR, expected/observed), 47,160 person-years: - overall lung cancer: 1.51 (13.9/21), - 5 yrs exposure: 1.26 (7.9/10) - > 5 yrs exposure: 1.86 (5.9/11) - iron foundries: 2.70 (3.7/10), 7,549 person-years - steel foundries: 0.00 (1.5/0), 3,986 person-years Nonferrous foundries: 1.43 (0.7/1), 1,213 person-years SMRs are not statistically significant increased compared to reference group Reference population,176,468 person-years: 1.45 (42.2/61)	design Subgroup analyses included: age, duration of exposure, foundry type, and job title No data on smoking habits collected, but authors report that excess risk by smoking is not likely; no data on 95% confidence intervals Reliability 2
Nested case-control in a cohort described by Koskela et al. (1976); iron foundries (N=13); Finland; male workers with at least one year of employment in foundry (N=3,425); registers used from 1918- 1972, cases included up to 1976; reference group, general male population in Finland Tola et al. (1979)[15]; data included data from cohort by Koskela et al. (1976)[37]	*Exposure*: based on history data (rough classification by type of work, and by current exposure to PAH (low, some and heavy exposure) *Mortality*: see Koskela et al. (1976)[37] Data on smoking habits included (57% of works smoked)	Outcome: positive association for lung cancer; no association with type of work and with PAH exposure Study based on the assumption that an association between iron foundry work and lung cancer exists. Goal is to assess the hazard N=51 lung cancer cases N=544 death cases (all causes) Lung cancer, proportional mortality: 1.44 (35.3 expected cases, 51 observed cases), p<0.05 No clear associations between type of work or current exposure to PAH	Appropriate study design No data on 95% confidence interval; no adjustments for well-known confounding factors, such as smoking habits Reliability 2

		and lung cancer, except for: - type of work (casters): risk ratio 4.6 (1.9 expected/7 observed), p<0.01 - Heavy PAH exposure: risk ratio 1.71 (66 controls/ 29 cases)	
Danish national silicosis survey; iron and steel foundries (N=more than 50); Denmark; male workers who had x-ray examination in 1967-1969 and 1972-1974 (N=6,144); follow-up for disease development 1967 - 1985; reference group, general Danish population [B,C,D]Sherson et al. (1991)[38]	*Exposure*: years of working in foundry and type of workplace Data: data retrieved from Central Population Register, Cancer Register; cause specified according to international classification of diseases	Outcome: positive association for lung and bladder cancer Standardized mortality ratios (95% confidence interval, expected/observed) Only data shown with statistically significant outcome *Type of cancer* - all malignant neoplasms: 1.09 (1.01-1.18), 594.4/647 - lung cancer: 1.30 (1.12-1.51), 127.8/166 *Years working in foundry* - 20-29 yrs (N=900): - lung cancer: 1.28 (0.93-1.76), 26.6/38 - bladder cancer: 1.72 (1.05-2.66), 11.6/20 - ≥ 30 yrs (N=613): - lung cancer: 1.85 (1.39-2.45), 25.9/48 - bladder cancer: 1.65 (0.96-2.65), 10.3/17 No association between type of workplace in foundry and lung and bladder cancer risk	Appropriate study design Common confounding factors not taken into account, such as smoking habits Note: of the workers included in the study, 144 were diagnosed with silicosis. Workers with silicosis did not had significant more cancer than the non-silicosis group Reliability 2
Metal foundry industry; Denmark; male moulders (identified from files of a nationwide registry), N=632 (6,069 person-years-at-risk); follow-up 10 years (1970-	*Exposure*: no data on exposure levels; no data on duration of exposure, job titles or working area	Outcome: positive association with bladder cancer and 'other types of malignant neoplasms', no association with lung cancer Standardized mortality ratios (95%	Appropriate study design No data on exposure; no data on other types of

1980); reference group, another cohort of unexposed skilled workers, N=51,747 (481,642 person-years-at-risk) [C,D]Hansen (1991)[39]	*Mortality*: Danish Bureau of Statistics (national register of deaths); diseases classified according to International Classification of Diseases	confidence interval, expected/observed) - cancer (all): 1.52 (1.00-2.21), 17.78/27 - lung cancer: 1.37 (0.63-2.60), 6.57/9 - bladder cancer: 8.96 (3.29-19,49), 0.67/6 - other malignant neoplasms: 1.14 (0.59-1.99), 10.54/12	cancer; no adjustments on common confounding factors, such as smoking habits Reliability 2

Steel foundry, Dominion Foundries and Steel Ltd, Canada; workers (in the past and present) alive in 1967 and over 45 years of age, N=1,542; reference group, urban population in Toronto
 	
[A,C,D]Gibson et al. 1977[40]
	Exposure: foundry (N= 439, working in foundry for at least 5 years) and non-foundry group (N=1,103, at least 5 year working in plant, but less than 5 year in foundry); job categories; in 1967 exposure levels were measured (personal sampling, particulates and metals)
	
	Mortality: death certificates from attending physician and insurance carrier; cause specified according to international classification of diseases
		Outcome: positive association with lung cancer
		
		Standardized mortality ratios (SMR, 95% confidence interval, expected/observed)
		
		Lung cancer
		- Foundry: 2.55 (1.55-3.82), 8.4/21, p<0.005
		- Non-foundry: 0.66 (0.33-1.19), 16.58/11
		- exposure > 20 yrs
		  - foundry (N=128): 2.59, 1.25/11, p=0.025
		  - non-foundry (N=640): 0.69, 11.59/8
		
		All cancer
		Foundry: 1.38 (no data), 26.75/37, p<0.01
		Non-foundry: 0.92 (no data), 53.27/49
			Appropriate study design
			
			A smoking survey in 1973 showed no difference in smoking habits between foundry and non-foundry workers
			
			Limited data on confidence intervals
			
			Reliability 2

Historical prospective cohort; Steel foundries (N=10), member of SCRATA (CTI); the UK; mean follow-up period, 29.2 years; production workers (N=10,438), first employed in the period 1946-1965, with at least one year working experience; reference	*Exposure:* mean duration of employment, 9.3 years *Mortality*: data from National Health Service Central Register or National Insurance records (1946-1990);	Outcome: positive association with lung and stomach cancer Standardized Mortality Ratios (95% confidence interval), expected/observed All cancer types: 1.19 (1.12-1.26), 948.4/1,129, p<0.001	Appropriate study design Certain groups with eastern surnames were excluded due to suspicious low overall mortality

population, general population of England and Wales [C,D]Sorahan et al. 1994[41] (earlier results published: Fletcher and Ades (1984) and Sorahan et al. 1989))[42]	diseases classified according to International Classification of Diseases Subgroup analyses on follow-up period, start of working; foundry site	Lung cancer: 1.46 (1.34-1.58), 378.3/551, p<0.001 Stomach cancer: 1.34 (1.11-1.60), 92.5/1.24, p<0.01 *Lung cancer, specified by duration of employment history (relative risk)* - ever: 1.21 (0.98-1.51), N=185 - up to 5 yrs: 1.44 (1.13-1.82), N=129 - ≥ 15 yrs: 1.26 (0.95-1.67), N=80	No data on exposure levels; no data on smoking habits or other confounding factors Reliability 2
Nested case-control study from retrospective cohort described by [B,C,D]Rotimi et al. (1993); one iron foundry; the USA; total number of lung cancer cases is 231; 408 controls Note (1): cases and control represent total of one iron foundry and two engine plants (data on iron foundry alone not reported) Note (2): cohort by [B,C,D]Rotimi et al. (2013)[43] not described in the present report, because no distinction is made between different types of industries Austin *et al.,* (1997)[44]	Complete work histories of cases and controls obtained from plant personnel files; information on other lung cancer risk factors, including cigarette smoking, was collected by interview. Mortality: from death certificate; cases include 9 with lung cancer as secondary cause of death	Outcome: positive association with lung cancer in workers handling material; no association among workers with other job activities Odds ratios (95% confidence intervals, cases/controls), lung cancer mortality *Working area/job activities in iron foundry only (adjusted for smoking)* - Quality control: 6.3 (0.71-56), 6/1 - Material handling: 5.1 (1.5-17), 13/6 - Maintenance: 0.87 (0.54-1.4), 31/62 - Core room: 1.0 (0.57-56), 21/41 - Melting: 0.10 (0.01-1.5), 1/6 - Molding: 1.0 (0.48-2.1), 14/24 - Cleaning/finishing: 0.92 (0.44-1.9), 15/28 *Duration of employment at iron foundry* - non: 1.0 (-), 82/139 - <10 yrs: 0.79 (0.49-1.3), 53/104 - 10-19 yrs: 1.1 (0.66-1.8), 45/67 - ≥20 yrs: 0.90 (0.55-1.5), 51/98	Appropriate study design Lack of data on exposure levels; no data on other types of cancer Reliability 2
Historical prospective cohort, including a nested case-control study; one stainless steel and metallic alloys plant;	*Exposure*: assessed by job history (specific job-exposure matrix); mean duration of	Outcome: no associations found Lost in follow-up, 1%	Appropriate study design Lack of objective

France; male and female workers ever employed for at least one year between 1968 and 1991 (N=4,288 males, 609 females); follow-up mortality 1968-1992 (mean length 18 years); reference group, general French male population [A,C]Moulin et al. 2000[16] (earlier results on cohort published: [B,D]Moulin et al. 1993)[45]	employment, 16.7 years; exposure levels of certain substances based on knowledge of exposure levels that might have occurred (for the nested case-control study) *Mortality*: death certificates (INSERM), diseases classified according to International Classification of Diseases Analyses included confounding factors, such as smoking habits	*Historical cohort* Standardized mortality ratios (95% confidence interval), expected/ observed (adjusted for sex and age) Malignant neoplasms - men: 0.98 (0.85-1.12), 210.3/206 - both sexes: 0.82 (0.85-1.11), 222/216 Lung cancer: not increased Bladder cancer: not increased *Nested case-control study (odds ratios, 54 cases/162 controls)* PAH and silica exposure: increased trends observed by increasing duration of exposure (PAH, OR 1.46, p=0.01; silica, OR 1.55, p<0.01) and estimated increased exposure levels (PAH, OR 1.42, p=0.06; silica, OR 1.32, p=0.04) No significant differences: - smokers versus non-smokers - among job categories - by substance (metals, asbestos)	exposure levels Reliability 2
Historical prospective cohort; iron foundries (N=37); Germany; production workers first employed between 1950-1985 with at least one year work experience (N=17,708); reference group, German general population; follow-up mortality 1950-1993 [C]Adzersen et al. (2003)[11]	*Exposure*: duration of exposure *Mortality*: data from national mortality statistics West Germany; diseases classified according to International Classification of Diseases	Outcome: positive association with lung and liver cancer Lost in follow-up: 5.1% Standardized mortality ratios (95% confidence interval), expected/ (estimated) observed: - malignant neoplasms: 1.24 (1.02-1.53), 881.3/1,091 - trachea, bronchus, lung: 1.64 (1.24-2.23), 253.2/415 - liver: 3.23 (1.50-8.45), 12.4/40.1 Cancer mortality (all cancers) by duration of exposure and time since first exposure: only statistically	Appropriate study design No data on exposure levels; observed excess of lung cancer could be explained by smoking Reliability 2

		significantly increased in group with less 10 years of exposure combined with more than 30 years since first exposure: 1.36 (1.04-1.99), 131.4/178.5. This was mainly explained by occurrence of lung cancer Overall, no trends in duration of employment observed	
Automotive iron foundry; the USA; workers with potential exposure for at least 6 months between 1960-1987 (n=8,147 men, N=627 women); data retrieved from the period 1950-1984/1989; reference groups, external US population Additional analyses: (1) analyses of work area; workers categorized according 6 work areas, Andjelkovich et al. (1992)[46] (2) nested case-control study on lung cancer; formaldehyde exposure, airborne silica exposure, Andjelkovich et al. (1994)[47] (3) subcohort; formaldehyde and silica exposure (cohort, N= 3,929 exposed men, N= 2,032 no exposure; follow-up 1950-1989), Andjelkovich et al. (1995)[48] [B,C,D]Andjelkovich et al. (1990)[49]	*Exposure*: duration of exposure based on work history; exposure levels of substances expressed as low, medium or high; mean years of employment 9.5 years *Mortality*: data from Social Security Administration (up to 1988), Pension Benefit Information (from 1988) and National Death Index; diseases classified according to International Classification of Diseases Smoking habits taken into account (percentage smokers: 75.2% of exposed workers, 72.4% of unexposed workers)	Outcome: positive association with lung cancer in sub group only; no associations with other cancer types, working area, and exposure to formaldehyde or airborne silica Results concern men only Standardized mortality ratio (95% confidence interval), expected/observed: *White men (N=5,337)*: - all malignant neoplasms: 0.98 (0.84-1.14), 180/177 - lung cancer: 1.23 (0.96-1.54), 58.8/72 - stomach cancer: 1.67 (0.91-2.81), 8.4/14 *Nonwhite men (2,810)*: - all malignant neoplasms: 1.16 (0.99-1.34), 159.2/184 - lung cancer: 1.32 (1.02-1.67), 50.8/67 - stomach cancer: 1.11 (0.59-1.90), 11.7/13 No association observed between duration of exposure and cancer. *Additional analysis (1)* No associations found between type of working area and lung cancer; data probably influenced by smoking habits	Appropriate study design The authors report that lung cancer cases might be associated with smoking No measurements on exposure levels; crude analysis method of smoking habits Reliability 2

		Additional analysis (2) N=220 lung cancer deaths between 1950-1989; no associations found between formaldehyde and/or airborne silica exposure and lung cancer *Additional analysis (3)* - lung cancer: 200 cases - all causes: 2,141 cases No association observed between formaldehyde exposure and lung cancer. Authors observed an significant association between smoking combined with silica exposure, and lung cancer	
Iron and steel foundries (N=208); South Korea; N = 14,611 male workers (between 1992-2000; N=11,793 production workers; N= 2.818 non-production workers); follow-up first day of employment or January 1992 up to December 2008; reference group, Korean male population, and non-production workers in foundries (not exposed) [B]Yoon and Ahn 2014[50]	*Exposure:* based on job title, jobs classified in categories, year first employed, age first employed *Mortality*: data retrieved from Korea National Statistical Office; causes of death classified according to International Classification of Diseases	Outcome: positive association among production workers for stomach and lung cancer; no associations found for colon, liver, pancreas and urinary bladder cancer Standardized mortality ratio (95% confidence interval), no. observed cases (reference, Korean men): Stomach: 1.08 (0.81 – 1.41), 53 Lung: 1.06 (0.80 – 1.38), 56 Relative risk (compared to non-production workers) (95% confidence interval), no. observed cases: All types: 1.90 (1.36 – 2.64), 274 Stomach: 3.96 (1.41 – 11.06), 53 Lung: 2.08 (1.01 – 4.30), 56	Appropriate study design No data on smoking habits or other lifestyle factors that may have influenced the outcome; no data on exposure levels Reliability 2
Iron and steel foundry in a railway rolling stock manufacture; New Zealand; male workers for at least 3 months working in foundries	*Exposure*: exposed or not exposed, based on longest held job title. *Mortality*: data retrieved	Outcome: no association found among iron and steel workers regarding all cancers and lung cancer	Appropriate study design, but limited reporting on iron and steel workers

between 1945 and 1991 (N= 3,522 all types of jobs); reference group, administrative workers of the same manufacture with no exposure to any contaminant [B]Firth et al. (1997)[51]	from personnel records; death registration records by the Department of Justice; causes of death classified according to International Classification of Diseases	Standardized mortality ratio (95% confidence interval), no. observed cases: All cancers - exposed: 1.03 (0.59 – 1.67), 16 cases - non-exposed: 1.06 (0.89 – 1.24), 147 cases Lung cancer - exposed: 1.11 (0.35 – 2.62), 5 cases - non-exposed: 1.04 (0.75- 1.40), 42 cases	Authors report on possible effects due to smoking and other lifestyle factors No data on exposure levels reported Reliability 2
Iron and steel foundries; Denmark; N = 3,056 foundry workers exposed prior to 1970; follow-up, 1970 – 1992; reference group, workers employed in other industries (not exposed, N=43,024) [B]Hansen 1997[52]	*Exposure*: workers exposed before 1970; exposed versus unexposed *Data collection*: record linking with Danish Bureau of Statistics; cause of death indicated according international classification of disease (ICD)	Outcome: no association found Standardized mortality ratio (95% confidence interval), observed cases of death: All cancers: 1.10 (0.97 – 1.25) 255 Respiratory tract: 1.01 (0.80 – 1.25), 84 Digestive system: 1.15 (0.90 – 1.44), 74 Urinary organs: 1.31 (0.85 – 1.95), 25 Blood and lymph: 1.49 (0.97 – 2.19), 26 cases	Appropriate study design; limited reporting No data on smoking habits or other lifestyle factors that may have influenced the outcome; no data on exposure levels Reliability 2
Gray iron foundry of an industrial plant; the USA; male workers for at least one year between 1938 and 1967 (N=2,861); reference group, general US male population [B,D]Decoufle and Wood 1979[53]	*Exposure*: duration of exposure (ever employed (N=2,861), employed for > 5 years (N=867)) *Mortality*: data retrieved from company personnel records, Social Security Administration, and death certificates; diseases classified according to International Classification of	Outcome: study is too limited to draw conclusions Standardized mortality ratios (expected/observed), white/nonwhite men: ≥ *1 month employment* - cancer (all types): 1.11 (49.4/55), 0.88 (39.6/35) ≥ 5 years employment - cancer (all types): 1.13 (20.4/23), 1.05 (17.2/18) Most cancers were observed in the stomach and respiratory system. No statistically significant	Appropriate study design, but limited reporting No exposure levels determined; no data on confounding factors, such as smoking habits; limited data reported on statistical analyses and standardized mortality ratios

	Diseases	associations found between being exposed and cancer development	Reliability 4
Nested case-control study within cohort; steel manufacturing plant; the USA; male production workers (with 10 or more years of employment, N=16 bladder cancer cases); 4 controls (N=74) selected per case Mallin et al. (1998)[12]	*Exposure*: no data presented *Mortality and other data*: cases and controls selected from company records	Outcome: positive association with bladder cancer in heaters; no association with bladder cancer in other job titles Study reported only on bladder cancer Age-adjusted odds ratios (95% confidence interval, number of exposed cases) *Job title* - Heater: 21.1 (2.2-205.8), 3 cases, p<0.01 (OR, logit estimate of relative risk) - Labourer: 0.9 (0.3-2.8), 4 cases - Machine operator/operator learner: 1.1 (0.3-4.4), 3 cases	Appropriate study design Smoking habits were taken into account It was not possible to adjust analyses for smoking habits due to missing data; heat may have influenced the outcome for heaters Reliability 2
Cohort study plus nested case-control study; gray iron foundry; the USA; male and female workers, employed for at least 10 years and who died between 1970-1981 (n=278); reference group, general population, US death registry Silverstein et al. (1986)[54]	*Exposure*: air samples (including breathing zone) taken 17 times between 1947 and 1976; exposure levels determined of dust, carbon monoxide and other contaminants (PAH); exposure classification made by type of work *Mortality*: based on records using various sources, such as local union death benefit fund and Social Security Administration; diseases classified according to International Classification of	Outcome: positive association with lung cancer and leukaemia Standardized proportional mortality rates (95% confidence interval): *All cancers*: - white workers (N=221): 1.18 (0.95-1.47), 61 cases - nonwhite workers (N=56): 1.17 (0.71-1.93), 12 cases *Lung cancer:* - white workers: 1.48 (1.04-2.10), 28 cases - nonwhite workers: 0.85 (0.17-2.49), 3 cases *Leukaemia:* - white workers: 2.84 (1.23-6.55), 5 cases - nonwhite workers: 0 cases Ever smokers had higher risks than non-smokers (white workers):	Appropriate study design, small study No data on exposure levels presented Reliability 2

	Diseases; smoking habits were recorded (71% of workers were classified as ever smokers) Some data adjusted for age, formerly employed in coal mines or other foundries, and smoking habits	*All cancers:* - never (N=45): 0.70 (0.38-1.27), 8 cases - ever (N=167): 1.30 (1.30-1.66), 51 cases, p<0.05 *Lung cancer:* - never: 0.96 (0.24-2.44), 4 cases - ever: 1.59 (1.08-2.33), 23 cases, p<0.05 *Nested-case control study*: No associations observed between type of work and lung cancer development.	
Proportional mortality study; members of the International Moulders and Allied Workers Union (IMAW); the USA; N=2,990 death cases between 1971-1975; reference group, deaths in general US male population Egan-Baum et al. (1981)[55]	*Exposure*: no information given *Mortality*: data obtained from IMAW; diseases classified according to International Classification of Diseases *Smoking habits*: authors expect limited influence on results since differences in smoking habits between exposed and non exposed subjects is considered small	Outcome: positive association with lung cancer Proportional mortality ratio (expected/observed): *All cancers*: - White workers (N=2,651): 1.10 (497.65/545), p<0.05 - Nonwhite workers (N=339): 1.24 (69.29/86), p<0.05 *Lung cancer*: - white workers: 1.44 (155.17/224), p<0.01 - nonwhite workers: 1.76 (22.10/39), p<0.01 Other types of cancer not associated with exposure in foundry	Appropriate study design No data on 95% confidence intervals; data not adjusted for common confounding factors, such as smoking habits Reliability 2
Iron foundries (N=10); Sweden; male workers employed for at least 1 year between 1913-2005 (N=3,045); morbidity data obtained between 1958-2004; reference group, general population of Sweden [B,C]Westberg et al. (2013)[14]	*Exposure*: respirable dust and quartz measurements (340 personal samples taken between 2005-2006) plus historical measurement data from surveys from the 1960s *Morbidity*: data	Outcome: positive association with lung cancer Standardized incidence ratios (95% confidence interval, expected/observed) Only data shown with statistically significant increased SIR *All workers*	Appropriate study design Data not adjusted for common confounding factors, such as smoking habits Reliability 2

	retrieved from company personnel records, and Swedish cancer Registry; diseases classified according to International Classification of Diseases
	
	Smoking habits taken into account (never/ever smoker)
		- all cancer types: 1.00 (0.90-1.11), 347.2/347
		- primary lung cancer: 1.61 (1.20-2.12), 32.24/52
		
		Duration of exposure
		No association between duration of exposure and cancer development
		
		Latency time and duration of employment (lung cancer)
		- Latency 0-19 yrs: no association
		- Latency ≥ 20 yrs
		  - duration 10-19 yrs: 2.35 (1.12-4.31), 4.27/10
		  - duration ≥ 20 yrs: 1.72 (1.08-2.61), 12.76/22
		
		Latency time and cumulative quartz exposure (lung cancer)
		- Latency 0-19 yrs: no association
		- Latency ≥ 20 yrs
		  - low exposure: 2.05 (1.32-3.02), 12.22/25
		  - medium exposure: 1.72 (1.00-1.75), 9.89/17
		  - high exposure: 1.26 (0.26-3.69), 2.38/3
		No dose-related trend observed	

Nested-case control study, Swedish cohort; iron foundries (N=10); 52 cases of lung cancer; for each case 5 controls were used Andersson et al. (2012)[56] (for cohort details see also Westberg et al. 2013)[14]	*Exposure*: see Westberg et al. (2013), focus on exposure to quartz; data presented on job titles *Data*: data retrieved from company personnel records, and Swedish cancer Registry; diseases classified according to International Classification of	Outcome: no associations found regarding exposure to quartz No association found between iron foundry work (expressed as quartz exposure) and lung cancer risk Highest odds ratio for lung cancer: 1.17 (95% confidence interval 0.53-2.55) for medium exposure group (1-1.9 mg quartz dust/m^3)	Appropriate study design, small study Reliability 2

	Diseases		
Iron steel plant; Anshan, China; male iron and steel workers, at least employed for six months and alive in 1980 (N=50,134); follow-up 14 yrs (1980-1993); internal reference group, non-exposed blue-collar workers (N=39,048); reference group, male population in Angang and residential area of Anshan [B,C]Hoshuyama et al. (2006)[57]	*Exposure*: assessment by job exposure matrix, job title; exposure to 15 agents assessed (yes/no exposure), exposure was linked by one job only *Data*: data retrieved from company personnel records and company death registry, municipal death registry; diseases classified according to International Classification of Diseases	Outcome: positive association with lung cancer when combined PAH-exposure with one or two other dust types Standardized mortality ratios (SMR) (95% confidence interval, no. of observed cases): *Lung cancer*: - exposed workers: 0.96 (0.88-1.02), 750 cases - internal reference: 0.88 (0.80-0.96), 507 cases *Liver cancer*: - exposed workers: 0.85 (0.76-0.94), 376 cases - internal reference: 0.81 (0.72-0.92), 265 cases *Stomach cancer*: - exposed workers: 0.86 (0.77-0.96), 321 cases - internal reference: 0.81 (0.72-0.92), 225 cases *Specified by exposure agents* (standardized rate ratios (SRR)): - silica, coal, grinding, wood and carbon monoxide: no association with cancer - iron, welding, cement, asbestos, heat, PAH, oil mist, acid mist, benzene: positive association for different types of cancer, such as cancer in the lungs, stomach, and liver (SRR >1.00 with 95% confidence intervals > 1.00) Combined exposure to PAH and one or two dust types: SRR 6.54 (1.13-3.780) for lung cancer	Appropriate study design No data on smoking habits or other lifestyle factors; limited data on actual exposure levels; SMR analyses showed healthy worker effect Reliability 2
Proportional mortality study; member of the Iron Moulders Society of South Africa (IMS-	*Exposure*: workers categorized according job title and age	Outcome: positive association with lung cancer in age group higher than 65 years old	Appropriate study design, small study

SA); South Africa; N=578 deaths recorded between 1961-1983; reference group, deaths in general white male population Sitas et al. (1989)[13]	*Mortality*: data retrieved from IMS-SA and South African national death records; diseases classified according to International Classification of Diseases	Proportional mortality ratios (expected/observed) - age 20-64 yrs (N=372): - all cancers: 0.75 (53.7/40), p=0.03 - lung cancer: 0.84 (15.48/13), p=0.31 - age ≥ 65 yrs (N=206): - all cancers: 0.91 (36.12/33), p=0.34 - lung cancer: 1.71 (8.75/15), p=0.03	According to the authors smoking cannot fully explain increased mortality ratios (data not presented) Reliability 2
Iron and steel foundries (N=2); South Korea; male workers (N=44,974) employed between 1968-2001 and who were alive in 1992; follow-up 1992-2001 (10 years); reference group, general Korean male population [B,C]Park et al. (2005)[58]	*Exposure*: data on work area/job classes; personal breathing zone air sampling (obtained from one plant during 1994-2000, probably representing worst case scenarios), substances identified were for instance benzene, chromium and other metals, PAH, and carbon monoxide; data on duration of employment *Data*: deaths identified by the Korean National Statistical Office; diseases classified according to International Classification of Diseases; analyses included lag-time Smoking habits obtained from part of	Outcome: positive association with "all types of cancer"; no association with individual types of cancer During follow-up: 806 death cases (=2% of population at risk) Standardized rate ratio (95% confidence interval, number of deaths) - stainless steel production areas: - all cancer: 3.26 (1.37-6.49), N=7 No associations found regarding: - type of cancer - duration of employment Authors reported large healthy worker effect for "all death causes", and "cancer" Smoking habits: during follow-up percentage of smokers decreased in both foundries (Plant 1 from 59.9% to 14.4%; Plant 2 from 55.4% to 33.3%)	Appropriate study design, large study No analyses performed on exposure levels of substances Reliability 1

	workers		
Small-sized iron foundries; South Korea (N=208); N=17,098 male and female workers, working any time between 1992-2000; reference group, Korean general population; follow-up, cancer diagnosis between 1992-2005 Ahn et al. (2010)[59]	*Exposure:* based on job title (production (N=13,100) and office work (N=3,998)), and job area Cancer incidence: data retrieved from Korea Central Cancer Registry; statistical analyses included adjustments for confounding factors (sex and age)	Outcome: positive association with lung cancer and lympho-haematopoietic cancer Standardized Incidence Rate Ratio (SIR, 95% confidence interval, number of cases) Only data shown with statistically significant increased SIR *Types of cancer among production workers*: - all cancers: 1.14 (1.03-1.26), 409 - lung cancer: 1.45(1.11-1.87), 61 - lympho-haematopoietic cancer: 1.58 (1.00-2.37), 23 *Job duration:* Less than 10 years: - all cancers: 1.22 (1.07-1.37), 261 - stomach cancer: 1.35 (1.05-1.71), 68 - lung cancer: 1.66 (1.20-2.24), 43 - lympho-haematopoietic cancer: 1.81 (1.01-2.99), 15 More than 10 years: no exposure-related increase in any type of cancer observed Most cases of lung and stomach cancer were found in production workers during molding and core making, and fettling	Appropriate study design No data on smoking habits Reliability 2
Cohort study; the USA; 2,167 male workers at seven steel foundries; period of employment 1953; period of follow-up 1953 -1970; reference group, total steelworker population in the same plants	*Exposure:* no data *Data collection*: deaths confirmed by death certificates; cause of death indicated according international classification of disease	Standardized mortality ratio (SMR), observed/expected deaths *Lung cancer*: A: 1.14, 20/17.7 B: 1.00, 34/34 C: 1.16, 23/20.1 G*enito-urinary cancer*:	Limitations in study design Selection of reference group is not common; no data on smoking habits

[C,D]Breslin (1979)[60]	(ICD) Subcohorts: A: first job in 1953 was in the foundry (N=1,173) B: ever employed in the foundry through 1953 (N=2,167) C: employed in the foundry for et least 5 years through 1953 (N=958)	A: 1.75, 12/7.1 B: 1.28, 17/13.6 C: 1.62, 14/8.9 *All cancers*: A: 1.20*, 71/60.3 B: 1.08, 123/115.2 C: 1.16, 80/70.3 * statistically significant, p≤0.05 Data as reported by Bosetti et al. (95% confidence interval), complete cohort: *Lung cancer*: SMR 1.00 (0.7-1.4), 34 death cases *Bladder cancer*: SMR 1.00 (0.2-2.8), 3 death cases *Kidney cancer*: 1.6 (0.4-4.1), 4 death cases	Reliability 3
Iron and steel foundries: Sweden; male workers with silicosis (N=428), selection period 1959-1977; reference group selected from Silicosis Register(N=476), and general population; cancer registration followed between 1961-1980 Westerholm et al. (1986)[61]	*Exposure*: mean duration of exposure, 28 years; no data n exposure levels *Data collection*: data retrieved from Silicosis Register, Swedish Register of Causes of Death, Swedish Cancer Registry, Swedish Tuberculosis Index	Outcome: the data are too limited to draw a conclusion *Lung cancer mortality (mortality ratio, expected/observed)* - 3.9, 2.6/10, p<0.05 -observed case/control ratio, 1.7 (not statistically significant) *Lung cancer incidence (incidence ratio, expected/observed)* - 1.8, 3.3/6 (not statistically significant) -observed case/control ratio, 0.6 (not statistically significant)	Study design is not appropriate for assessing cancer risk among healthy workers Only workers with silicosis included; limited data on statistical analyses; data not adjusted for smoking habits; no data on exposure levels Study is not relevant

[A, B, C, D] Data of the study used in meta-analysis by Singh et al. 2018 (A), Alicandro et al. 2016 (B), Rota et al. 2014 (C), and/or Bosetti et al. 2006 (D).

1

F Epidemiology: case-control studies

Study design and population	**Data on exposure and health assessment**	**Results**	**Remarks and reliability** (annex J)
Population-based study design; steel industry or foundry workers; eastern Pennsylvania, the USA; N=335 white men who died from 1974 to 1977 from lung cancer; controls (N=332) men, matched to the cases by race, age, sex, county and year of death, and free from respiratory cancer or chronic respiratory disease Blot et al. (1983)[18]	*Data collection*: Face-to face interview with next-of-kin, recording occupational history, smoking history and residential history *Disease verification*: pathologically verified primary lung cancer; data retrieved from population mortality registers	Outcome: positive association found for lung cancer Response rate 94% Odds ratios (95% confidence interval, cases/control) *Lung cancer* Employed in steel industry ("usual industry"): 2.2 (1.5-3.3), 80/43 Employed as foundry worker, mold maker (6 cases and 1 control): 7.1 (1.2-42.3), 6/1 Smoking did not influence outcomes	Appropriate study design, small study Adjustment for smoking and age as potential confounders No data on exposure levels or employment duration; no data on other types of cancer Reliability 2
Population-based study design; foundries; Poland; N= 901 deaths from lung cancer in 1980-1985 among males in Crakow; N=875 controls selected among men dying from causes other than respiratory cancer or chronic respiratory disease, frequency matched to the cases with regard to age Becher et al. (1989)[17]	*Data collection*: Next of-kin interviewed to obtain a residential, occupational and smoking history. *Disease verification*: data retrieved from death certificates from Crakow death register;	Outcome: positive association for lung cancer in longest exposed worker population Response rate: 70.7% (cases) and 73.5% (controls) N=106 cases and 72 references in steel and iron foundries Simultaneous relative risk (95% confidence interval, cases/control) *Lung cancer* Years of employment in foundry - 1-20 yrs or unknown: 1.28 (0.75-2.20) - 20-30 years: 1.58 (0.94-2.66) - >30 years: 2.66 (1.31-5.42)	Appropriate study design, small study Adjustment for age, smoking, other occupational exposures as potential confounders No data on exposure levels; no data on other types of cancer Reliability 2

		No data on other types of cancer; no data on cases/controls	
Population-based study design; area of two steel producing plants, of which one has a substantial foundry operation; Canada; subjects (N=967) were men who died of lung cancer from 1979-1983 (Hamilton and Sault Ste-Marie, Ontario); controls were men who died from other causes (N=2,827) Finkelstein (1994)[22]	*Data collection*: Job and industry recorded from the death certificates; job histories obtained from employers *Disease verification*: not reported	Outcome: no association found for lung cancer Relative lung cancer risks (95% confidence interval, number of cases) - Steelworkers Sault St-Marie: 0.85 (0.58-1.23), 73 cases - Steelworkers Hamilton: 1.10 (0.89-1.37), 145 cases (Adjusted for age and time period) - Foundry work for >5 years (Hamilton): 1.94 (0.75-5.2), 12 cases No association between work in foundries and lung cancer risk	Appropriate study design, small study No smoking Adjustment; no data on exposure levels; no data on other types of cancer Reliability 2
Population-based study design; area of former coal, iron, and steel industries; Germany; cases and controls obtained from three hospitals in Eastern Ruhr area (diagnosed in period 1984-1988; cases are male workers who were employed for at least 10 years in one of the three industries, prior to investigation Golka *et al.,* (1998)[23]	*Data collection*: categorization based on type of work; questionnaire on occupations performed and smoking habits; Smoking habits: - Cases: 58.3% smokers, 12.2% ex-smokers - Controls: 35.3% smokers, 9.7% ex-smokers	Outcome: no association found for bladder cancer Odds ratio (95% confidence interval, cases/controls) for urothelial cancer (adjusted for smoking habits) Iron and steel foundry workers 1.1 (0.69-1.69), 8/3, p=0.735	Appropriate study design Adjusted for smoking No data on other types of cancer; no data on exposure levels Reliability 2
Case-control study on worker population in one large iron and steel foundry; Asturias, Spain; male workers, cases were identified by job records	*Exposure*: no data on exposure levels; categorisation by production process.	Outcome: positive association found for lung cancer when working in blast furnace area; no associations found for lung cancer in other work areas	Appropriate study design, small study Adjusted for

and cancer registries (period 1952-1995), N=144 lung cancer cases; N=558 age-matched controls (workers) not having lung cancer RodrÍguez et al. (2000)[19]	*Data collection*: Tumor Registry of the General Hospital of Asturias and Tmour Registry of Asturias; diseases classified according to International Classification of Diseases; data on smoking habits (cases/controls: N=131/436 ever smokers, N=1/108 never smoker	Odds ratios (95% confidence interval, cases/controls) of lung cancer (data adjusted for smoking and age) Ever employed in: - foundry: 1.64 (0.69-3.91), 10/24 - blast furnace: 2.55 (1.25-5.21), 16/36 By longest held job in: -foundry: 1.91 (0.74-4.93), 9/18 -blast furnace: 2.11 (0.78-5.73), 7/17	smoking and age No data on other types of cancer; no data on exposure levels Reliability 2
Case-control study on worker population in a large iron-steel complex; Anshan, China; cases selected from active and retired workers which were diagnosed with cancer in the period 1987-1993 (primary lung cancer) and 1989-1993 (stomach cancer); N=610 cases of primary lung cancer, N=293 cases of stomach cancer in employees with at least 10 years of employment Xu et al. (1996)[20,21]	*Exposure:* no data on exposure levels; data retrieved (personnel records) on duration of exposure and job activities/working areas *Cancer data collection*: municipal cancer registry; medical records from hospitals; interviews of cases, controls or next of kin	Outcome: positive association with lung and stomach cancer Odds ratios (95% confidence interval, cases/controls) of lung and stomach cancer (data adjusted smoking and age) *Lung cancer (foundry workers; 172 cases, 411 controls)* - ever worked: 1.8 (1.1-2.8), 48/47 - worked < 15 yrs: 2.7 (1.3-5.7), 21/15 - worked ≥ 15 yrs: 1.4 (0.8-2.4), 27/32 *Stomach cancer (foundry workers; 91 cases, 411 controls):* - ever worked: 2.0 (1.1-3.5), 30/47 - worked < 15 yrs: 3.9 (1.7-9.0), 15/14 - worked ≥ 15 yrs: 1.2 (0.6-2.5), 15/33	Appropriate study design Adjustments made for smoking and age Reliability 2
Study is part of Occupational Cancer Monitoring (OCCAM) project; Italy, area of Umbria (Perugia and Terni); focus on	*Exposure*: No data on exposure levels; duration of exposure divided into three	Outcome: positive association found for brain cancer; no trend for years of employment	Appropriate study design No data on other

iron and steel foundry workers; cases selected from male workers occupied for at least 1 year since 1974, aged between 35-74 years at diagnosis (N=13,589), and controls from same population matched for sex, province of residence and 5-y age class (N=44,474) Oddone et al. (2014)[62]	groups: 0-4 yrs 5-9 yrs ≥ 10 yrs *Data on cancer*: Umbria Regional Cancer Registry (data retrieved from period 2002-2008)	Odds ratios (90% confidence interval, cases/controls) of brain cancer (adjusted for age and sex) Iron and steel foundry in Terni: - overall: 9.59 (2.76-33.34), 16 cases, p=0.003 Duration of employment: - 0-4 yrs: 1.00 (-), 2 cases - 5-9 yrs: 13.64 (3.27-56.96), 4 cases, p=0.003 - ≥10 years: 8.58 (2.40-30.75), 10 cases, p=0.006	types of cancer; 90% confidence interval instead of the usual 95% confidence interval, wide spread of confidence interval noted Reliability 2

1

G Classification on germ cell mutagenicity

Source: Section 3.5 (Germ cell mutagenicity) of Regulation No. 1272/2008 of the European Parliament and of the council of 10 August 2009 on classification, labelling and packaging of substances.[6]

3.5.1. Definitions and general considerations

3.5.1.1. A mutation means a permanent change in the amount or structure of the genetic material in a cell. The term 'mutation' applies both to heritable genetic changes that may be manifested at the phenotypic level and to the underlying DNA modifications when known (including specific base pair changes and chromosomal translocations). The term 'mutagenic' and 'mutagen' will be used for agents giving rise to an increased occurrence of mutations in populations of cells and/or organisms.

3.5.1.2. The more general terms 'genotoxic' and 'genotoxicity' apply to agents or processes which alter the structure, information content, or segregation of DNA, including those which cause DNA damage by interfering with normal replication processes, or which in a non-physiological manner (temporarily) alter its replication. Genotoxicity test results are usually taken as indicators for mutagenic effects.

3.5.2. Classification criteria for substances

3.5.2.1. This hazard class is primarily concerned with substances that may cause mutations in the germ cells of humans that can be transmitted to the progeny. However, the results from mutagenicity or genotoxicity tests in vitro and in mammalian somatic and germ cells in vivo are also considered in classifying substances and mixtures within this hazard class.

3.5.2.2. For the purpose of classification for germ cell mutagenicity, substances are allocated to one of two categories as shown in Table 3.5.1.

3.5.2.3 Specific considerations for classification of substances as germ cell mutagens

3.5.2.3.1. To arrive at a classification, test results are considered from experiments determining mutagenic and/or genotoxic effects in germ and/or somatic cells of exposed animals. Mutagenic and/or genotoxic effects determined in in vitro tests shall also be considered.

3.5.2.3.2. The system is hazard based, classifying substances on the basis of their intrinsic ability to induce mutations in germ cells. The scheme is, therefore, not meant for the (quantitative) risk assessment of substances.

Table 3.5.1 Hazard categories for germ cell mutagens

Categories	Criteria
CATEGORY 1:	Substances known to induce heritable mutations or to be regarded as if they induce heritable mutations in the germ cells of humans. Substances known to induce heritable mutations in the germ cells of humans.
Category 1A:	The classification in Category 1A is based on positive evidence from human epidemiological studies. Substances to be regarded as if they induce heritable mutations in the germ cells of humans.
Category 1B:	The classification in Category 1B is based on: — positive result(s) from in vivo heritable germ cell mutagenicity tests in mammals; or — positive result(s) from in vivo somatic cell mutagenicity tests in mammals, in combination with some evidence that the substance has potential to cause mutations to germ cells. It is possible to derive this supporting evidence from mutagenicity/ genotoxicity tests in germ cells in vivo, or by demonstrating the ability of the substance or its metabolite(s) to interact with the genetic material of germ cells; or — positive results from tests showing mutagenic effects in the germ cells of humans, without demonstration of transmission to progeny; for example, an increase in the frequency of aneuploidy in sperm cells of exposed people.
CATEGORY 2:	Substances which cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans. The classification in Category 2 is based on: - positive evidence obtained from experiments in mammals and/or in some cases from in vitro experiments, obtained from: - somatic cell mutagenicity tests in vivo, in mammals; or - other in vivo somatic cell genotoxicity tests which are supported by positive results from in vitro mutagenicity assays. *Note*: Substances which are positive in in vitro mammalian mutagenicity assays, and which also show chemical structure activity relationship to known germ cell mutagens, shall be considered for classification as Category 2 mutagens.

3.5.2.3.3. Classification for heritable effects in human germ cells is made on the basis of well conducted, sufficiently validated tests, preferably as described in Regulation (EC) No 440/2008 adopted in accordance with Article 13(3) of Regulation (EC) No 1907/2006 ('Test Method Regulation') such as those listed in the following paragraphs. Evaluation of the test results shall be done using expert judgement and all the available evidence shall be weighed in arriving at a classification.

3.5.2.3.4. In vivo heritable germ cell mutagenicity tests, such as:
— rodent dominant lethal mutation test;
— mouse heritable translocation assay.

3.5.2.3.5. In vivo somatic cell mutagenicity tests, such as:
— mammalian bone marrow chromosome aberration test;

— mouse spot test;
— mammalian erythrocyte micronucleus test.

3.5.2.3.6. Mutagenicity/genotoxicity tests in germ cells, such as:
(a) mutagenicity tests:
- mammalian spermatogonial chromosome aberration test;
- spermatid micronucleus assay;

(b) Genotoxicity tests:
- sister chromatid exchange analysis in spermatogonia;
- unscheduled DNA synthesis test (UDS) in testicular cells.

3.5.2.3.7. Genotoxicity tests in somatic cells such as:
— liver Unscheduled synthesis test (UDS) in vivo;
— mammalian bone marrow Sister Chromatid Exchanges (SCE);

3.5.2.3.8. In vitro mutagenicity tests such as:
— in vitro mammalian chromosome aberration test;
— in vitro mammalian cell gene mutation test;
— bacterial reverse mutation tests.

3.5.2.3.9. The classification of individual substances shall be based on the total weight of evidence available, using expert judgement (See 1.1.1). In those instances where a single well-conducted test is used for classification, it shall provide clear and unambiguously positive results. If new, well validated, tests arise these may also be used in the total weight of evidence to be considered. The relevance of the route of exposure used in the study of the substance compared to the route of human exposure shall also be taken into account.

3.5.3 Classification criteria for mixtures

3.5.3.1. Classification of mixtures when data are available for all ingredients or only for some ingredients of the mixture

3.5.3.1.1. The mixture shall be classified as a mutagen when at least one ingredient has been classified as a Category 1A, Category 1B or Category 2 mutagen and is present at or above the appropriate generic concentration limit as shown in Table 3.5.2 for Category 1A, Category 1B and Category 2 respectively.

Table 3.5.2 Generic concentration limits of ingredients of a mixture classified as germ cell mutagens that trigger classification of the mixture.

	Concentration limits triggering classification of a mixture as:

Ingredient classified as:	Category 1A mutagen	Category 1B mutagen	Category 2 mutagen
Category 1A mutagen	≥ 0,1 %	-	-
Category 1B mutagen	-	≥ 0,1 %	-
Category 2 mutagen	-	-	≥ 1,0 %

Note. The concentration limits in the table above apply to solids and liquids (w/w units) as well as gases (v/v units).

3.5.3.2. Classification of mixtures when data are available for the complete mixture

3.5.3.2.1. Classification of mixtures will be based on the available test data for the individual ingredients of the mixture using concentration limits for the ingredients classified as germ cell mutagens. On a case-by-case basis, test data on mixtures may be used for classification when demonstrating effects that have not been established

from the evaluation based on the individual ingredients. In such cases, the test results for the mixture as a whole must be shown to be conclusive taking into account dose and other factors such as duration, observations, sensitivity and statistical analysis of germ cell mutagenicity test systems. Adequate documentation supporting the classification shall be retained and made available for review upon request.

3.5.3.3 Classification of mixtures when data are not available for the complete mixture: bridging principles

3.5.3.3.1. Where the mixture itself has not been tested to determine its germ cell mutagenicity hazard, but there are sufficient data on the individual ingredients and similar tested mixtures (subject to paragraph 3.5.3.2.1), to adequately characterise the hazards of the mixture, these data shall be used in accordance with the applicable bridging rules set out in section 1.1.3.

3.5.4. Hazard communication

3.5.4.1. Label elements shall be used in accordance with Table 3.5.3, for substances or mixtures meeting the criteria for classification in this hazard class.

Table 3.5.3 Label elements of germ cell mutagenicity

Classification	Category 1A or Category 1B	Category 2
GHS Pictograms		
Signal word	Danger	Warning
Hazard Statement	H340: May cause genetic defects (state route of exposure if it is conclusively	H341: Suspected of causing

	proven that no other routes of exposure cause the hazard)	genetic defects (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)
Precautionary Statement Prevention	P201, P202, P281	P201, P202, P281
Precautionary Statement Response	P308 + P313	P308 + P313
Precautionary Statement Storage	P405	P405
Precautionary Statement Disposal	P501	P501

3.5.5. Additional classification considerations

It is increasingly accepted that the process of chemical-induced tumorigenesis in humans and animals involves genetic changes for example in proto-oncogenes and/or tumour suppresser genes of somatic cells. Therefore, the demonstration of mutagenic properties of substances in somatic and/or germ cells of mammals in vivo may have implications for the potential classification of these substances as carcinogens (see also Carcinogenicity, section 3.6, paragraph 3.6.2.2.6).

H Classification on carcinogenicity

The Committee expresses its conclusions in the form of standard phrases:[a]

Category	Judgement of the Committee (GR_{GHS})	Comparable with EU Category[b] (before 16 December 2008)	Comparable with EU Category[b] (as from 16 December 2008)
1A	*The compound is known to be carcinogenic to humans.* • It acts by a stochastic genotoxic mechanism. • It acts by a non-stochastic genotoxic mechanism. • It acts by a non-genotoxic mechanism. • Its potential genotoxicity has been insufficiently investigated. Therefore, it is unclear whether the compound is genotoxic.	1	1A
1B	*The compound is presumed to be as carcinogenic to humans.* • It acts by a stochastic genotoxic mechanism. • It acts by a non-stochastic genotoxic mechanism. • It acts by a non-genotoxic mechanism. • Its potential genotoxicity has been insufficiently investigated. Therefore, it is unclear whether the compound is genotoxic.	2	1B
2	*The compound is suspected to be carcinogenic to man.*	3	2
(3)	*The available data are insufficient to evaluate the carcinogenic properties of the compound.*	not applicable	not applicable
(4)	*The compound is probably not carcinogenic to man.*	not applicable	not applicable

[a] See guideline to the classification of carcinogenic compounds, the Health Council (2010).[63]

[b] See Section 3.6 (Carcinogenicity) of Regulation No. 1272/2008 of the European Parliament and of the council on classification, labelling and packaging of substances.[6]

I Criteria for testing reliability of animal and in vitro studies

To assess the reliability of animal and in vitro studies, the Committee uses the criteria set by Klimisch et al. 1997.[64] A summary of the criteria of the reliability scores is given below. Only studies with a reliability score of 1 or 2 are considered in assessing genotoxicity and carcinogenicity.

Reliability 1 (reliable without restriction)
For example, guideline study (OECD, etc.); comparable to guideline study; test procedure according to national standards (DIN, etc.).

Reliability 2 (reliable with restrictions)
For example, acceptable, well-documented publication/study report which meets basic scientific principles; basic data given: comparable to guidelines/standards; comparable to guideline study with acceptable restrictions.

Reliability 3 (not reliable)
For example, method not validated; documentation insufficient for assessment; does not meet important criteria of today standard methods; relevant methodological deficiencies; unsuitable test system.

Reliability 4 (not assignable)
For example, only short abstract available; only secondary literature (review, tables, books, etc.).

J Reliability testing of epidemiological studies

To assess the reliability of epidemiological studies, the Committee uses the criteria set by Money et al.(2013).[65] A summary of the reliability categories set by Money et al. (2013) is given below. Only studies with a reliability score of 1 or 2 are considered in assessing genotoxicity and carcinogenicity.

Reliability 1 (reliable without restriction)

Chronic, non-specific outcomes
Appropriate study design to research question.
(1) Selected subjects or persons at risk represent appropriate exposure distributions. Adequate procedures of follow-up and reduction of loss to follow up were performed.
(2) Exposure assessment was made independent of outcome with validated methods, preferentially with individual exposure data.
(3) Effect data were collected independently from exposure status, using standardized data collection procedures/registries.
(4) The possibility of serious bias has been reduced by design, controlled through statistical adjustment, and/or quantified through sensitivity analyses.
(5) The sample/exposure range was sufficient to study the question under investigation, so that effects estimates are not constrained by high imprecision.
(6) The data were analysed using appropriate statistical techniques to address the research questions and model assumptions.
(7) The methodology and results were comprehensively and transparently reported according to relevant guidelines (*e.g.*, the STROBE guidelines for observational data, Von Elm et al. 2007).[66]

Acute or specific outcomes
The same principles should be applied as for chronic, non-specific outcomes. The focus lies more with how well exposure has been characterised, and the disease outcome is defined.

Reliability 2 (reliable with restrictions)

Chronic, non-specific outcomes
Applies to studies which possess most of the qualities of studies with reliability 1. The overall quality is comprised due to minor, but obvious, methodological limitations. Examples include well-designed and conducted studies, but with limited measurement data, possibility of some residual confounding, some imprecision due to small sample size or low exposure range.

Acute or specific outcomes
The same principles should be applied as for chronic, non-specific outcomes. Examples of shortcomings may include a lack of individual exposure data, and effects derived from self-reported outcomes.

Note: some studies with serious methodological limitations may provide reliable information for an acute or specific outcome.

Reliability 3 (not reliable)

The studies fail to meet one or more of the most basic standards necessary to interpret epidemiologic research, such as appropriate study design to the research question. Shortcomings may include using census job titles as a surrogate for exposure.

Reliability 4 (not assignable)

This includes studies or data which do not give sufficient details about methodology used, or which are short listed in abstracts or secondary literature.

The Committee

- R.A. Woutersen, *chairman*
  Emeritus professor of translational toxicology, Wageningen University and Research Centre
- P.J. Boogaard
  Professor of environmental health and human biomonitoring, Wageningen University and Research Centre, and toxicologist, SHELL International BV, The Hague
- M.J.M. Nivard
  Molecular biologist and genetic toxicologist, Leiden University Medical Center, Leiden
- H.P.J. te Riele
  Professor of molecular biology, VU University Amsterdam, and Netherlands Cancer Institute, Amsterdam
- J.J. Vlaanderen
  Epidemiologist, Institute for Risk Assessment Sciences, Utrecht
- J. van Benthem, *structurally consulted expert*
  Genetic toxicologist, RIVM, Bilthoven
- K.W.R. Woutersen, *observer*
  Bureau REACH, RIVM, Bilthoven
- J.M. Rijnkels, *scientific secretary*
  The Health Council of the Netherlands, The Hague

The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the chairperson and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. For each substance to be evaluated, the members are asked about their potential conflicts of interest. An expert with a personal financial interest cannot be a member of the Committee. In case of other, less clearly marked interests, experts can be consulted as non-members when their expertise is considered essential for the advisory report. By law, an expert working at an organization that is part of a Ministry cannot be a member of a Health Council Committee. Such an expert can be consulted as a non-member when there are no conflicting interests involved. It is the responsibility of the President of the Health Council, after consulting the chairman of the Committee, to assess the interests indicated and decides on the consequences for a possible membership.