

# Iron and steel founding emissions

Evaluation of the carcinogenicity and genotoxicity

To: The State Secretary of Social Affairs and Employment  
No. 2020/02, The Hague, February 18, 2020

---

Health Council of the Netherlands



# contents

<b>Samenvatting</b>	<b>4</b>	<b>03 International classification</b>	<b>14</b>
<b>Executive summary</b>	<b>6</b>	3.1 European Commission	15
<b>01 Scope</b>	<b>8</b>	3.2 IARC	15
1.1 Background	9	3.3 The Health Council of the Netherlands	15
1.2 Committee and procedure	9	<b>04 Monitoring</b>	<b>16</b>
1.3 Data	9	4.1 Environmental exposure monitoring	17
1.4 Quality assessment	10	4.2 Biological exposure monitoring	17
1.5 Criteria for classification	10	<b>05 Manufacture and uses</b>	<b>18</b>
<b>02 Identity of the iron and steel founding emissions</b>	<b>11</b>	5.1 Manufacture	19
2.1 Iron and steel founding	12	5.2 Identified uses	19
2.2 Composition of the iron and steel founding emissions	13	<b>06 Summary of (toxico)kinetics</b>	<b>20</b>
2.3 Physicochemical properties	13		



## 07 Germ cell mutagenicity 22

---

- |     |   |    |
|-----|---|----|
| 7.1 | Summary and relevance of the provided information on (germ cell) mutagenicity | 23 |
| 7.2 | Evaluation of the germ cell mutagenicity                                      | 25 |
| 7.3 | Recommendation on the classification for germ cell mutagenicity               | 25 |

## 08 Carcinogenicity 26

---

- |     |  |    |
|-----|--|----|
| 8.1 | Summary and relevance of the provided information on carcinogenicity | 27 |
| 8.2 | Evaluation of the carcinogenicity                                    | 30 |
| 8.3 | Recommendation on the classification for carcinogenicity             | 30 |

## References 31

---

## Annexes 37

---

- |   |   |    |
|---|---|----|
| A | IARC evaluation and conclusion  | 38 |
| B | Reliability testing of animal and in vitro studies  | 40 |
| C | Reliability testing of epidemiological studies  | 41 |
| D | Classification on germ cell mutagenicity  | 43 |
| E | Classification on carcinogenicity   | 48 |
| F | Individual components that can be found in the emission during iron and steel founding                      | 49 |
| G | Substances identified in the emissions of iron and steel founding, which are classified for carcinogenicity | 53 |
| H | Genotoxicity: mutagenicity x  | 55 |
| I | Genotoxicity in humans  | 58 |
| J | Epidemiology: meta-analyses   | 63 |
| K | Epidemiology: cohorts studies   | 66 |
| L | Epidemiology: case-control studies  | 83 |



# samenvatting

Op verzoek van de Minister van Sociale Zaken en Werkgelegenheid heeft de Gezondheidsraad beoordeeld of emissies die ontstaan tijdens het ijzer- en staalgieten een genotoxisch effect hebben en tot kanker kunnen 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 samenstelling van de subcommissie is te vinden achterin dit advies. 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](http://www.gezondheidsraad.nl).

## Het gieten van ijzer en staal

In dit advies worden de emissies die ontstaan tijdens het ijzer- en staalgieten 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 en het afwerken van het gietsel. 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 individuele stoffen, mengsels of emissies genotoxisch en kankerverwekkend zijn 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 de criteria die gebruikt worden in 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 de emissies van 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 commissie concludeert dat beroepsmatige blootstelling aan de emissies van ijzer- en staalgieten kankerverwekkend zijn voor de mens, en beveelt aan deze emissies in categorie 1A (*“stof is kankerverwekkend voor de mens”*) te classificeren. De kankerverwekkende effecten worden waarschijnlijk veroorzaakt door een stochastisch genotoxisch werkingsmechanisme.



# executive summary

At request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands assessed whether emissions, which are formed during iron and steel founding, may induce genotoxic effects and may cause cancer. 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 membership of the Subcommittee is given on the last page of this advisory report. 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](http://www.gezondheidsraad.nl).

## **Iron and steel founding**

In the present advisory report, the evaluation concerns the emissions that are formed during the iron and steel founding. Individual substances that can be found in the emissions are not considered. Iron and steel founding comprises creating a mould, melting and treating the basic material, pouring into moulds, cooling down the metal, and removing and cleaning the castings. 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 individual substances, mixtures or emissions. 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 criteria for assessing hazard categories, as 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 iron and steel founding emissions 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 committee concludes that iron and steel founding emissions are carcinogenic to humans, and recommends classifying the emissions in category 1A (*“known to have carcinogenic potential for humans”*). The carcinogenic effects are most likely caused by a stochastic genotoxic mode of action.



# 01 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 (individual substances, mixtures or emissions), 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. A letter of the request can be found on the website of the Health Council.

This report contains the evaluation of the mutagenicity and carcinogenicity of the emissions that are formed during iron and steel founding. Iron and steel founding comprises creating a mould, melting and treating the basic material, pouring into moulds, cooling down the metal, and removing and cleaning the castings. The evaluation concerns the emissions as a whole. Individual substances that can be found in the emissions 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 evaluated 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 iron and steel founding emissions, such an IARC-monograph is available, of which the summary and conclusion is inserted in Annex A.

Data published after the last IARC evaluation were retrieved from the online databases Medline, Toxline, Chemical Abstracts, and RTECS. The last online search was in August 2019. 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\*. All data retrieved (i.e., data from the IARC Monograph and new data) were summarized in tables in the annexes of the present advisory report.

#### 1.4 Quality assessment

The Committee evaluates the data retrieved on reliability and quality, by using criteria set by others, and by expert judgment. For animal experiments and in vitro assays, the criteria set by Klimisch et al. (1997) are used.<sup>1</sup> For epidemiological studies, the reliability criteria set by Money et al. (2013) are used.<sup>2</sup> A summary of the reliability criteria is given in Annex B and C, respectively.

In Chapter 7 and 8, studies with sufficient reliability (with or without restrictions) are described, and taken into account for the hazard assessment. Studies with lower quality are incorporated in the summary tables in the annexes, but not considered for the hazard assessment.

#### 1.5 Criteria for classification

For recommending a classification on mutagenicity in germ cells, the Committee uses the criteria described in Section 3.5 of Annex I of the European regulation No. 1272/2008 (see annex D), in combination with expert judgement.<sup>3</sup> Although the criteria mentioned in the regulation are set for substances that are evaluated according to the CLP-regulation,

the Committee considers them useful in recommending a classification as mutagenic in germ cells for substances, mixtures and emissions, for which the regulation does not apply. The criteria are based on the Globally Harmonized System, and can be universally applied.

In 2010, the Health Council published a *Guideline to the classification of carcinogenic compounds*, for classifying substances in terms of their carcinogenic properties, and for assessing the mode of action.<sup>4</sup>

The criteria and the classification on carcinogenic properties are based on the Globally Harmonized System, which is also used by the European Union for the classification, labelling and packaging of substances and mixtures (Regulation EC 1272/2008, Section 3.6 Carcinogenicity).<sup>3</sup>

Annex E summarizes the classification system for carcinogenic substances, as used by the Committee. For the assessment of the carcinogenicity, the Committee uses four categories of evidence. These categories are described in detail in the *Guideline to the classification of carcinogenic compounds* (Health Council, 2010).<sup>4</sup>

The proposal for a classification is expressed in standard sentences, combined with a category number.



# 02

## identity of the iron and steel founding emissions



The information in this chapter is abstracted from IARC Monographs.<sup>5-7</sup>

## 2.1 Iron and steel founding

The present evaluation concerns the occupational exposure to the emissions that are formed during iron and steel founding operations.

No distinction is made between iron founding and steel founding; steel is an alloy of iron and carbon. The differences in composition and founding operations between iron and steel founding fall within the general diversity in materials and founding processes of ferrous materials.

In short, iron and steel founding comprises patternmaking, creating a mould, melting and pouring the melted metals in moulds, and fettling:

- *Patternmaking.* A pattern is a three-dimensional negative image of the desired product. The materials and design of the pattern depend upon the method of casting production, and the intended shape of the desired product. Materials used to make patterns may include wood, natural and synthetic waxes or polystyrene foam materials. Patterns are created for single (expendable) or permanent use.
- *Creating a mould.* Using the patterns, a mould or matrix, which contains a hollow negative image of the desired product, is made from sand (silica (quartz) or bentonite), metal or other materials, which do not melt together with the melted iron or steel, and which does not distort during the moulding process. The choice of material depends on the desired size of the product, the production volume, and type of metal needed to

make the product. Natural bonding or synthetic sand casting is one of the simplest types of casting. The sand is bonded together using clays, chemical binders (e.g., furan, phenolic isocyanate, sulphonic acids) or polymerized oils and resins (e.g., urea-formaldehyde, polyester urethane). Also, organic additives to control for the atmosphere are added in the (green-sand) moulds, such as pulverized coal dust or coal-dust replacements (e.g., synthetic polymers (such as polystyrene, polymeric petroleum products), products of coal or petroleum distillation (e.g., mixture of heavy hydrocarbons, aromatic components and naphthenes), asphalts (bitumen), and coal-tar pitches. Moulds can be produced for single (disposable, non-reusable) or permanent use.

- *Melting and pouring.* So-called cupolas (iron casting; charge material, pig iron and scrap), electric-induction furnaces (iron and steel casting), electric arc furnaces (steel casting; open-heart and reverberatory furnaces), or combinations are used to melt iron and steel. Holding furnaces may serve as a reservoir of the melted metal at the pouring temperature. To get the desired composition of the desired product, additional charge materials existing of ferroalloys of pure metal are added, such as ferrochromium and ferromanganese. In addition, calcium compounds (e.g., calcium silicide, calcium carbide), and magnesium metal may be added to control the melting and casting. The scrap may contain undesired metal constituents, such as lead, zinc and cadmium, which are evaporated during melting, together with pyrolysis products of any oil, grease, plastics or rubber present in the



charge material. During the melting process, reagents may be added to purify, deoxidise, degas, inoculate or refine the alloy. Furnace temperatures are about 1,400 (cast irons) degrees Celsius or higher. The pouring is a delicate process, in which the pouring rate and temperature are crucial factors to prevent deterioration of the mould and casting. To minimize a temperature drop of the melted metal, a preheating system is used. During and after pouring, lighting and gas evolving from the hot mould may enter the workplace atmosphere. When cooled down, the moulds are shaken-out by, for instance, pneumatic tools, hammers, and vibratory tables, during which dust exhaust may be released into the workplace atmosphere.

- *Fettling*. After the shake-out, the finished casting is cleaned by removing adherent sand residues (manually or mechanically), and separating excess metal (feeders, risers, gates and sprues; by sawing, flame- or compressed air-cutting, and/or grinding). During the fettling process, the iron or steel casting may undergo a heat treatment and primer painting.

## 2.2 Composition of the iron and steel founding emissions

As is described in the previous section, the iron and steel foundry industry is very diverse in materials and processes. This results in occupational exposures to a wide variety of substances (gases, aerosols and particles), some likely involving almost all workers, some only concerning specific job titles or working areas in the foundry. Substances that can be found in

the emissions 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 the main substances to which workers are likely exposed during iron and steel founding is given by IARC (1984; see also Annex F of the present advisory report).<sup>5</sup> In the more recently published IARC Monograph (2012), a new summary description is given of the main substances in combination with data on exposure levels: respirable dust and respirable quartz, carbon monoxide, binder compounds, polycyclic aromatic hydrocarbons, metals, and/or refractory ceramic fibres (see Annex F).

## 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.



# 03 international classification



### 3.1 European Commission

Not evaluated.

### 3.2 IARC

In 2012, the Working Group of IARC summarized that there is sufficient evidence in humans for the carcinogenicity of occupational exposures during iron and steel founding.<sup>7</sup> 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. Overall, IARC concluded that 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. Annex G shows a list of individual components, which can most likely be found in the emission of iron and steel founding, and which are classified by IARC.

### 3.3 The Health Council of the Netherlands

Not evaluated. Annex G shows a list of individual components, which can most likely be found in the emissions of iron and steel founding, and which are officially classified in the Netherlands.



# 04 monitoring





#### 4.1 Environmental exposure monitoring

Exposure to the iron and steel founding emissions 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

Not specified.



# 05 manufacture and uses



## 5.1 Manufacture

The emissions are unintentionally formed during iron and steel founding operations.

## 5.2 Identified uses

Iron and steel founding is used to produce a large variety of semi-finished and finished metal products for a wide range of construction and engineering applications, such as machine and motor parts, cookware, pipes, pumps, valves, nails, and ship paddles.



# 06 summary of (toxico)kinetics



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



# 07 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 H. Three studies were considered sufficiently reliable. In these studies, samples of aerosols and fumes, which are formed during iron and steel founding, and obtained from several plants in various countries, induced 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.<sup>8</sup> As shown in Table 1, the extracts increased the number of cells with micronuclei in a dose-dependent matter. No other studies are available.

#### *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).<sup>8</sup> 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 B)
Micronucleus test Humfrey et al. (1996) <sup>8</sup>	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



**Table 2.** Unscheduled DNA synthesis.

Method and reference	Cell type and conditions	Source test substance and doses applied in test system	Results	Reliability (Annex B)
Unscheduled DNA synthesis Humfrey et al. (1996) <sup>8</sup>	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	<i>Rabbit tracheal cells</i> Statistically significant dose-related increase in net nuclear grains reported <i>Rat hepatocytes</i> 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

The committee remarks 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 evidence 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 iron and steel founding emissions induce 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 I. The small studies have been performed with iron and steel foundry workers from which blood samples were taken. In the

studies the concentration of benzo(a)pyrene, a well-known mutagenic and carcinogenic substance, served as exposure marker to the emission of iron and steel founding.

In a single study, no increased mutations were found in the hypoxanthine-guanine phosphoribosyl transferase (HPRT) gene in white blood cells with and without adjustment for smoking habits.

In another single study, no difference was observed 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<sup>3</sup>; low, 0.0-0.006 µg/m<sup>3</sup>).<sup>9</sup> Two other studies on chromosome aberrations and sister chromatid exchanges could not be interpreted by the committee due to low quality.





In four studies, moderate to clear increases in DNA-adduct formation were observed, but in only two studies the increase reached statistical significance. However, since DNA-adduct formation is more an indication of exposure rather than an indication for genotoxicity, these data are not further evaluated.

Overall, the number of studies on human materials obtained from foundry workers is very limited, and those with sufficient quality do not show mutagenic or clastogenic activity.

### 7.1.2 Summary of genotoxicity tests in mammalian somatic or germ cells in vivo

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

## 7.2 Evaluation of the germ cell mutagenicity

No data have been found on germ cell mutagenicity in humans or mammals. In addition, no genotoxicity tests in germ cells have been performed with samples taken from iron and steel founding emissions. Therefore, the committee concludes that there is a lack of evidence to classify iron and steel founding emissions in category 1 (*“known to induce heritable mutations in the germ cells of humans”*).

Extracts from the emissions of iron and steel founding showed to be mutagenic in *in vitro* test systems. Additional information in two of the three mutagenicity studies showed that in these extracts benzo(a)pyrene or coal tar pitch was present, two substances, which are well known to have carcinogenic and mutagenic potential. Limited evidence is available on the clastogenic properties of extracts of the emissions of iron and steel founding (*in vitro* and *in vivo* tests). To the opinion of the Committee, all these findings indicate that a classification in category 2 (*“cause of concern for humans owing to the possibility that it may induce heritable mutations in the germ cells of humans”*) is warranted.

## 7.3 Recommendation on the classification for germ cell mutagenicity

Based on the available data, the Committee recommends classifying iron and steel founding emissions as a germ cell mutagen in category 2 (*“Cause of concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans”*).



# 08 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 J (meta-analyses), K (cohort studies), and L (case-control studies). The publications contain data from studies of industrial workers worldwide, which are exposed to the emissions of iron and steel founding at varying exposure levels, and under various exposure circumstances.

#### *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, which is an update from Bosetti et al. (2006).<sup>10,11</sup> 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).<sup>10</sup> 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.<sup>12</sup> Singh et al. (2018) focused on PAH exposure-associated lung cancer and therefore included only three studies (two were also included in Rota et al. (2014), one was described

in a conference abstract only.<sup>13</sup> Therefore this study will not be further discussed by the committee.

*Notes by the committee.* 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 most cohort studies data on smoking habits or other potentially confounding factors were not collected or reported, and therefore were not taken into account in the meta-analyses.

Overall, the meta-analyses demonstrate a 30% excess risk for cancer of the lung in iron and steel foundry industries, and no excess risk for hematopoietic cancers. The potential impact of unmeasured confounding factors cannot be fully excluded.

#### *Cohort studies*

Twenty-five retrospective cohort studies have been performed on cancer mortality among iron and steel workers, of which five studies were not considered by the committee due to low quality. Overall, in fifteen of the twenty studies a positive association with statistical significance have been found between occupational exposure to the iron and steel founding emissions and certain types of cancer, such as lung, stomach and bladder cancer. In five studies (limited) data on smoking habits were available; in three of these studies, the association was still positive when data were adjusted for these smoking habits, or after indicating that there was no



difference in percentage of smokers between exposed and reference group.

In fifteen studies data on exposure-response relationships were presented, using years of employment, job title, employment history, or age, as indicators for cumulative exposure. For instance, Adzersen et al. (2003) found increased lung cancer mortality among workers with more than 30 years of exposure since first exposure compared to workers with less than 10 years of exposure since first exposure (standardized mortality ratio (SMR), 1.36, 95% confidence interval 1.04-1.99).<sup>14</sup> 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.<sup>15</sup> 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.<sup>16</sup> In addition, Westberg et al. (2013) reported a positive association between a latency period (period between exposure and cancer development) of more than 20 years and lung cancer mortality, irrespective of the duration of employment (0-19 years of employment, SMR, 2.35 (95% confidence interval 1.12-4.32); more than 20 years of employment, SMR, 1.72 (95% confidence interval 1.08-2.61)).<sup>17</sup>

However, in the majority of the cohort studies no associations have been found between duration of tenure in the iron and steel founding industry, and cancer mortality.

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.<sup>18</sup> 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,  $p=0.06$ ).<sup>19</sup> The estimated PAH exposures were based on exposure levels that might have occurred in the past, and thus may contain a degree of uncertainty.

*Notes by the committee.* 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. However, the majority of the retrospective cohort studies showed an association between exposure to iron and steel foundry emissions and increased cancer development.

#### *Case-control studies*

Seven case-control studies were available on workers 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.<sup>20-24</sup> In five 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),<sup>20</sup> whereas Xu et al. (1996) found positive associations in groups of workers with less than 15 years of employment.<sup>23</sup> In two population-based studies no associations were found for lung cancer or bladder cancer and working in iron and steel foundries.<sup>25,26</sup>

*Notes by the committee.* 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. Overall, taking into account these notes, in case-control studies associations were found between exposure to iron and steel foundry emissions and increased cancer development.

#### *Conclusion on observations in humans*

Occupational exposure to the emissions of 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 or confounding was taken into account, such as smoking habits and the healthy worker effect. Smoking is strongly associated with lung and bladder cancer, and thus may have influenced the outcome of the cohort studies if smoking rates between the iron and steel founding workers differed from the reference population. Three cohort studies explored this issue and demonstrated that it is unlikely that smoking behavior fully explained the excess cancer

risk among iron and steel founding workers. Therefore, the Committee does not preclude beforehand the studies with no or insufficient data on smoking habits for the hazard assessment, unless it is clear that the reference population is not comparable with the exposed population. This may also account for co-morbidities. The ‘healthy worker’ effect may have resulted in an underestimation of work-related cancer cases in retrospective and case-control studies to some degree. However, it is reasonable to assume that this phenomenon has only a minor influence on the number of cancer cases, because cancer development may take many years before complaints start to occur, whereas complaints are a reason for a worker to leave the workplace early. Therefore exclusion of the these types of studies for the hazard assessment is not necessary.

Overall and taking into account potential bias and confounding, the majority of the cohort studies showed an association between exposure to the emissions of iron and steel founding and increased cancer mortality, in particular lung cancer mortality. The case-control studies support the findings from the cohort studies. In conclusion, the committee is of the opinion that there is sufficient evidence of an association between occupational exposure to iron and steel founding emissions of and increased 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 emissions of iron and steel founding.<sup>8</sup> Male and female Wistar rats (N=50 animals/sex/group) were exposed to iron foundry fume extracts in pellets by intrabroncheal installation in a two-year rodent bioassay. The authors did not find tumours that could be related to fume extract exposure, although preneoplastic lesions in the bronchial epithelium were observed in treated animals when compared to control animals. The committee noted that the chosen exposure route is irrelevant for the human working situation. Furthermore, reporting on tumour development was limited (no data on general toxicity, body weight gain, food consumption, etc.). Therefore, the committee considers this study too limited for a conclusion. So far known, no other animal experiments have been performed.

## 8.2 Evaluation of the carcinogenicity

Several observational studies among workers in the iron and steel foundry industry show a positive association between exposure to the emissions of 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, and taking into account bias and confounding, the Committee concludes that there is sufficient evidence for an association between exposure during iron and

steel founding and lung cancer development in humans. According to the criteria, the exposure should be considered as “*known to be carcinogenic to humans*”, which corresponds to classification in category 1A.

Genotoxicity data from in vitro test systems show that extracts from the emissions of iron and steel founding induced mutations. This suggests that the emissions likely cause cancer by a stochastic genotoxic mode of action. A further indication that this type of carcinogenic mechanism may play a role comes from two of the three mutagenicity studies using the reverse mutation assay, in which benzo(a)pyrene or coal tar pitch were detected in the test samples. These substances are well known for their mutagenic activity.

## 8.3 Recommendation on the classification for carcinogenicity

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

In addition, the committee concludes that the emissions are likely to cause cancer by a stochastic genotoxic mode of action.



# references



- <sup>1</sup> Klimisch HJ, Andreae M and Tillmann U. *A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data*. Regul Toxicol Pharmacol 1997; 25(1): 1-5.
- <sup>2</sup> Money CD, Tomenson JA, Penman MG, Boogaard PJ and Jeffrey Lewis R. *A systematic approach for evaluating and scoring human data*. Regul Toxicol Pharmacol 2013; 66(2): 241-7.
- <sup>3</sup> European Union. *Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures*. 2009.
- <sup>4</sup> The Health Council. *Guideline to the classification of carcinogenic compounds. Guide for classifying compounds in terms of their carcinogenic properties and for assessing their genotoxicity*. The Hague, report no. A10/07E, 2010.
- <sup>5</sup> IARC. *Polynuclear aromatic compounds, Part 3, Industrial exposures in aluminium production, coal gasification, coke production, and iron and steel founding*. IARC Monograph 34, 1984: 1-219.
- <sup>6</sup> IARC. *Overall evaluations of carcinogenicity: an updating of IARC Monographs volumes 1-42*. IARC Monograph Suppl 7, 1987: 1-440.
- <sup>7</sup> IARC. *Occupational exposures during iron and steel founding*. IARC Monograph 100F, 2012: 497-507.
- <sup>8</sup> Humfrey C, Levy L and Faux S. *Potential Carcinogenicity of foundry fumes: a comparative In Vivo-In Vitro study*. Food Chem Toxicol 1996; 34: 1103-11.
- <sup>9</sup> Kubiak R, Belowski J, Szczeklik J, Smolik E, Mielzynska D, Baj M, et al. *Biomarkers of carcinogenesis in humans exposed to polycyclic aromatic hydrocarbons*. Mutat Res 1999; 445: 175-80.
- <sup>10</sup> Rota M, Bosetti C, Boccia S, Boffetta P and La Vecchia C. *Occupational exposures to polycyclic aromatic hydrocarbons and respiratory and urinary tract cancers: an updated systematic review and a meta-analysis to 2014*. Arch Toxicol 2014; 88: 1479-90.
- <sup>11</sup> Bosetti C, Boffetta PF and La VC. *Occupational exposures to polycyclic aromatic hydrocarbons, and respiratory and urinary tract cancers: a quantitative review to 2005*. Annals of Oncology 2007; 18: 431-46.
- <sup>12</sup> Alicandro G, Rota M, Boffetta P and La Vecchia C. *Occupational exposure to polycyclic aromatic hydrocarbons and lymphatic and hematopoietic neoplasms: a systematic review and meta-analysis of cohort studies*. Arch Toxicol 2016; 90(11): 2643-56.
- <sup>13</sup> Singh A, Kamal R, Ahamed I, Wagh M, Bihari V, Sathian B, et al. *PAH exposure-associated lung cancer: an updated meta-analysis*. Occup Med (Lond) 2018; 68(4): 255-61.
- <sup>14</sup> Adzersen K, Becker N, Steindorf K and Frentzel-Beyme R. *Cancer mortality in a cohort of male German iron foundry workers*. Am J Ind Med 2003; 43: 295-305.
- <sup>15</sup> Mallin K. *A nested case-control study of bladder cancer incidence in a steel manufacturing plant*. Am J Ind Med 1998; 34(4): 393-8.





- <sup>16</sup> Sitas F, Douglas A and Webster E. *Respiratory disease mortality patterns among South African iron moulders*. Br J Ind Med 1989; 46: 310-5.
- <sup>17</sup> Westberg H, Andersson L, Bryngelsson I, Ngo Y and Ohlson C. *Cancer morbidity and quartz exposure in Swedish iron foundries*. Int Arch Occup Environ Health 2013; 86: 499-507.
- <sup>18</sup> Tola S, Koskela R, Hernberg S and Jarvinen E. *Lung cancer mortality among iron foundry workers*. J Occup Med 1979; 21: 753-9.
- <sup>19</sup> Moulin JJ, Clavel T, Roy D, Dananche B, Marquis N, Fevotte J, et al. *Risk of lung cancer in workers producing stainless steel and metallic alloys*. Int Arch Occup Environ Health 2000; 73(3): 171-80.
- <sup>20</sup> Becher H, Jedrychowski W, Flak E, Gomola K and Wahrendorf J. *Lung cancer, smoking, and employment in foundries*. Scand J Work Environ Health 1989; 15: 38-42.
- <sup>21</sup> Blot W, Brown L, Pottern L, Stone B and Fraumeni J. *Lung cancer among long-term steel workers*. Am J Epidemiol 1983; 117: 706-16.
- <sup>22</sup> Rodriguez V, Tardon A, Kogevinas M, Prieto C, Cueto A, Garcia M, et al. *Lung cancer risk in iron and steel foundry workers: a nested case control study in Asturias, Spain*. Am J Ind Med 2000; 38: 644-50.
- <sup>23</sup> Xu Z, Brown LM, Pan GW, Liu TF, Gao GS, Stone BJ, et al. *Cancer risks among iron and steel workers in Anshan, China, Part II: Case-control studies of lung and stomach cancer*. Am J Ind Med 1996; 30(1): 7-15.
- <sup>24</sup> Xu Z, Pan GW, Liu LM, Brown LM, Guan DX, Xiu Q, et al. *Cancer risks among iron and steel workers in Anshan, China, Part I: Proportional mortality ratio analysis*. Am J Ind Med 1996; 30(1): 1-6.
- <sup>25</sup> Finkelstein M. *Lung cancer among steelworkers in Ontario*. Am J Ind Med 1994; 26: 549-57.
- <sup>26</sup> Golka K, Bandel T, Schlaefke S, Reich S, Reckwitz T, Urfer W, et al. *Urothelial cancer of the bladder in an area of formal coal, iron and steel industries in Germany: a case-control study*. International Journal of Occupational and Environmental Health 1998; 4: 79-84.
- <sup>27</sup> von Elm E, Altman DG, Egger M, Pocock SJ, Gotsche PC, Vandembroucke JP, et al. *The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies*. J Clin Epidemiol 2008; 61(4): 344-9.
- <sup>28</sup> Skytta E, Schimberg R and Vainio H. *Mutagenic activity in foundry air*. Arch Toxicol Suppl 1980; 4: 68-72.
- <sup>29</sup> Bryant D and McCalla D. *Mutagenicity and lung cancer in a steel foundry environment*. Book: Mutagenicity: new horizons in genetic toxicology, Chapter 4, Heddle, J.A., Academic Press Inc., 1st Edition, 1982: 89-115.
- <sup>30</sup> Gibson E, McCalla D, Kaiser-Farrell C, Kerr A, Lockington J, Hertzman C, et al. *Lung cancer in a steel foundry: a search for causation*. J Occup Med 1983; 25: 573-8.



- <sup>31</sup> McCalla D, Kaiser-Farrell C, Kerr A, Lockington J and Gibson E. *Distribution of extractable mutagenic activity in steel foundry air particulates of different sizes*. Environ Mutagen 1983; 5: 881-9.
- <sup>32</sup> Kaiser-Farrell C, Sheldrake C, McCalla D, Gibson E, Kerr A and Lockington J. *The mutagenicity of emissions from eight binder systems used in steel foundries*. Am Ind Hyg Assoc J 1986; 47: 578-86.
- <sup>33</sup> Tomkins DJ, McCalla DR and Gibson ES. *Comparison of in vivo somatic cell mutation, chromosome aberration, sister chromatid exchange, micronuclei formation and urine mutagenicity in steel foundry workers*. Prog Clin Biol Res 1990; 340C: 377-86.
- <sup>34</sup> Tomkins DJ. *Genetic toxicologic monitoring of human populations: smokers, quitters and life-time non-smokers*. Can J Public Health 1986; 77, Suppl 1: 140-3.
- <sup>35</sup> Perera F, Dickey C, Santella R, O'Neill J, Albertini R, Ottman R, et al. *Carcinogen-DNA adducts and gene mutation in foundry workers with low-level exposure to polycyclic aromatic hydrocarbons*. Carcinogenesis 1994; 15: 2905-10.
- <sup>36</sup> Rudek Z. *Chromosome aberrations and sister chromatid exchange in the inhabitants of an area surrounding a large metallurgical plant*. Folia Biol 1990; 38: 75-82.
- <sup>37</sup> Phillips D, Hemminki K, Alhonen A, Hewer A and Grover P. *Monitoring occupational exposure to carcinogens: detection by <sup>32</sup>P-postlabeling of aromatic DNA adducts in white blood cells from iron foundry workers*. Mutat Res 1988; 204: 531-41.
- <sup>38</sup> Reddy M, Hemminki K and Randerath K. *Postlabeling analysis of polycyclic aromatic hydrocarbon-DNA adducts in white blood cells of foundry workers*. J Toxicol Environ Health 1991; 34: 177-85.
- <sup>39</sup> Santella R, Hemminki K, Tang D, Paik M, Ottman R, Young T, et al. *Polycyclic aromatic hydrocarbon-DNA adducts in white blood cells and urinary 1-hydroxypyrene in foundry workers*. Cancer Epidemiol Biomarkers Prev 1993; 2: 59-62.
- <sup>40</sup> Park RM, Ahn YS, Stayner LT, Kang SK and Jang JK. *Mortality of iron and steel workers in Korea*. Am J Ind Med 2005; 48(3): 194-204.
- <sup>41</sup> Yoon JH and Ahn YS. *Cause-specific mortality due to malignant and non-malignant disease in Korean foundry workers*. PLoS One 2014; 9(2): e88264.
- <sup>42</sup> Ahn YS, Won JU and Park RM. *Cancer morbidity of foundry workers in Korea*. J Korean Med Sci 2010; 25(12): 1733-41.
- <sup>43</sup> Rotimi C, Austin H, Delzell E, Day C, Macaluso M and Honda Y. *Retrospective follow-up study of foundry and engine plant workers*. Am J Ind Med 1993; 24: 485-98.
- <sup>44</sup> Austin H, Delzell E, Lally C, Rotimi C and Oestenstad K. *A case-control study of lung cancer at a foundry and two engine plants*. Am J Ind Med 1997; 31: 414-21.
- <sup>45</sup> Moulin J, Wild P, Mantout B, Fournier-Betz M, Mur J and Smagghe G. *Mortality from lung cancer and cardiovascular diseases among stainless-steel producing workers*. Cancer Causes Control 1993; 4: 75-81.



- <sup>46</sup> Gibson E, Martin R and Lockington J. *Lung cancer mortality in a steel foundry*. J Occup Med 1977; 19: 807-12.
- <sup>47</sup> Silverstein M, Maiziish N, Park R, Silverstein B, Brodsky L and Mirer F. *Mortality among ferrous foundry workers*. Am J Ind Med 1986; 10: 27-43.
- <sup>48</sup> Andersson L, Bryngelsson I-L, Ngo Y, Ohlson C-G and Westberg H. *Exposure assessment and modeling of quartz in Swedish iron foundries for a nested case-control study on lung cancer*. J Occup Environ Hyg 2012; 9: 110-9.
- <sup>49</sup> Hoshuyama T, Pan G, Tanaka C, Feng Y, Yu L, Liu T, et al. *Mortality of iron-steel workers in Anshan, China: a retrospective cohort study*. Int J Occup Environ Health 2006; 12(3): 193-202.
- <sup>50</sup> Firth HM, Elwood JM, Cox B and Herbison GP. *Historical cohort study of a New Zealand foundry and heavy engineering plant*. Occup Environ Med 1999; 56(2): 134-8.
- <sup>51</sup> Hansen ES. *A cohort mortality study of foundry workers*. Am J Ind Med 1997; 32(3): 223-33.
- <sup>52</sup> Koskela RS, Hernberg S, Karava R, Jarvinen E and Nurminen M. *A mortality study of foundry workers*. Scand J Work Environ Health 1976; 2 Suppl 1: 73-89.
- <sup>53</sup> Koskela RS. *Mortality, morbidity and health selection among metal workers*. Scand J Work Environ Health 1997; 23 Suppl 2: 1-80.
- <sup>54</sup> Sherson D, Svane O and Lynge E. *Cancer incidence among foundry workers in Denmark*. Arch Environ Health 1991; 46(2): 75-81.
- <sup>55</sup> Hansen ES. *Cancer mortality among Danish molders*. Am J Ind Med 1991; 20(3): 401-9.
- <sup>56</sup> Andjelkovich D, Mathew R, Yu R, Richardson R and Levine R. *Mortality of iron foundry workers: II Analysis by work area*. J Occup Med 1992; 34: 391-401.
- <sup>57</sup> Andjelkovich D, Shy C, Brown M, Janszen D, Levine R and Richardson R. *Mortality of iron foundry workers: III Lung cancer case-control study*. J Occup Med 1994; 36: 1301-9.
- <sup>58</sup> Andjelkovich D, Jansze D, Brown M, Richardson R and Miller F. *Mortality of iron foundry workers: IV Analysis of a subcohort exposed to formaldehyde*. J Occup Environ Med 1995; 37: 826-37.
- <sup>59</sup> Andjelkovich D, Mathew R, Richardson R and Levine R. *Mortality of iron foundry workers: I Overall findings*. J Occup Med 1990; 32: 529-40.
- <sup>60</sup> Sorahan T, Faux A and Cooke M. *Mortality among a cohort of United Kingdom steel foundry workers with special reference to cancers of the stomach and lung, 1946-90*. Occup Environ Med 1994; 51: 316-22.
- <sup>61</sup> Sorahan T and Cooke M. *Cancer mortality in a cohort of United Kingdom steel foundry workers: 1946-85*. Brit J Ind Med 1989; 46: 74-81.
- <sup>62</sup> Decoufle P and Wood D. *Mortality patterns among workers in a gray iron foundry*. Am J Epidemiol 1979; 109: 667-75.
- <sup>63</sup> Breslin P. *Mortality among foundry men in steel mills*. Editor: Lemen R, Dement, JM (eds). Dusts and Disease: IL: Pathotox Publishers, 1979; pages 439-447;



- <sup>64</sup> Egan-Baum E, Miller B and Waxweiler R. *Lung cancer and other mortality patterns among foundrymen*. Scand J Work Environ Health 1981; 7: 147-55.
- <sup>65</sup> Oddone E, Scaburri A, Bai E, Modonesi C, Stracci F, Marchionna G, et al. *Occupational brain cancer risks in Umbria (Italy), with a particular focus on steel foundry workers*. G Ital Med Lav Erg 2014; 36: 111-7.



# annexes



## A IARC evaluation and conclusion

Iron and steel founding was considered by IARC Working Groups in 1984, 1987 and in 2012.<sup>5-7</sup> 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).<sup>5</sup> 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)*.



## B reliability testing of animal and in vitro studies

### *Reliability 4 (not assignable)*

For example, only short abstract available; only secondary literature (review, tables, books, etc.).

To assess the reliability of animal and in vitro studies, the Committee uses the criteria set by Klimisch et al. 1997.<sup>1</sup> 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.





## C reliability testing of epidemiological studies

To assess the reliability of epidemiological studies, the Committee uses the criteria set by Money et al.(2013).<sup>2</sup> 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).<sup>27</sup>

#### *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.



## D 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.<sup>3</sup>

### 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: <ul style="list-style-type: none"> <li>- positive result(s) from in vivo heritable germ cell mutagenicity tests in mammals; or</li> <li>- 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</li> <li>- 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.</li> </ul>

Categories	Criteria
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: <ul style="list-style-type: none"> <li>- positive evidence obtained from experiments in mammals and/or in some cases from in vitro experiments, obtained from: <ul style="list-style-type: none"> <li>- somatic cell mutagenicity tests in vivo, in mammals; or</li> <li>- other in vivo somatic cell genotoxicity tests which are supported by positive results from in vitro mutagenicity assays.</li> </ul> </li> </ul> <p><i>Note:</i> 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.</p>

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;
  - nscheduled 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.

Ingredient classified as:	Concentration limits triggering classification of a mixture 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 proven that no other routes of exposure cause the hazard)	H341: Suspected of causing 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).



## E classification on carcinogenicity

In 2010, the committee published a guideline for classifying substances in terms of their carcinogenic properties, and for assessing their genotoxicity.<sup>4</sup> The classification on carcinogenic properties is based on the Globally Harmonized System which is also used by the European Union for the classification, labelling and packaging of substances and mixtures (Regulation EC 1272/2008, Section 3.6 Carcinogenicity).<sup>3</sup>

Category	Judgement of the Committee (GRGHS)	Comparable with EU Category
1A	<p><i>The compound is known to be carcinogenic to humans.</i></p> <p>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.</p>	1A
1B	<p><i>The compound is presumed to be as carcinogenic to humans.</i></p> <p>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.</p>	1B
2	<p><i>The compound is suspected to be carcinogenic to man.</i></p>	2
(3)	<p><i>The available data are insufficient to evaluate the carcinogenic properties of the compound.</i></p>	not applicable
(4)	<p><i>The compound is probably not carcinogenic to man.</i></p>	not applicable





# F individual components that can be found in the emission during iron and steel founding

**Source IARC Monograph 100F (2012, pages 497 - 507), compilation of Table 1.1 and text in section 1.2**

*“Substantial exposures to silica and carbon monoxide continue to occur in many foundries. Occupational exposures to airborne polycyclic aromatic hydrocarbons (PAHs) are also present, resulting mainly from the thermal decomposition of carbonaceous ingredients commonly added to foundry sand. In addition, some steel foundry workers (e.g. fettlers) are exposed to airborne chromium and nickel compounds. The introduction of organic binder materials in the late 1950s has resulted in exposures of foundry workers to other chemicals, including phenol, formaldehyde, isocyanates and various amines. Earlier exposure studies have been reviewed previously (IARC, 1984). More recent studies are presented here and summarized in Table 1.1.”*

**Table 1.1** (Geometric) mean air levels, data published after 1984

Substance name	Mean level	Lowest level	Highest level	Range	Note
Respirable dust (in air, µg/m <sup>3</sup> )	n.d.p.	580	580	20 – 31,000	Exposure level depending on job title or content
Respirable quartz (in air, µg/m <sup>3</sup> )	n.d.p.	28	28	3 – 2,100	Exposure level depending on job title or content
Carbon monoxide (in air, µg/m <sup>3</sup> )	n.d.p.	n.d.p.	n.d.p.	n.d.p.	No data
Binder components*: isocyanates (in air, µg/m <sup>3</sup> )	n.d.p.	3.4	200	< 4 – 1,600	Exposure level depending on job title or content
Polycyclic aromatic hydrocarbons (in air, µg/m <sup>3</sup> ):					Exposure level depending on job title or content
- Pyrene	n.d.p.	0.0	0.22	n.d.p.	
- Benzo[a]pyrene	n.d.p.	0.0	0.04	n.d.p.	
- Sum of 15 PAHs	n.d.p.	0.58	11.17	n.d.p.	
Metals					Exposure level depending on job title; confirmed exposure to lead and cadmium; data missing on job history
- Thallium (in urine, µg/l)	n.d.p.	0.22	0.38	0.06 – 1.22	
- Manganese (in blood, µg/l)	2.5 ± 5	n.d.p.	n.d.p.	n.d.p.	
- Cadmium (in urine, µg/l)	9.52	n.d.p.	n.d.p.	3.19 – 22.07	
- Cobalt (in urine, µg/l)	8.18	n.d.p.	n.d.p.	3.06 – 23.30	
- Nickel (in urine, µg/l)	33.10	n.d.p.	n.d.p.	13.90	
- Lead (in urine, µg/l)	53.50	n.d.p.	n.d.p.	– 78.90 28.90 – 85.60	
Refractory ceramic fibres					Exposure level depending on job title
- in fibres/mL air	1	n.d.p.	23	n.d.p.	
- in fibres/cm <sup>3</sup> of lavage fluid	34 - 930	0.01	930	< 0.01 – 0.29	

n.d.p., No data presented.



\* Binder components. “Organic binder materials for cores and moulds include furan, phenol-formaldehyde, urea-formaldehyde and urethane resins as well as oleo-resinous oils. These ingredients may volatilize into the workplace air during mixing, blowing, ramming, drying or baking operations. Curing reactions and thermal decomposition give rise to formation of additional compounds, which are released during pouring and shakeout. When organic binders are subjected to high temperatures, pyrolysis may produce gases and smoke aerosols. Only a few components of these emissions have been identified: aliphatic components include methane, ethane, ethylene, acetylene, and smaller amounts of high molecular-weight compounds; aromatic substances include benzene, toluene, xylenes, naphthalenes and a variety of PAHs in lower concentrations. Nitrogen compounds such as ammonia, cyanides and amines may be formed from the nitrogen-containing urea, ammonium salts and hexamethylenetetramine that are used as binder chemicals. Urethane resins may emit free isocyanates under moulding and pouring conditions. No-bake catalysts, based on arylsulphonic acids, may produce sulfur dioxide and hydrogen sulphide by thermal processes. If phosphoric acid is used as a catalyst, phosphine can be formed in the strongly reducing atmosphere of the hot emissions. In air, phosphine rapidly oxidizes to phosphorus oxide. Furan binders contain free furfuryl alcohol, which can volatilize during mixing, moulding or core-making. Similarly, furan and phenolic resins may emit formaldehyde, phenol and other derivatives by volatilization or thermal decomposition. Core oils and alkyd-isocyanate resins are partly composed of natural drying oils, and heating of these materials gives rise to acrolein, various aldehydes, ketones, acids and esters as well as aliphatic hydrocarbons. When organic solvents are used in sand binders, the vapours may add to the exposure of workers (Toeniskoetter & Schafer, 1977; IARC, 1984).”

**Source: IARC Monograph 34 (1984, pages 133 - 190), compilation of Table 4 and text in section 3.1**

“A wide variety of occupational health hazards is present in iron and steel foundries: airborne crystalline silica is virtually ubiquitous in foundries that use quartz and for moulding and coremaking; metallic fumes are present during melting, pouring, welding and flame-cutting processes; and metal dusts are associated with abrasive grinding operations. The cupola and casting operations may emit carbon monoxide into the working environment. Phenol, formaldehyde, furfuryl alcohol, isocyanates and amines are used as ingredients of organic binders in mould and core sands. Furthermore, several carbonaceous materials are in contact with molten metal during pouring and thus various pyrolysis products, including polynuclear aromatic compounds, are formed.”

“Main airborne contaminants to which workers may be exposed are given in Table 4.”



**Table 4. Airborne substances (and cases of substances) found in iron and steel foundries<sup>a</sup>**

Material	Principle uses or sources of emission
<i>Common airborne contaminants</i>	
(e.g., hexamethylenetetramine triethylamine; Dimethylethyl amine, aniline)	Urethane binders, amine gassing of urethane resins, thermal decomposition of urea, urethane or shell binders
Ammonia	Thermal decomposition of hexamethylenetetramine in shell moulding, decomposition of urea or urethane binders
Bentonite	Foundry sand, refractory materials
Carbon	Coal powder, graphite and soot in foundry sand, coke in cupola melting, core and mould coatings, constituent of ferrous alloys, electrodes in arc melting and gouging
Carbon dioxide	Combustion of carbonaceous materials in foundry sand, cupola melting, fuel combustion in furnaces, ovens, heaters and engines, carbon dioxide gassing of silicate binders, inert gas welding
Carbon monoxide	Combustion of carbonaceous materials in foundry sand, cupola melting, fuel combustion in furnaces, ovens, heaters and engines, flame cutting and welding
Chromite	Foundry sand, refractory materials
Chromium and chromium oxides (chromium VI, chromium III, chromium metallic)	Steel alloys, melting, pouring, cutting, grinding and welding operations
Chlorinated hydrocarbons (e.g., 1,1,1-trichloroethane)	Solvents
Cristobalite	Refractory materials, high-temperature transformation of silicon dioxide
Fluorides	Melting, slagging and welding
Formaldehyde	Urea, phenol and furan resins, thermal decomposition of organic materials in core baking and casting
Furfuryl alcohol	Furan resins

Material	Principle uses or sources of emission
Hydrocarbons, aliphatic and aromatic (e.g., benzene, toluene, xylene, naphthalene)	Solvents for binders and paints, pattern resins and glues, core and mould dressings, metal primers, petroleum fuels, thermal decomposition of organic materials in foundry sand
Hydrogen sulphide	Water quenching of furnace slag, thermal decomposition of sulphur compounds in foundry sand
Iron and iron oxides	Ferrous alloys, melting, pouring, cutting, grinding and welding
Isocyanates (e.g., 4,4'-methylenediphenyl diisocyanate)	Urethane resins, thermal decomposition of urethane binders in foundry sands
Lead and lead oxides*	Scrap melting, spray painting operations
Magnesium and magnesium oxide	Inoculation process in production of nodular iron
Manganese and manganese oxides	Ferrous alloys, melting, pouring, cutting, grinding and welding operations
Nickel and nickel oxides	Steel alloys, melting, pouring, cutting, grinding and welding operations
Nitrogen oxides	Thermal decomposition of urea or urethane binders in foundry sand, flame cutting and welding, internal combustion engines
Olivine	Foundry sand, refractory materials
Phenols (e.g., cresol, phenol, xylenol)	Phenolic binders, thermal decomposition of organic materials in foundry sand
Polynuclear aromatic hydrocarbons	Coal-tar pitch, thermal decomposition of carbonaceous materials in foundry sand, fuel combustion in furnaces, ovens, heaters and engines
Silica, quartz	Foundry sand, refractory materials, sand blasting
Sulphur dioxide	Combustion of sulphurous fuels, sulphur-dioxide gassing and decomposition of furan resins
Tridymite	Refractory materials, high-temperature, phase transformation of quartz
Vanadium and vanadium oxides (vanadium pentoxide)	Steel alloying



Material	Principle uses or sources of emission
Zinc and zinc oxides	Scrap melting
Zircon	Foundry sand, refractory materials
<i>Other airborne contaminants</i>	
Acrolein	Thermal decomposition of vegetable oils in care baking and casting
Alcohols, aliphatic (e.g., isopropanol)	Solvents for binders and paints, carriers for care and mould dressings, components of urethane resins
Asbestos	Thermal or electrical insulation in furnaces and ovens; coverings, troughs and clothing in pouring areas
Cadmium and cadmium oxide	Scrap melting
Calcium carbide, calcium carbonate, calcium silicide, calcium oxide	Melting, alloying and slagging
Carbon disulphide	Decomposition of furan resins with sulphonic acid catalysts
Carbonyl disulphide	Decomposition of furan resins with sulphonic acid catalysts
Copper and copper oxides	Scrap melting, arc gouging with coated carbon electrodes
Cyanides (e.g., hydrogen cyanide)	Thermal decomposition of urea or urethane binders, heat treatment of special castings
Esters (e.g. glycerol diacetate, butyl acetate)	Ester-silicate process, foundry solvents
Ethyl silicate	Silicate binders
Ferromanganese, ferromolybdenum, ferrosilicon, ferrovanadium	Melting and alloying
Methylethylketone peroxide	Sulphur-dioxide gassing process
Nitrogen heterocyclics (e.g., pyridine)	Coal-tar pitch, thermal decomposition of carbonaceous materials in foundry sand
Nitrosamines (e.g., N-nitrosodimethylamine*, N-nitrosodiethylamine)	Reaction of nitrogen oxides with amines in foundry sand

Material	Principle uses or sources of emission
Oxygen heterocyclics (e.g., furan, methylfuran)	Furan resins
Ozone	Inert gas welding
Phosphine	Reaction of water with phosphides in ferroalloys, decomposition of furan binder, furan resins catalysed with phosphoric acid
Phosphoric acid	Catalyst for furan resins
Radon	Zircon sands
Sulphonic acids (e.g., toluene/sulphonic acid)	Catalyst for furan resins
Sulphur heterocyclics (e.g., thiophene)	Decomposition of furan resins
Talc	Core and mould dressings

Note IARC: The list includes chemicals (or classes of chemicals) used in or formed in iron and steel founding operations, and the processes during which they are used or formed or during which exposures are most likely to occur. It was compiled from information collected during the preparation of the monograph and cannot pretend to be exhaustive.



## G substances identified in the emissions of iron and steel founding, which are classified for carcinogenicity

**Substances identified in the emissions of iron and steel founding, which are classified for carcinogenicity by IARC** (Source [www.iarc.fr](http://www.iarc.fr); last visited, September 30, 2019)

IARC classification	Substance name
Group 1 (the agent is carcinogenic to humans)	Asbestos Benzene Benzo[a]pyrene (PAH) Cadmium Cadmium oxide Chromium VI compounds Coal tar pitch Cristabolite Formaldehyde Isopropanol Nickel oxides Respirable quartz
Group 2A (the agent is probably carcinogenic to humans)	Lead oxides Nitrosamines

IARC classification	Substance name
Group 2B (the agent is possibly carcinogenic to humans)	Cobalt Furan Furfuryl alcohol Lead Naphthalene Nickel Nitrosamines Refractory ceramic fibres Vanadium pentoxide
Group 3 (the agent is not classified as to its carcinogenicity to humans)	1,1,1-trichloroethane 4,4'-methylenediphenyl diisocyanate Aniline Chromium III compounds Chromium metal Ferrochromium Fluorides Lead Phenol Pyrene (PAH) Talc Toluene Xylene
Group 4 (the agent is probably not carcinogenic to humans)	-



**Substances identified in the emissions of iron and steel founding, which are classified for carcinogenicity in The Netherlands**

*Source:* CMR-list of the Dutch Ministry of Social Affairs and Employment. The list comprises substances classified in category 1A or 1B for carcinogens, according to the Dutch legislation (Staatscourant, website: <https://zoek.officielebekendmakingen.nl>; last visited, September 30, 2019).

- Asbestos
- Benzene
- Benzo[a]pyrene
- Cadmium
- Cadmium oxide
- Chromium VI compounds
- Formaldehyde
- Furan
- Nickel oxide
- Nitrosamines (e.g., N-nitrosodiethanolamine, N-nitrosodiethylamine, N-nitrosodiisopropylamine, N-nitrosodimethylamine, N-nitrosodi-n-butylamine, nitrosodipropylamine, N-nitrosomethylethylamine, N-nitrosomethylvinylamine, N-nitrosoethylureum, N-nitrosomethylureum, N-nitrosomorfoline, N-nitrosopiperidine, N-nitrosopyrrolidine)
- Refractory ceramic fibres

- Respirable crystalline silica
- Work that involves exposure to polycyclic aromatic hydrocarbons, which is present in soot and tar from coal
- Work that involves exposure to work activities that generate respirable crystalline silica



# H genotoxicity: mutagenicity in vitro

Method and reference	Cell type and conditions	Source test substance and doses applied in test system	Results	Reliability (Annex B)
Reverse mutation (Ames test) Skyttä et al. (1980) <sup>28</sup>	<i>Salmonella typhimurium</i> 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 <sup>3</sup>  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) <sup>29</sup>	<i>Salmonella typhimurium</i> 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



Method and reference	Cell type and conditions	Source test substance and doses applied in test system	Results	Reliability (Annex B)
Reverse mutation (Ames test) Humfrey et al. (1996) <sup>8</sup>	<i>Salmonella typhimurium</i> 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 (authors remarked that the positive control compounds “demonstrated the sensitivity of the assay and the metabolic activity of the S-9 mix”; no data on statistical analysis  Reliability 2
Reverse mutation (Ames test) Gibson et al. (1983) <sup>30</sup>	<i>Salmonella typhimurium</i> TA98, with (+) and without (-) metabolic activation (S9)	Ferrous foundries; foundry-air particulate was collected and filtered, and 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 <sup>3</sup> , modified data from literature): Steel foundry: 0.43 Iron foundry: 0.94	Foundry areas (foundry not specified): positive (+/- S9) + S9 gave higher mutation rates than -S9  Bulk of total mutagenicity associated with particulates <1.1 µm diameter  Moulding materials: negative	Study design not appropriate  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) <sup>31</sup>	<i>Salmonella typhimurium</i> 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





Method and reference	Cell type and conditions	Source test substance and doses applied in test system	Results	Reliability (Annex B)
Reverse mutation (Ames test) Kaiser-Farell et al. (1986) <sup>32</sup>	<i>Salmonella typhimurium</i> 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 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-acetyl-amino-fluorene, 1-nitropyrene and 2-nitrofluorene Negative control: ambient background	+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
Reverse mutation (Ames test) Kaiser et al. (1981) (Source: IARC 1984) <sup>5</sup>	<i>Salmonella typhimurium</i> 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; <i>Salmonella typhimurium</i> TA98) Tomkins et al. (1990) <sup>33</sup> , Tomkins et al. (1986) <sup>34</sup>	Urinary 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.  Reverse mutations (smoking status) - never: 1.65-2.00 rev/ml - current: 3.81-4.09 rev/ml  No other data presented.	Only one strain tested; lack of detailed information on results, such as number of workers among groups, and number of smokers  Reliability 4



# I 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 B)
Somatic gene mutation ( <i>HPRT</i> locus) Perera et al. (1994) <sup>35</sup>	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 <sup>3</sup> , N=20 - medium: 5-12 ng/m <sup>3</sup> , N=26 - high: >12 ng/m <sup>3</sup> , N=18	<i>HPRT</i> mutations (mutation frequency/106 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 B)
Micronuclei frequency Kubiak et al. (1999) <sup>9</sup>	Peripheral lymphocytes obtained from steel foundry workers (N=91)  Samples were taken in 1991, 1993 and 1996  Lymphocytes were cytokinesis-blocked	Polish steel foundry  Ambient PAH levels at the work stand (mean $\mu\text{g B(a)P}/\text{m}^3$ , 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 ( $\mu\text{moles}/\text{Mol creatinine}$ ): - Coke oven workers: $10.78 \pm 13.44$ ( $p=0.0008$ ) - Rollers: $0.76 \pm 0.63$	Mean micronuclei frequency: - Coke oven workers: $12.4 \pm 0.77$ , $p=0.84$ - Rollers: $11.3 \pm 0.59$ Difference between groups not statistically significant  No relationship between micronuclei frequency and duration of work.	Small study  Information on smoking, drinking, protective equipment and current or prior occupational exposures  Reliability 2
Chromosome aberrations (CA); Sister chromatid exchange (SCE); micronuclei  Tomkins et al. (1990), <sup>33</sup> Tomkins et al. (1986) <sup>34</sup>	Blood samples obtained from Canadian steel foundry workers (N=125)  Groups: - high-risk (crane operators) - intermediate-risk (moulders 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



Method and reference	Cell type and conditions	Source test substance and doses applied in test system	Results	Quality score (see Annex B)
Chromosome aberrations (CA); Sister chromatid exchange (SCE)  Rudek (1990) <sup>36</sup>	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 period 1986-1988; CA counted in 150-200 metaphases/ sample, SCE counted in 50 metaphases/ sample	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



## DNA-adduct formation

Method and reference	Cell type and conditions	Source test substance and doses applied in test system	Results	Quality score (see Annex B)
Aromatic DNA adducts (32P-postlabelling assay)  Phillips et al. (1988) <sup>37</sup>	Peripheral white blood cells from healthy iron foundry workers (N=24)  Unexposed controls: subjects from different parts of Finland (N=9)	Finnish iron foundry  Industrial hygiene measurements for PAH in 1978-1980 (as B(a)P)]. Workers divided into three exposure groups; - low (<0.05 µg/m <sup>3</sup> ), N=16 - medium (0.05-0.2 µg/m <sup>3</sup> ), N=6 - high (>0.2 µg/m <sup>3</sup> ), N=2	Mean no. of adducts/108 nucleotides (range): - low: 0.06 (0-0.6) - high/medium: 1.8 (0-10.0) - controls: 0.2 (0-1.9)  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	Small study  Variability in exposure levels; no data on statistical analysis  Reliability 2
Aromatic DNA adducts (32P-postlabelling assay)  Reddy (1991) <sup>38</sup>	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/108 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 <sup>3</sup> ) - medium (0.05-0.2 µg/m <sup>3</sup> ) - high (>0.2 µg/m <sup>3</sup> )	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



Method and reference	Cell type and conditions	Source test substance and doses applied in test system	Results	Quality score (see Annex B)
<p>Aromatic DNA adducts (32P-postlabelling assay)</p> <p>Santella et al. (1993)<sup>39</sup></p>	<p>Peripheral white blood cells from healthy iron male and female foundry workers (N=48; 37 males, 11 females)</p> <p>Employment period ranges from 2 to 46 years (average 13 years)</p>	<p>Finnish iron foundry</p> <p>Personal exposure to PAH (determination of B(a)P) ranged between 2 and 60 ng/m<sup>3</sup>):</p> <ul style="list-style-type: none"> <li>- Low: &lt; 5 ng/m<sup>3</sup></li> <li>- Medium: 5-12 ng/m<sup>3</sup></li> <li>- High: &gt;12 ng/m<sup>3</sup></li> </ul> <p>Mean 1-hydroxypyrene levels (µmol/mol creatinine) in group:</p> <ul style="list-style-type: none"> <li>- Low: 2.7±2.2</li> <li>- Medium: 1.8±1.2</li> <li>- High: 3.6±2.5</li> </ul>	<p>Mean DNA adducts (adducts/108 nucleotides, adjusted for smoking habits):</p> <ul style="list-style-type: none"> <li>- Low: 5.1±4.1</li> <li>- Medium: 6.1±4.3</li> <li>- High: 9.6±8.1</li> </ul> <p>Dose-related increase with exposure (r=0.28, p=0.08); exposure groups did not differ significantly from each other</p> <p>No Influence of cigarette smoking on formation of DNA adducts (54% of workers were smokers)</p>	<p>Small study</p> <p>Large inter-individual variability; study did not include reference group without exposure, lowest exposure group served as reference</p> <p>Reliability 2</p>
<p>Aromatic DNA adducts (32P-postlabelling assay)</p> <p>PAH-DNA adducts (competitive ELISA)</p> <p>Somatic gene mutation (<i>HPRT</i> locus)</p> <p>Perera et al. (1994)<sup>35</sup></p>	<p>Peripheral white blood cells from healthy iron male and female foundry workers (N=64; 51 males, 13 females)</p> <p>Average length of employment: 14 years (range 1 to 47 years)</p> <p>One or two samples were taken in 1990 (year 1) and/or in 1991 (year 2)</p> <p>50% current smokers</p>	<p>Finnish iron foundry</p> <p>Workers were divided into exposure groups (in B(a)P):</p> <ul style="list-style-type: none"> <li>- low: &lt; 5 ng/m<sup>3</sup>, N=20</li> <li>- medium: 5-12 ng/m<sup>3</sup>, N=26</li> <li>- high: &gt;12 ng/m<sup>3</sup>, N=18</li> </ul>	<p>Aromatic DNA adducts (mean no. of adducts/108 nucleotides; year 1, 2, 1+2)</p> <ul style="list-style-type: none"> <li>- low: 2.2±0.8, 1.3±0.6, 1.9±0.9</li> <li>- medium: 2.1±1.4, 1.5±1.1, 2.0±1.4</li> <li>- high: 2.5±1.2, 2.3±2.0, 2.5±1.2</li> </ul> <p>PAH-DNA adducts (mean no. of adducts/108 nucleotides; year 1, year 2 and year 1+2):</p> <ul style="list-style-type: none"> <li>- low: 5.2±4.1, 1.5±1.4, 4.4±3.9</li> <li>- medium: 6.1±4.3, 2.9±3.1, 5.2±4.2</li> <li>- high: 9.6±8.1*, 3.9±4.1, 9.6±8.1</li> </ul> <p>* p&lt;0.05 (low versus high exposure)</p>	<p>Small study</p> <p>Adjustments made for smoking</p> <p>Variability in exposure levels within groups; study did not include reference group without exposure, lowest exposure group served as reference</p> <p>Reliability 2</p>



## J 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 C)
<p>Cohort studies on workers employed in iron and steel foundries with data on lymphatic and haematopoietic neoplasms (N=12)*</p> <p>Alicandro et al. (2016)<sup>12</sup></p> <p>* Decoufle et al. 1979; Anjelkovich 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 K (indicated as B)</p>	<p><i>Search period:</i> up to February 2016</p> <p><i>Inclusion criteria:</i> workers exposed to PAH; incidence or mortality risk from (non-) Hodgkin lymphomas, multiple myeloma or leukemia, related to PAH exposure; publications in English, French or Italian; cause specified according to international classification of diseases</p> <p><i>Quality assessment individual studies:</i> not reported</p> <p><i>Meta-analyses:</i> 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</p>	<p>Outcome: no associations found</p> <p>Meta-relative risks (95% confidence interval, number of cases, I-squared (%), p for heterogeneity:</p> <p>Hodgkin lymphoma 1.38 (0.95-2.01), 26 cases, 0%, <math>p=0.53</math></p> <p>Non-Hodgkin lymphoma 0.94 (0.73-1.22), 57 cases, 0%, <math>p=0.87</math></p> <p>Multiple myeloma 1.00 (0.67-1.51), 23 cases, 0%, <math>p=0.26</math></p> <p>Leukaemia 1.13 (0.93-1.39), 103 cases, 4%, <math>p=0.41</math></p> <p>No significant between-study heterogeneity was observed; no indications for publication bias</p>	<p>Appropriate design and reporting</p> <p>No quality assessment of individual studies performed; smoking habits not taken into account</p> <p>Reliability 2</p>



Selected studies and study population	Study selection criteria	Results	Remarks and reliability ( Annex C)
<p>Cohort studies on workers employed in industries with potential PAH exposure (N=13, iron and steel foundries)*</p> <p>Rota et al. (2014)<sup>10</sup>, Update from Bosetti et al. (2006)</p> <p>* 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 K (indicated as C)</p>	<p><i>Search period:</i> 1958 – 2014</p> <p><i>Inclusion criteria:</i> cancer/tumours on respiratory and urinary tracts; PAH exposure; retrospective, longitudinal and prospective cohorts; one publication per cohort (most informative); cancer cases and deaths</p> <p><i>Quality assessment individual studies:</i> not included</p> <p><i>Meta-analyses:</i> standard mortality ratios, pooled relative risks; random-effects models to take into account heterogeneity</p> <p><i>Heterogeneity:</i> <math>p &lt; 0.10</math> is indicative for substantial heterogeneity (variation between studies)</p>	<p>Outcome: positive association for certain cancer types</p> <p>Standard mortality ratios (SMR) and pooled relative risk (RR) (95% confidence interval), observed/expected, p value for heterogeneity:</p> <p><i>Respiratory tract</i></p> <ul style="list-style-type: none"> <li>- all: SMR 1.05, pooled RR 1.31 (1.08-1.59), 2,932/2,784, <math>p &lt; 0.0001</math></li> <li>- lung cancer: SMR 1.05, pooled RR 1.31 (1.07-1.61), 2,903/2,762, <math>p &lt; 0.0001</math></li> <li>- larynx: SMR 1.43, pooled RR 1.48 (1.14-1.91), 59/41, <math>p = 0.537</math></li> </ul> <p><i>Bladder cancer</i></p> <p>SMR 1.18, pooled RR 1.38 (1.00-1.91), 151/127, <math>p = 0.001</math></p> <p><i>Cancer in the kidneys</i></p> <p>SMR 0.98, pooled RR 1.03 (0.78-1.35), 68/69, <math>p = 0.304</math></p>	<p>Appropriate design and reporting</p> <p>No quality assessment of individual studies performed; smoking habits not taken into account</p> <p>Authors report that workers may be exposed in the past to various potential carcinogenic substances other than PAH</p> <p>Reliability 2</p>
<p>Cohort studies on workers in the iron and steel foundry with potential PAH exposure (N=10)*</p> <p>Bosetti et al. 2006<sup>11</sup></p> <p>*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 K (indicated as D)</p>	<p><i>Search period:</i> Up to December 2005</p> <p><i>Inclusion criteria:</i> 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)</p> <p><i>Quality assessment individual studies:</i> not performed or reported</p> <p><i>Meta-analysis:</i> 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</p>	<p>Outcome: positive association for cancer in the lungs, respiratory tract and the bladder; no association for kidney cancer</p> <p>Order: standardized mortality ratio (SMR), observed/expected no. of cases, pooled RR (95% confidence intervals), <math>p</math>-value for heterogeneity</p> <p><i>Lung cancer (9 cohorts)</i></p> <p>SMR, 1.39, 975/703.7, 1.40 (1.32-1.49), <math>p = 0.007</math></p> <p><i>Respiratory tract cancers (10 cohorts)</i></p> <p>SMR, 1.38, 1,004/726, 1.40 (1.31-1.49), <math>p = 0.012</math></p> <p><i>Bladder cancer (7 cohorts)</i></p> <p>SMR, 1.19, 99/83, 1.29 (1.06-1.57), <math>p &lt; 0.001</math></p> <p><i>Kidney cancer (4 cohorts)</i></p> <p>SMR, 1.29, 40/31, 1.30 (0.095-1.77), <math>p = 0.91</math></p>	<p>Appropriate design and reporting</p> <p>No quality assessment of individual studies performed; smoking habits not taken into account</p> <p>Reliability 2</p>





Selected studies and study population	Study selection criteria	Results	Remarks and reliability ( Annex C)
<p>Cohort studies on workers employed in industries with potential PAH exposure (N=3, iron and steel foundries, total of 5,658 subjects)*</p> <p>Singh et al. 2018<sup>13</sup></p> <p>* Gibson et al. 1977; Moulin et al. 2000; Koskela et al. 1997. Details of the individual studies are shown in Annex K (indicated as A)</p>	<p><i>Search period:</i> 1977-2017</p> <p><i>Inclusion criteria:</i> 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</p> <p><i>Quality assessment individual studies:</i> not included</p> <p><i>Meta-analyses:</i> standard mortality ratios, pooled relative risks; random-effects models to take into account heterogeneity; fixed effect models</p> <p><i>Subgroup analyses:</i> job title</p>	<p>Outcome: Focus on PAH exposure, not on iron and steel founding per se, therefore only a limited number of studies included. Two of the three studies also included in Rota, for the 3rd study the reference is questionable (conference abstract only). Therefore this publication is not relevant.</p> <p>Pooled relative risk (95% confidence interval)</p> <p><i>Lung cancer</i> 1.52 (1.05-2.21), 135 cases (incidence and mortality combined)</p> <p>Authors reported on wide variation in smoking habits and exposure to PAH, but data on PAH exposure levels not reported</p>	<p>Appropriate design</p> <p>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</p> <p>Reliability 2</p>



## K epidemiology: cohorts studies

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).

### Prospective cohort studies

Study design and population	Data on exposure and health assessment	Results	Remarks and reliability (annex C)
No studies.			



## Retrospective cohort studies (data on smoking habits)

Study design and population	Data on exposure and health assessment	Results	Remarks and reliability (annex J)
<p>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</p> <p><sup>B,C</sup>Park et al. (2005)<sup>40</sup></p>	<p><i>Exposure:</i> 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</p>	<p>Outcome: positive association with “all types of cancer”; no association with individual types of cancer</p> <p>During follow-up: 806 death cases (=2% of population at risk)</p> <p>Standardized rate ratio (95% confidence interval, number of deaths)</p> <ul style="list-style-type: none"> <li>- stainless steel production areas:</li> <li>- all cancer: 3.26 (1.37-6.49), N=7</li> </ul>	<p>Appropriate study design, large study</p> <p>No analyses performed on exposure levels of substances</p> <p>Reliability 2</p>
<p>Note by the DECOS: most likely partly overlap of the study population with the populations in the studies by Yoon and Ahn (2014)<sup>41</sup> and Ahn et al. (2010)<sup>42</sup></p>	<p><i>Data:</i> deaths identified by the Korean National Statistical Office; diseases classified according to International Classification of Diseases; analyses included lag-time</p> <p>Smoking habits obtained from part of workers</p>	<p>No associations found regarding:</p> <ul style="list-style-type: none"> <li>- type of cancer</li> <li>- duration of employment</li> </ul> <p>Authors reported large healthy worker effect for “all death causes”, and “cancer”</p> <p>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%).</p> <p>Authors note “<i>The current smoking rate was similar across categories of last job. The overall smoking rate of study subjects in 1994 was about 15% lower than that of Korean male population in that year in the same age range</i>”.</p>	



Study design and population	Data on exposure and health assessment	Results	Remarks and reliability (annex J)
<p>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</p> <p><sup>B,C</sup>Westberg et al. (2013)<sup>17</sup></p>	<p><i>Exposure:</i> respirable dust and quartz measurements (340 personal samples taken between 2005-2006) plus historical measurement data from surveys from the 1960s</p> <p><i>Morbidity:</i> data retrieved from company personnel records, and Swedish cancer Registry; diseases classified according to International Classification of Diseases</p> <p>Smoking habits were obtained by questionnaire among 500 participants; percentage of ex-smokers and smokers were 68%, 65% and 84% in the low-medium and high-exposed groups (exposure to respirable quartz), data on individual smoking habits were not available.</p>	<p>Outcome: positive association with lung cancer</p> <p>Standardized incidence ratios (95% confidence interval, expected/ observed) (data without taking into account smoking habits)</p> <p>Only data shown with statistically significant increased SIR</p> <p><i>All workers</i></p> <ul style="list-style-type: none"> <li>- all cancer types: 1.00 (0.90-1.11), 347.2/347</li> <li>- primary lung cancer: 1.61 (1.20-2.12), 32.24/52</li> </ul> <p><i>Duration of exposure</i></p> <p>No association between duration of exposure and cancer development</p> <p><i>Latency time and duration of employment (lung cancer)</i></p> <ul style="list-style-type: none"> <li>- Latency 0-19 yrs: no association</li> <li>- Latency ≥ 20 yrs</li> <li>- duration 10-19 yrs: 2.35 (1.12-4.31), 4.27/10</li> <li>- duration ≥ 20 yrs: 1.72 (1.08-2.61), 12.76/22</li> </ul> <p><i>Latency time and cumulative quartz exposure (lung cancer)</i></p> <ul style="list-style-type: none"> <li>- Latency 0-19 yrs: no association</li> <li>- Latency ≥ 20 yrs</li> <li>- low exposure: 2.05 (1.32-3.02), 12.22/25</li> <li>- medium exposure: 1.72 (1.00-1.75), 9.89/17</li> <li>- high exposure: 1.26 (0.26-3.69), 2.38/3</li> </ul> <p>No dose-related trend observed</p>	<p>Appropriate study design</p> <p>Authors performed internal comparison in their dose-response analyses to adjust for differences in smoking habits or other confounders between foundry workers and the general population: the increased lung cancer risk disappeared when the exposure groups were compared.</p> <p>Reliability 2</p>



Study design and population	Data on exposure and health assessment	Results	Remarks and reliability (annex J)
<p>Nested case-control study from retrospective cohort described by <sup>B,C,D</sup>Rotimi et al. (1993); one iron foundry; the USA; total number of lung cancer cases is 231; 408 controls</p> <p>Note (1): cases and control represent total of one iron foundry and two engine plants (data on iron foundry alone not reported)</p> <p>Note (2): cohort by <sup>B,C,D</sup>Rotimi et al. (2013)<sup>43</sup> not described in the present report, because no distinction is made between different types of industries</p> <p>Austin et al., (1997)<sup>44</sup></p>	<p>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.</p> <p>Mortality: from death certificate; cases include 9 cases with lung cancer as secondary cause of death</p>	<p>Outcome: positive association with lung cancer in workers handling material; no association among workers with other job activities</p> <p>Odds ratios (95% confidence intervals, cases/controls), lung cancer mortality</p> <p><i>Working area/job activities in iron foundry only (adjusted for smoking)</i></p> <ul style="list-style-type: none"> <li>- Quality control: 6.3 (0.71-56), 6/1</li> <li>- Material handling: 5.1 (1.5-17), 13/6</li> <li>- Maintenance: 0.87 (0.54-1.4), 31/62</li> <li>- Core room: 1.0 (0.57-56), 21/41</li> <li>- Melting: 0.10 (0.01-1.5), 1/6</li> <li>- Molding: 1.0 (0.48-2.1), 14/24</li> <li>- Cleaning/finishing: 0.92 (0.44-1.9), 15/28</li> </ul> <p><i>Duration of employment at iron foundry</i></p> <ul style="list-style-type: none"> <li>- non: 1.0 (-), 82/139</li> <li>- &lt;10 yrs: 0.79 (0.49-1.3), 53/104</li> <li>- 10-19 yrs: 1.1 (0.66-1.8), 45/67</li> <li>- ≥20 yrs: 0.90 (0.55-1.5), 51/98</li> </ul>	<p>Appropriate study design</p> <p>Lack of data on exposure levels; no data on other types of cancer; adjustments made for smoking habits</p> <p>Reliability 2</p>



Study design and population	Data on exposure and health assessment	Results	Remarks and reliability (annex J)
<p>Historical prospective cohort, including a nested case-control study; one stainless steel and metallic alloys plant; 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</p> <p><sup>A,C</sup>Moulin et al. 2000<sup>19</sup> (earlier results on cohort published: B,DMoulin et al. 1993)<sup>45</sup></p>	<p><i>Exposure:</i> assessed by job history (specific job-exposure matrix); mean duration of 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)</p> <p><i>Mortality:</i> death certificates (INSERM), diseases classified according to International Classification of Diseases</p> <p>Analyses included confounding factors, such as smoking habits</p>	<p>Outcome: no associations found</p> <p>Lost in follow-up, 1%</p> <p><i>Historical cohort</i></p> <p>Standardized mortality ratios (95% confidence interval), expected/ observed (adjusted for sex and age)</p> <p>Malignant neoplasms</p> <ul style="list-style-type: none"> <li>- men: 0.98 (0.85-1.12), 210.3/206</li> <li>- both sexes: 0.82 (0.85-1.11), 222/216</li> </ul> <p>Lung cancer: not increased</p> <p>Bladder cancer: not increased</p> <p><i>Nested case-control study (odds ratios, 54 cases/162 controls)</i></p> <p>PAH and silica exposure: increased trends observed by increasing duration of exposure (PAH, OR 1.46, p=0.01; silica, OR 1.55, p&lt;0.01) and estimated increased exposure levels (PAH, OR 1.42, p=0.06; silica, OR 1.32, p=0.04)</p> <p>No significant differences:</p> <ul style="list-style-type: none"> <li>- smokers versus non-smokers</li> <li>- among job categories</li> <li>- by substance (metals, asbestos)</li> </ul>	<p>Appropriate study design</p> <p>Lack of objective exposure levels; data on smoking habits available</p> <p>Moulin et al. 1993: "A survey of smoking habits performed among those in employment 1986 (24% of the cohort) showed a slightly higher percentage of smokers among the SS plant workers, than in the national average. This could not explain the high lung cancer rate in the foundry workers."</p> <p>Reliability 2</p>
<p>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</p> <p><sup>A,C,D</sup>Gibson et al. 1977<sup>46</sup></p>	<p><i>Exposure:</i> 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)</p> <p><i>Mortality:</i> death certificates from attending physician and insurance carrier; cause specified according to international classification of diseases</p>	<p>Outcome: positive association with lung cancer</p> <p>Standardized mortality ratios (SMR, 95% confidence interval, expected/observed)</p> <p><i>Lung cancer</i></p> <ul style="list-style-type: none"> <li>- Foundry: 2.55 (1.55-3.82), 8.4/21, p&lt;0.005</li> <li>- Non-foundry: 0.66 (0.33-1.19), 16.58/11</li> <li>- exposure &gt; 20 yrs</li> <li>- foundry (N=128): 2.59, 1.25/11, p=0.025</li> <li>- non-foundry (N=640): 0.69, 11.59/8</li> </ul> <p><i>All cancer</i></p> <ul style="list-style-type: none"> <li>Foundry: 1.38 (no data), 26.75/37, p&lt;0.01</li> <li>Non-foundry: 0.92 (no data), 53.27/49</li> </ul>	<p>Appropriate study design</p> <p>A smoking survey in 1973 showed no difference in smoking habits between foundry and non-foundry workers</p> <p>Limited data on confidence intervals</p> <p>Reliability 2</p>



Study design and population	Data on exposure and health assessment	Results	Remarks and reliability (annex J)
<p>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</p> <p>Silverstein et al. (1986)<sup>47</sup></p>	<p><i>Exposure:</i> 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</p> <p><i>Mortality:</i> based on records using various sources, such as local union death benefit fund and Social Security Administration; diseases classified according to International Classification of Diseases; smoking habits were recorded (71% of workers were classified as ever smokers)</p> <p>Some data adjusted for age, formerly employed in coal mines or other foundries, and smoking habits</p>	<p>Outcome: positive association with lung cancer and leukaemia</p> <p>Standardized proportional mortality rates (95% confidence interval):</p> <p><i>All cancers:</i></p> <ul style="list-style-type: none"> <li>- white workers (N=221): 1.18 (0.95-1.47), 61 cases</li> <li>- nonwhite workers (N=56): 1.17 (0.71-1.93), 12 cases</li> </ul> <p><i>Lung cancer:</i></p> <ul style="list-style-type: none"> <li>- white workers: 1.48 (1.04-2.10), 28 cases</li> <li>- nonwhite workers: 0.85 (0.17-2.49), 3 cases</li> </ul> <p><i>Leukaemia:</i></p> <ul style="list-style-type: none"> <li>- white workers: 2.84 (1.23-6.55), 5 cases</li> <li>- nonwhite workers: 0 cases</li> </ul> <p>Ever smokers had higher risks than non-smokers (white workers):</p> <p><i>All cancers:</i></p> <ul style="list-style-type: none"> <li>- never (N=45): 0.70 (0.38-1.27), 8 cases</li> <li>- ever (N=167): 1.30 (1.30-1.66), 51 cases, p&lt;0.05</li> </ul> <p><i>Lung cancer:</i></p> <ul style="list-style-type: none"> <li>- never: 0.96 (0.24-2.44), 4 cases</li> <li>- ever: 1.59 (1.08-2.33), 23 cases, p&lt;0.05</li> </ul> <p><i>Nested-case control study:</i></p> <p>No associations observed between type of work and lung cancer development.</p>	<p>Small study</p> <p>Data on standardized proportional mortality rates is notoriously prone to bias; no data on exposure levels presented</p> <p>Reliability 4</p>



## Retrospective cohort studies (no data on smoking habits)

Study design and population	Data on exposure and health assessment	Results	Remarks and reliability (annex J)
<p>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)</p> <p><sup>B</sup>Yoon and Ahn 2014<sup>41</sup></p> <p>Note by the DECOS: most likely partly overlap of the study population with the populations in the studies by Park et al. (2005)<sup>40</sup> and Ahn et al. (2010)<sup>42</sup></p>	<p><i>Exposure:</i> based on job title, jobs classified in categories, year first employed, age first employed</p> <p><i>Mortality:</i> data retrieved from Korea National Statistical Office; causes of death classified according to International Classification of Diseases</p>	<p>Outcome: positive association among production workers for stomach and lung cancer; no associations found for colon, liver, pancreas and urinary bladder cancer</p> <p>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</p> <p>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</p>	<p>Appropriate study design</p> <p>No data on smoking habits or other lifestyle factors that may have influenced the outcome; no data on exposure levels</p> <p>Reliability 2</p>
<p>Nested-case control study, Swedish cohort; iron foundries (N=10); 52 cases of lung cancer; for each case 5 controls were used</p> <p>Andersson et al. (2012)<sup>48</sup></p> <p>(for cohort details see also Westberg et al. 2013)<sup>17</sup></p>	<p><i>Exposure:</i> see Westberg et al. (2013), focus on exposure to quartz; data presented on job titles</p> <p><i>Data:</i> data retrieved from company personnel records, and Swedish cancer Registry; diseases classified according to International Classification of Diseases</p>	<p>Outcome: no associations found regarding exposure to quartz</p> <p>No association found between iron foundry work (expressed as quartz exposure) and lung cancer risk</p> <p>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<sup>3</sup>)</p>	<p>Appropriate study design, small study</p> <p>No data on smoking habits, or socioeconomic status</p> <p>Reliability 2</p>





Study design and population	Data on exposure and health assessment	Results	Remarks and reliability (annex J)
<p>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</p> <p>Ahn et al. (2010)<sup>42</sup></p> <p>Note by the DECOS: most likely partly overlap of the study population with the populations in the studies by Park et al. (2005)<sup>40</sup> and Yoon and Ahn et al. (2014)<sup>42</sup></p>	<p><i>Exposure:</i> based on job title (production (N=13,100) and office work (N=3,998)), and job area</p> <p>Cancer incidence: data retrieved from Korea Central Cancer Registry; statistical analyses included adjustments for confounding factors (sex and age)</p>	<p>Outcome: positive association with lung cancer and lympho-haematopoietic cancer</p> <p>Standardized Incidence Rate Ratio (SIR, 95% confidence interval, number of cases)</p> <p>Only data shown with statistically significant increased SIR</p> <p><i>Types of cancer among production workers:</i></p> <ul style="list-style-type: none"> <li>- all cancers: 1.14 (1.03-1.26), 409</li> <li>- lung cancer: 1.45(1.11-1.87), 61</li> <li>- lympho-haematopoietic cancer: 1.58 (1.00-2.37), 23</li> </ul> <p><i>Job duration:</i></p> <p>Less than 10 years:</p> <ul style="list-style-type: none"> <li>- all cancers: 1.22 (1.07-1.37), 261</li> <li>- stomach cancer: 1.35 (1.05-1.71), 68</li> <li>- lung cancer: 1.66 (1.20-2.24), 43</li> <li>- lympho-haematopoietic cancer: 1.81 (1.01-2.99), 15</li> </ul> <p>More than 10 years: no exposure-related increase in any type of cancer observed</p> <p>Most cases of lung and stomach cancer were found in production workers during moulding and core making, and fettling</p>	<p>Appropriate study design</p> <p>No data on smoking habits</p> <p>Reliability 2</p>



Study design and population	Data on exposure and health assessment	Results	Remarks and reliability (annex J)
<p>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</p> <p><sup>B,C</sup>Hoshuyama et al. (2006)<sup>49</sup></p>	<p><i>Exposure:</i> assessment by job exposure matrix, job title; exposure to 15 agents assessed (yes/no exposure), exposure was linked by one job only</p> <p><i>Data:</i> data retrieved from company personnel records and company death registry, municipal death registry; diseases classified according to International Classification of Diseases</p>	<p>Outcome: positive association with lung cancer when combined PAH-exposure with one or two other dust types</p> <p>Standardized mortality ratios (SMR) (95% confidence interval, no. of observed cases):</p> <p><i>Lung cancer:</i></p> <ul style="list-style-type: none"> <li>- exposed workers: 0.96 (0.88-1.02), 750 cases</li> <li>- internal reference: 0.88 (0.80-0.96), 507 cases</li> </ul> <p><i>Liver cancer:</i></p> <ul style="list-style-type: none"> <li>- exposed workers: 0.85 (0.76-0.94), 376 cases</li> <li>- internal reference: 0.81 (0.72-0.92), 265 cases</li> </ul> <p><i>Stomach cancer:</i></p> <ul style="list-style-type: none"> <li>- exposed workers: 0.86 (0.77-0.96), 321 cases</li> <li>- internal reference: 0.81 (0.72-0.92), 225 cases</li> </ul> <p><i>Specified by exposure agents</i> (standardized rate ratios (SRR)):</p> <ul style="list-style-type: none"> <li>- silica, coal, grinding, wood and carbon monoxide: no association with cancer</li> <li>- 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 &gt;1.00 with 95% confidence intervals &gt; 1.00)</li> </ul> <p>Combined exposure to PAH and one or two dust types: SRR 6.54 (1.13-3.780) for lung cancer</p>	<p>Appropriate study design</p> <p>No data on smoking habits or other lifestyle factors; limited data on actual exposure levels; SMR analyses showed healthy worker effect</p> <p>Reliability 2</p>
<p>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</p> <p><sup>C</sup>Adzersen et al. (2003)<sup>14</sup></p>	<p><i>Exposure:</i> duration of exposure</p> <p><i>Mortality:</i> data from national mortality statistics West Germany; diseases classified according to International Classification of Diseases</p>	<p>Outcome: positive association with lung and liver cancer</p> <p>Lost in follow-up: 5.1%</p> <p>Standardized mortality ratios (95% confidence interval), expected/ (estimated) observed:</p> <ul style="list-style-type: none"> <li>- malignant neoplasms: 1.24 (1.02-1.53), 881.3/1,091</li> <li>- trachea, bronchus, lung: 1.64 (1.24-2.23), 253.2/415</li> <li>- liver: 3.23 (1.50-8.45), 12.4/40.1</li> </ul> <p>Cancer mortality (all cancers) by duration of exposure and time since first exposure: only statistically 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</p> <p>Overall, no trends in duration of employment observed</p>	<p>Appropriate study design</p> <p>No data on exposure levels; no data on smoking history collected, however, the authors suggested that some of the observed excess of lung cancer could be explained by smoking (when comparing data on smoking habits collected by others (Federal Statistical Office (general population), and Borgers and Menzel 1984 (foundry workers); no data on other confounding factors</p> <p>Reliability 2</p>



Study design and population	Data on exposure and health assessment	Results	Remarks and reliability (annex J)
<p>Iron and steel foundry in a railway rolling stock manufacture; New Zealand; male workers for at least 3 months working in foundries 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</p> <p><sup>B</sup>Firth et al. (1999)<sup>50</sup></p>	<p><i>Exposure:</i> exposed or not exposed, based on longest held job title.</p> <p><i>Mortality:</i> data retrieved from personnel records; death registration records by the Department of Justice; causes of death classified according to International Classification of Diseases</p>	<p>Outcome: no association found among iron and steel workers regarding all cancers and lung cancer</p> <p>Standardized mortality ratio (95% confidence interval), no. observed cases:</p> <p>All cancers</p> <ul style="list-style-type: none"> <li>- exposed: 1.03 (0.59-1.67), 16 cases</li> <li>- non-exposed: 1.06 (0.89-1.24), 147 cases</li> </ul> <p>Lung cancer</p> <ul style="list-style-type: none"> <li>- exposed: 1.11 (0.35-2.62), 5 cases</li> <li>- non-exposed: 1.04 (0.75-1.40), 42 cases</li> </ul>	<p>Appropriate study design, but limited reporting on iron and steel workers</p> <p>Authors report that the prevalence of smoking was unknown, and that it could not be excluded as a reason for the increased lung cancer risk in the total workforce, or in different occupational groups</p> <p>No data on exposure levels reported</p> <p>Reliability 2</p>
<p>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</p> <p>Mallin et al. (1998)<sup>15</sup></p>	<p><i>Exposure:</i> no data presented</p> <p><i>Mortality and other data:</i> cases and controls selected from company records</p>	<p>Outcome: positive association with bladder cancer in heaters; no association with bladder cancer in other job titles</p> <p>Study reported only on bladder cancer</p> <p>Age-adjusted odds ratios (95% confidence interval, number of exposed cases)</p> <p><i>Job title</i></p> <ul style="list-style-type: none"> <li>- Heater: 21.1 (2.2-205.8), 3 cases, p&lt;0.01 (OR, logit estimate of relative risk)</li> <li>- Labourer: 0.9 (0.3-2.8), 4 cases</li> <li>- Machine operator/operator learner: 1.1 (0.3-4.4), 3 cases</li> </ul>	<p>Appropriate study design</p> <p>Smoking habits were collected, however It was not possible to adjust analyses for smoking habits due to missing data; heat may have influenced the outcome for heaters</p> <p>Reliability 2</p>
<p>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)</p> <p><sup>B</sup>Hansen (1997)<sup>51</sup></p>	<p><i>Exposure:</i> workers exposed before 1970; exposed versus unexposed</p> <p><i>Data collection:</i> record linking with Danish Bureau of Statistics; cause of death indicated according international classification of disease (ICD)</p>	<p>Outcome: no association found</p> <p>Standardized mortality ratio (95% confidence interval), observed cases of death:</p> <p>All cancers: 1.10 (0.97-1.25) 255</p> <p>Respiratory tract: 1.01 (0.80-1.25), 84</p> <p>Digestive system: 1.15 (0.90-1.44), 74</p> <p>Urinary organs: 1.31 (0.85-1.95), 25</p> <p>Blood and lymph: 1.49 (0.97-2.19), 26 cases</p>	<p>Appropriate study design; limited reporting</p> <p>No data on smoking habits or other lifestyle factors that may have influenced the outcome; no data on exposure levels</p> <p>Reliability 2</p>



Study design and population	Data on exposure and health assessment	Results	Remarks and reliability (annex J)
<p>Iron, steel and non-ferrous 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</p> <p><sup>C,D</sup>Koskela et al. (1976)<sup>52</sup></p> <p>Note: same cohort as described by Koskela et al. (1997)<sup>53</sup></p>	<p><i>Exposure:</i> duration of exposure, type of foundry, category of monoxide and dust exposure</p> <p><i>Mortality:</i> 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)</p> <p><i>Selection of subjects</i> Basic information from employers' records (history of foundry work); subjects traced from Population Data Register of the Social Insurance Institution</p>	<p>Outcome: no association found</p> <p>N=224 deaths recorded; loss in follow-up 1.3%</p> <p>Standardized mortality ratio (SMR, expected/observed), 47,160 person-years:</p> <ul style="list-style-type: none"> <li>- overall lung cancer: 1.51 (13.9/21),</li> <li>- 5 yrs exposure: 1.26 (7.9/10)</li> <li>- &gt; 5 yrs exposure: 1.86 (5.9/11)</li> <li>- iron foundries: 2.70 (3.7/10), 7,549 person-years</li> <li>- steel foundries: 0.00 (1.5/0), 3,986 person-years</li> <li>Nonferrous foundries: 1.43 (0.7/1), 1,213 person-years</li> </ul> <p>SMRs are not statistically significant increased compared to reference group</p> <p>Reference population, 176,468 person-years: 1.45 (42.2/61)</p>	<p>Appropriate study design</p> <p>Subgroup analyses included: age, duration of exposure, foundry type, and job title</p> <p>No data on smoking habits collected, but authors report that excess risk by smoking is not likely; no data on other confounding factors; no data on 95% confidence intervals</p> <p>Reliability 2</p>
<p>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</p> <p><sup>B,C,D</sup>Sherson et al. (1991)<sup>54</sup></p>	<p><i>Exposure:</i> years of working in foundry and type of workplace</p> <p>Data: data retrieved from Central Population Register, Cancer Register; cause specified according to international classification of diseases</p>	<p>Outcome: positive association for lung and bladder cancer</p> <p>Standardized mortality ratios (95% confidence interval, expected/observed)</p> <p>Only data shown with statistically significant outcome</p> <p><i>Type of cancer</i></p> <ul style="list-style-type: none"> <li>- all malignant neoplasms: 1.09 (1.01-1.18), 594.4/647</li> <li>- lung cancer: 1.30 (1.12-1.51), 127.8/166</li> </ul> <p><i>Years working in foundry</i></p> <ul style="list-style-type: none"> <li>- 20-29 yrs (N=900):</li> <li>- lung cancer: 1.28 (0.93-1.76), 26.6/38</li> <li>- bladder cancer: 1.72 (1.05-2.66), 11.6/20</li> <li>- ≥ 30 yrs (N=613):</li> <li>- lung cancer: 1.85 (1.39-2.45), 25.9/48</li> <li>- bladder cancer: 1.65 (0.96-2.65), 10.3/17</li> </ul> <p>No association between type of workplace in foundry and lung and bladder cancer risk</p>	<p>Appropriate study design</p> <p>Common confounding factors not taken into account, such as smoking habits</p> <p>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</p> <p>Reliability 2</p>



Study design and population	Data on exposure and health assessment	Results	Remarks and reliability (annex J)
<p>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 (1970-1980); reference group, another cohort of unexposed skilled workers, N=51,747 (481,642 person-years-at-risk)</p> <p><sup>C,D</sup>Hansen (1991)<sup>55</sup></p>	<p><i>Exposure:</i> no data on exposure levels; no data on duration of exposure, job titles or working area</p> <p><i>Mortality:</i> Danish Bureau of Statistics (national register of deaths); diseases classified according to International Classification of Diseases</p>	<p>Outcome: positive association with bladder cancer and 'other types of malignant neoplasms', no association with lung cancer</p> <p>Standardized mortality ratios (95% confidence interval, expected/observed)</p> <ul style="list-style-type: none"> <li>- cancer (all): 1.52 (1.00-2.21), 17.78/27</li> <li>- lung cancer: 1.37 (0.63-2.60), 6.57/9</li> <li>- bladder cancer: 8.96 (3.29-19.49), 0.67/6</li> <li>- other malignant neoplasms: 1.14 (0.59-1.99), 10.54/12</li> </ul>	<p>Appropriate study design</p> <p>No data on exposure; no data on other types of cancer; no adjustments on common confounding factors, such as smoking habits</p> <p>Reliability 2</p>



Study design and population	Data on exposure and health assessment	Results	Remarks and reliability (annex J)
<p>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</p> <p>Additional analyses:</p> <p>(1) analyses of work area; workers categorized according 6 work areas, Andjelkovich et al. (1992)<sup>56</sup></p> <p>(2) nested case-control study on lung cancer; formaldehyde exposure, airborne silica exposure, Andjelkovich et al. (1994)<sup>57</sup></p> <p>(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)<sup>58</sup></p>	<p><i>Exposure:</i> duration of exposure based on work history; exposure levels of substances expressed as low, medium or high; mean years of employment 9.5 years</p> <p><i>Mortality:</i> 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</p> <p>Smoking habits taken into account (percentage smokers: 75.2% of exposed workers, 72.4% of unexposed workers)</p>	<p>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</p> <p>Results concern men only</p> <p>Standardized mortality ratio (95% confidence interval), expected/observed:</p> <p><i>White men (N=5,337):</i></p> <ul style="list-style-type: none"> <li>- all malignant neoplasms: 0.98 (0.84-1.14), 180/177</li> <li>- lung cancer: 1.23 (0.96-1.54), 58.8/72</li> <li>- stomach cancer: 1.67 (0.91-2.81), 8.4/14</li> </ul> <p><i>Nonwhite men (2,810):</i></p> <ul style="list-style-type: none"> <li>- all malignant neoplasms: 1.16 (0.99-1.34), 159.2/184</li> <li>- lung cancer: 1.32 (1.02-1.67), 50.8/67</li> <li>- stomach cancer: 1.11 (0.59-1.90), 11.7/13</li> </ul> <p>No association observed between duration of exposure and cancer.</p> <p><i>Additional analysis (1)</i></p> <p>No associations found between type of working area and lung cancer; data probably influenced by smoking habits</p> <p><i>Additional analysis (2)</i></p> <p>N=220 lung cancer deaths between 1950-1989; no associations found between formaldehyde and/or airborne silica exposure and lung cancer</p> <p><i>Additional analysis (3)</i></p> <ul style="list-style-type: none"> <li>- lung cancer: 200 cases</li> <li>- all causes: 2,141 cases</li> </ul> <p>No association observed between formaldehyde exposure and lung cancer. Authors observed an significant association between smoking combined with silica exposure, and lung cancer</p>	<p>Appropriate study design</p> <p>The authors report that lung cancer cases might be associated with smoking in whites, but not in non-whites</p> <p>No measurements on exposure levels; crude analysis method of smoking habits; no data on other confounding factors</p> <p>Reliability 2</p>
<p>B,C,D Andjelkovich et al. (1990)<sup>59</sup></p>			



Study design and population	Data on exposure and health assessment	Results	Remarks and reliability (annex J)
<p>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 population, general population of England and Wales</p> <p><sup>C,D</sup>Sorahan et al. 1994<sup>60</sup> (earlier results published: Fletcher and Ades (1984) and Sorahan et al. 1989)<sup>61</sup></p>	<p><i>Exposure:</i> mean duration of employment, 9.3 years</p> <p><i>Mortality:</i> data from National Health Service Central Register or National Insurance records (1946-1990); diseases classified according to International Classification of Diseases</p> <p>Subgroup analyses on follow-up period, start of working; foundry site</p>	<p>Outcome: positive association with lung and stomach cancer</p> <p>Standardized Mortality Ratios (95% confidence interval), expected/observed</p> <p>All cancer types: 1.19 (1.12-1.26), 948.4/1,129, p&lt;0.001</p> <p>Lung cancer: 1.46 (1.34-1.58), 378.3/551, p&lt;0.001</p> <p>Stomach cancer: 1.34 (1.11-1.60), 92.5/1.24, p&lt;0.01</p> <p><i>Lung cancer, specified by duration of employment history (relative risk)</i></p> <ul style="list-style-type: none"> <li>- ever: 1.21 (0.98-1.51), N=185</li> <li>- up to 5 yrs: 1.44 (1.13-1.82), N=129</li> <li>- ≥ 15 yrs: 1.26 (0.95-1.67), N=80</li> </ul>	<p>Appropriate study design</p> <p>Certain groups with eastern surnames were excluded due to suspicious low overall mortality</p> <p>No data on exposure levels; no data on smoking habits or other confounding factors</p> <p>Reliability 2</p>
<p>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</p> <p>Tola et al. (1979)<sup>18</sup>; data included from cohort by Koskela et al. (1976)<sup>52</sup></p>	<p><i>Exposure:</i> based on history data (rough classification by type of work, and by current exposure to PAH (low, some and heavy exposure)</p> <p><i>Mortality:</i> see Koskela et al. (1976)<sup>37</sup></p> <p>Data on smoking habits included (57% of works smoked)</p>	<p>Outcome: positive association for lung cancer; no association with type of work and with PAH exposure</p> <p>Study based on the assumption that an association between iron foundry work and lung cancer exists. Goal is to assess the hazard</p> <p>N=51 lung cancer cases</p> <p>N=544 death cases (all causes)</p> <p>Lung cancer, proportional mortality: 1.44 (35.3 expected cases, 51 observed cases), p&lt;0.05</p> <p>No clear associations between type of work or current exposure to PAH and lung cancer, except for:</p> <ul style="list-style-type: none"> <li>- type of work (casters): risk ratio 4.6 (1.9 expected/7 observed), p&lt;0.01</li> <li>- Heavy PAH exposure: risk ratio 1.71 (66 controls/ 29 cases)</li> </ul>	<p>Appropriate study design</p> <p>No data on 95% confidence interval; no adjustments for well-known confounding factors, such as smoking habits (Internal contrast in risk not likely to be caused by smoking.)</p> <p>Reliability 2</p>



Study design and population	Data on exposure and health assessment	Results	Remarks and reliability (annex J)
<p>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</p> <p><sup>A</sup>Koskela et al. (1997)<sup>53</sup></p> <p>Note: same cohort as described by Koskela et al. (1976)<sup>52</sup></p>	<p><i>Exposure:</i> exposure levels: low, medium and high depending on physical job demands; data on duration of employment available</p> <p><i>Mortality and other data:</i> 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</p> <p><i>Selection of subjects</i> Basic information from employers' records (history of foundry work); subjects traced from Population Data Register of the Social Insurance Institution</p>	<p>Outcome: positive association for certain cancer types</p> <p>Standardized mortality ratio (95% confidence interval, expected/observed)</p> <p>Cancer development (134,660 person-years):</p> <ul style="list-style-type: none"> <li>- all types of tumours: 1.29 (1.13-1.47), 184.4/238, p&lt;0.001</li> <li>- lung cancer: 1.43 (1.17-1.74), 71.3/102, p&lt;0.001</li> <li>- cancer digestive organs: 1.50 (1.14-1.94), 39.3/59, p&lt;0.01</li> </ul>	<p>Appropriate study design</p> <p>No analyses by duration of exposure or job demands presented; no data on common confounding factors, such as smoking habits</p> <p>Reliability 2</p>
<p>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</p> <p><sup>B,D</sup>Decoufle and Wood 1979<sup>62</sup></p>	<p><i>Exposure:</i> duration of exposure (ever employed (N=2,861), employed for &gt; 5 years (N=867))</p> <p><i>Mortality:</i> data retrieved from company personnel records, Social Security Administration, and death certificates; diseases classified according to International Classification of Diseases</p>	<p>Outcome: study is too limited to draw conclusions</p> <p>Standardized mortality ratios (expected/observed), white/nonwhite men:</p> <p><i>≥ 1 month employment</i></p> <ul style="list-style-type: none"> <li>- cancer (all types): 1.11 (49.4/55), 0.88 (39.6/35)</li> </ul> <p><i>≥ 5 years employment</i></p> <ul style="list-style-type: none"> <li>- cancer (all types): 1.13 (20.4/23), 1.05 (17.2/18)</li> </ul> <p>Most cancers were observed in the stomach and respiratory system.</p> <p>No statistically significant associations found between being exposed and cancer development</p>	<p>Appropriate study design, but limited reporting</p> <p>No exposure levels determined; no data on confounding factors, such as smoking habits; limited data reported on statistical analyses and standardized mortality ratios</p> <p>Reliability 3</p>





Study design and population	Data on exposure and health assessment	Results	Remarks and reliability (annex J)
<p>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</p> <p>C,D Breslin (1979)<sup>63</sup></p>	<p><i>Exposure:</i> no data</p> <p><i>Data collection:</i> deaths confirmed by death certificates; cause of death indicated according international classification of disease (ICD)</p> <p>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 at least 5 years through 1953 (N=958)</p>	<p>Standardized mortality ratio (SMR), observed/expected deaths</p> <p><i>Lung cancer:</i>  A: 1.14, 20/17.7  B: 1.00, 34/34  C: 1.16, 23/20.1</p> <p><i>Genito-urinary cancer:</i>  A: 1.75, 12/7.1  B: 1.28, 17/13.6  C: 1.62, 14/8.9</p> <p><i>All cancers:</i>  A: 1.20*, 71/60.3  B: 1.08, 123/115.2  C: 1.16, 80/70.3</p> <p>* statistically significant, p≤0.05</p> <p>Data as reported by Bosetti et al. (95% confidence interval), complete cohort:  <i>Lung cancer:</i>  SMR 1.00 (0.7-1.4), 34 death cases  <i>Bladder cancer:</i>  SMR 1.00 (0.2-2.8), 3 death cases  <i>Kidney cancer:</i>  1.6 (0.4-4.1), 4 death cases</p>	<p>Limitations in study design</p> <p>Selection of reference group is not common (all steelworkers in the same plant instead of non-steelworkers in the same plants, or in the general population); no data on smoking habits</p> <p>Reliability 3</p>
<p>Proportional mortality study; member of the Iron Moulders Society of South Africa (IMS-SA); South Africa; N=578 deaths recorded between 1961-1983; reference group, deaths in general white male population</p> <p>Sitas et al. (1989)<sup>16</sup></p>	<p><i>Exposure:</i> workers categorized according job title and age</p> <p><i>Mortality:</i> data retrieved from IMS-SA and South African national death records; diseases classified according to International Classification of Diseases</p>	<p>Outcome: positive association with lung cancer in age group higher than 65 years old</p> <p>Proportional mortality ratios (expected/observed)</p> <ul style="list-style-type: none"> <li>- age 20-64 yrs (N=372):</li> <li>- all cancers: 0.75 (53.7/40), p=0.03</li> <li>- lung cancer: 0.84 (15.48/13), p=0.31</li> <li>- age ≥ 65 yrs (N=206):</li> <li>- all cancers: 0.91 (36.12/33), p=0.34</li> <li>- lung cancer: 1.71 (8.75/15), p=0.03</li> </ul>	<p>Small study</p> <p>Type of study design is notoriously prone to bias; according to the authors smoking cannot fully explain increased mortality ratios (data not presented)</p> <p>Reliability 4</p>



Study design and population	Data on exposure and health assessment	Results	Remarks and reliability (annex J)
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) <sup>64</sup>	<i>Exposure:</i> no information given  <i>Mortality:</i> data obtained from IMAW; diseases classified according to International Classification of Diseases  <i>Smoking habits:</i> 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): <i>All cancers:</i> - 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 <i>Lung cancer:</i> - 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	Data on proportional mortality ratios are prone to bias; no data on 95% confidence intervals; data not adjusted for common confounding factors, such as smoking habits  Reliability 4



# L epidemiology: case-control studies

Study design and population	Data on exposure and health assessment	Results	Remarks and reliability (annex C)
<p>Case-control study on worker population in one large iron and steel foundry; Asturias, Spain; male workers, cases were identified by job records and cancer registries (period 1952-1995), N=144 lung cancer cases; N=558 age-matched controls (workers) not having lung cancer</p> <p>Rodríguez et al. (2000)<sup>22</sup></p>	<p><i>Exposure:</i> no data on exposure levels; categorisation by production process.</p> <p><i>Data collection:</i> Tumor Registry of the General Hospital of Asturias and Tumour 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</p>	<p>Outcome: positive association found for lung cancer when working in blast furnace area; no associations found for lung cancer in other work areas</p> <p>Odds ratios (95% confidence interval, cases/controls) of lung cancer (data adjusted for smoking and age)</p> <p>Ever employed in:</p> <ul style="list-style-type: none"> <li>- foundry: 1.64 (0.69-3.91), 10/24</li> <li>- blast furnace: 2.55 (1.25-5.21), 16/36</li> </ul> <p>By longest held job in:</p> <ul style="list-style-type: none"> <li>-foundry: 1.91 (0.74-4.93), 9/18</li> <li>-blast furnace: 2.11 (0.78-5.73), 7/17</li> </ul>	<p>Appropriate study design, small study</p> <p>Adjusted for smoking and age</p> <p>No data on other types of cancer; no data on exposure levels</p> <p>Reliability 2</p>
<p>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</p> <p>Golka et al., (1998)<sup>26</sup></p>	<p><i>Data collection:</i> categorization based on type of work; questionnaire on occupations performed and smoking habits;</p> <p>Smoking habits:</p> <ul style="list-style-type: none"> <li>- Cases: 58.3% smokers, 12.2% ex-smokers</li> <li>- Controls: 35.3% smokers, 9.7% ex-smokers</li> </ul>	<p>Outcome: no association found for bladder cancer</p> <p>Odds ratio (95% confidence interval, cases/controls) for urothelial cancer (adjusted for smoking habits)</p> <p>Iron and steel foundry workers 1.1 (0.69-1.69), 8/3, p=0.735</p>	<p>Appropriate study design</p> <p>Adjusted for smoking; no data on other types of cancer</p> <p>Reliability 2</p>



Study design and population	Data on exposure and health assessment	Results	Remarks and reliability (annex C)
<p>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</p> <p>Xu et al. (1996)<sup>23, 24</sup></p>	<p><i>Exposure:</i> no data on exposure levels; data retrieved (personnel records) on duration of exposure and job activities/ working areas</p> <p><i>Cancer data collection:</i> municipal cancer registry; medical records from hospitals; interviews of cases, controls or next of kin</p>	<p>Outcome: positive association with lung and stomach cancer</p> <p>Odds ratios (95% confidence interval, cases/controls) of lung and stomach cancer (data adjusted smoking and age)</p> <p><i>Lung cancer (foundry workers; 172 cases, 411 controls)</i></p> <ul style="list-style-type: none"> <li>- ever worked: 1.8 (1.1-2.8), 48/47</li> <li>- worked &lt; 15 yrs: 2.7 (1.3-5.7), 21/15</li> <li>- worked ≥ 15 yrs: 1.4 (0.8-2.4), 27/32</li> </ul> <p><i>Stomach cancer (foundry workers; 91 cases, 411 controls):</i></p> <ul style="list-style-type: none"> <li>- ever worked: 2.0 (1.1-3.5), 30/47</li> <li>- worked &lt; 15 yrs: 3.9 (1.7-9.0), 15/14</li> <li>- worked ≥ 15 yrs: 1.2 (0.6-2.5), 15/33</li> </ul>	<p>Appropriate study design</p> <p>Adjustments made for smoking and age, however no smoking data presented</p> <p>Reliability 2</p>
<p>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</p> <p>Becher et al. (1989)<sup>20</sup></p>	<p><i>Data collection:</i> Next of-kin interviewed to obtain a residential, occupational and smoking history.</p> <p><i>Disease verification:</i> data retrieved from death certificates from Crakow death register</p>	<p>Outcome: positive association for lung cancer in longest exposed worker population</p> <p>Response rate: 70.7% (cases) and 73.5% (controls)</p> <p>N=106 cases and 72 references in steel and iron foundries</p> <p>Simultaneous relative risk (95% confidence interval, cases/control)</p> <p><i>Lung cancer</i></p> <p>Years of employment in foundry</p> <ul style="list-style-type: none"> <li>- 1-20 yrs or unknown: 1.28 (0.75-2.20)</li> <li>- 20-30 years: 1.58 (0.94-2.66)</li> <li>- &gt;30 years: 2.66 (1.31-5.42)</li> </ul> <p>No data on other types of cancer; no data on cases/controls</p>	<p>Appropriate study design, small study</p> <p>Adjustment for age, smoking, other occupational exposures as potential confounders</p> <p>No data on exposure levels; no data on other types of cancer</p> <p>Reliability 2</p>



Study design and population	Data on exposure and health assessment	Results	Remarks and reliability (annex C)
<p>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</p> <p>Blot et al. (1983)<sup>21</sup></p>	<p><i>Data collection:</i> Face-to face interview with next-of-kin, recording occupational history, smoking history and residential history</p> <p><i>Disease verification:</i> pathologically verified primary lung cancer; data retrieved from population mortality registers</p>	<p>Outcome: positive association found for lung cancer</p> <p>Response rate 94%</p> <p>Odds ratios (95% confidence interval, cases/control)</p> <p><i>Lung cancer</i></p> <p>Employed in steel industry (“usual industry”): 2.2 (1.5-3.3), 80/43</p> <p>Employed as foundry worker, mold maker (6 cases and 1 control): 7.1 (1.2-42.3), 6/1</p> <p>Smoking did not influence outcomes</p>	<p>Appropriate study design, small study</p> <p>Adjustment for smoking and age as potential confounders</p> <p>No data on exposure levels or employment duration; no data on other types of cancer</p> <p>Reliability 2</p>
<p>Study is part of Occupational Cancer Monitoring (OCCAM) project; Italy, area of Umbria (Perugia and Terni); focus on 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)</p> <p>Oddone et al. (2014)<sup>65</sup></p>	<p><i>Exposure:</i> No data on exposure levels; duration of exposure divided into three groups:</p> <p>0-4 yrs</p> <p>5-9 yrs</p> <p>≥ 10 yrs</p> <p><i>Data on cancer:</i> Umbria Regional Cancer Registry (data retrieved from period 2002-2008)</p>	<p>Outcome: positive association found for brain cancer; no trend for years of employment</p> <p>Odds ratios (90% confidence interval, cases/controls) of brain cancer (adjusted for age and sex)</p> <p>Iron and steel foundry in Terni:</p> <ul style="list-style-type: none"> <li>- overall: 9.59 (2.76-33.34), 16 cases, p=0.003</li> </ul> <p>Duration of employment:</p> <ul style="list-style-type: none"> <li>- 0-4 yrs: 1.00 (-), 2 cases</li> <li>- 5-9 yrs: 13.64 (3.27-56.96), 4 cases, p=0.003</li> <li>- ≥10 years: 8.58 (2.40-30.75), 10 cases, p=0.006</li> </ul>	<p>Appropriate study design</p> <p>No data on other types of cancer; 90% confidence interval instead of the usual 95% confidence interval, wide spread of confidence interval noted; no data on smoking habits</p> <p>Reliability 2</p>
<p>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)</p> <p>Finkelstein (1994)<sup>25</sup></p>	<p><i>Data collection:</i> Job and industry recorded from the death certificates; job histories obtained from employers</p> <p><i>Disease verification:</i> not reported</p>	<p>Outcome: no association found for lung cancer</p> <p>Relative lung cancer risks (95% confidence interval, number of cases)</p> <ul style="list-style-type: none"> <li>- Steelworkers Sault St-Marie: 0.85 (0.58-1.23), 73 cases</li> <li>- Steelworkers Hamilton: 1.10 (0.89-1.37), 145 cases</li> </ul> <p>(Adjusted for age and time period)</p> <ul style="list-style-type: none"> <li>- Foundry work for &gt;5 years (Hamilton): 1.94 (0.75-5.2), 12 cases</li> </ul> <p>No association between work in foundries and lung cancer risk</p>	<p>Appropriate study design, small study</p> <p>No smoking</p> <p>Adjustment; no data on exposure levels; no data on other types of cancer</p> <p>Reliability 2</p>



## The Committee

The membership of the Subcommittee on Classifying Carcinogenic Substances for the evaluation of the carcinogenicity and genotoxicity of iron and steel founding emissions

- H.P.J. te Riele, Professor of molecular biology, VU University Amsterdam, and Netherlands Cancer Institute, Amsterdam, chairman
- 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
- E. de Rijk, Toxicologic pathologist, Charles River Laboratories, 's Hertogenbosch
- J.J. Vlaanderen, Epidemiologist, Institute for Risk Assessment Sciences, Utrecht
- J. van Benthem, Genetic toxicologist, RIVM, Bilthoven, *structurally consulted expert*

## Observer

- M. Woutersen, Bureau REACH, RIVM, Bilthoven

## Scientific secretary

- J.M. Rijnkels, The Health Council of the Netherlands, The Hague



The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is “to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research...” (Section 22, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare and Sport, Infrastructure and Water Management, Social Affairs and Employment, and Agriculture, Nature and Food Quality. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

Most Health Council reports are prepared by multidisciplinary committees of Dutch or, sometimes, foreign experts, appointed in a personal capacity. The reports are available to the public.

This publication can be downloaded from [www.healthcouncil.nl](http://www.healthcouncil.nl).

Preferred citation:

Health Council of the Netherlands. Iron and steel founding emissions

The Hague: Health Council of the Netherlands, 2020; publication no. 2020/01.

All rights reserved

