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Gezondheidsraad

Occupational exposure during coal gasification

Evaluation of the carcinogenicity and genotoxicity

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

Comments before 17 February 2019

Preferentially by E-mail

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

Contents

Samenvatting

Op verzoek van de Minister van Sociale Zaken en Werkgelegenheid heeft de Gezondheidsraad beoordeeld of beroepsmatige blootstelling tijdens kolenvergassing 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 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.

Kolenvergassing

Kolenvergassing is een proces waarbij bruin- of steenkool bij hoge temperaturen en druk wordt vergast tot synthesegas. Het synthesegas wordt gebruikt voor energieopwekking en voor de productie van bijvoorbeeld kunststoffen, zoals kunstmest. Mensen die in fabrieken werken op plaatsen waar kolenvergassing plaats vindt, kunnen blootstaan aan allerlei stoffen die als gevolg van incomplete kolenvergassing vrij kunnen komen, zoal koolteer. In dit advies wordt de beroepsmatige blootstelling tijdens kolenvergassing als geheel in ogenschouw genomen. Individuele stoffen die in de emissie tijdens het kolenvergassingproces kunnen voorkomen worden niet afzonderlijk beoordeeld.

Beoordeling genotoxische en kankerverwekkende eigenschappen

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

Advies aan de minister

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

De commissie concludeert verder dat beroepsmatige blootstelling tijdens kolenvergassing kankerverwekkend is voor de mens, en beveelt aan deze blootstelling in categorie 1A (“*stof waarvan bekend is dat zij kankerverwekkend is voor de mens*”) te classificeren.

Executive summary

At request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands assessed whether occupational exposure during coal gasification 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 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.

Coal gasification

Coal gasification is a process in which lignite and black coal is turned into combustible gas under high temperatures and pressure. The syngas or synthesis gas is used as fuel for electricity generation, and as intermediate in manufacturing chemicals, such as chemical fertilizers. Workers who are involved in coal gasification, can be exposed to a mixture of substances, for instance as a result of incomplete combustion (e.g., coal tar). In the present advisory report, the evaluation accounts for the exposure during coal gasification as a whole. Individual substances that can be found in the emission of coal gasification are not considered.

Assessment of the genotoxicity and carcinogenicity

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

Recommendation

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

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

Furthermore, the committee concludes that occupational exposure during coal gasification is known to be carcinogenic to humans, and recommends classifying the exposure in category 1A ("*Known to have carcinogenic potential for humans*").

1 Scope

1.1 Background

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

This report contains the assessment of occupational exposure during (industrial) coal gasification. The evaluation accounts for the exposure to the emission as a whole; evaluation of individual substances to which workers can be exposed during coal gasification, is 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 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 committee’s recommendation is based on scientific data, which are publicly available. The starting points of the committees’ reports are, if possible, the monographs of the International Agency for Research on Cancer (IARC). This means that the original sources of the studies, which are mentioned in the IARC-monograph, are reviewed only by the committee when these are considered most relevant in assessing the carcinogenicity and genotoxicity of the substance in question. In the

case of exposure during coal gasification, such an IARC-monograph is available, of which the summary and conclusion is inserted in Annex A.

More recently published data were retrieved from the online databases Medline, Toxline, Chemical Abstracts, and RTECS. The last updated online search was in October 2018. The literature search was based on the following key words: “coal gasification”, “manufactured gas plant residue” and “coal tar from gas works”.

2 Identity of the substance

2.1 Name and other identifications

Coal gasification is part of a process to produce combustible gas (mixture of mainly hydrogen and carbon monoxide), also mentioned syngas or synthesis gas. See Section 5.1 for further explanation.

2.2 Composition of the emission of coal gasification

During coal gasification, workers may not only be exposed to hydrogen en carbon monoxide, but also to waste or by-products, as a result of incomplete combustion of the coal. The emitted products include: gases (*e.g.,* hydrogen sulphide, ammonia, hydrogen cyanide); hydrocarbon containing gases, aerosols and residues (*e.g*., polynuclear aromatic compounds, coal tar), and: mineral particulate residues (ash) and wastes. The type and amount of these waste and by-products emitted in the workplace air during coal gasification vary, due to variations in feed stocks (type of coal), and operating temperatures, pressures and residence times.
Coal tar is a waste product that is produced in large quantities during coal gasification. In coal tar, a number of polynuclear aromatic compounds has been identified, some of which are known for its carcinogenic properties (e.g., benzo(a)pyrene). In the scientific literature coal tar from coal gasification is denoted as manufactured gas plant residue (MGP), coal tar pitch volatiles, or coal gasification tar residue (CGTR).[1-3]

2.3 Physicochemical properties

Since the emission of coal gasification is a complex mixture of substances, no physicochemical properties are specified.

3 International classification

3.1 European Commission

Not evaluated.

3.2 IARC

IARC evaluated the genotoxicity and carcinogenicity of exposure during coal gasification several times, the latest in 2012.[1-3] It concluded that occupational exposure during coal gasification is carcinogenic to humans. Also there is sufficient evidence in experimental animals for the carcinogenicity of coal-tars from gas-works and manufactured gas plant residues. Furthermore, IARC stated that there is strong evidence of a genotoxic mechanism for coal gasification samples based on experiments. IARC considers it highly likely that genotoxicity is the mechanism for the carcinogenic effects of coal gasification emissions, predominantly due to the presence of mutagenic polycyclic aromatic hydrocarbons. Therefore, IARC classified coal gasification in Group 1 ("*sufficient evidence in humans for the carcinogenicity of occupational exposure during coal gasification*"). A summary of the latest evaluation and conclusion by IARC is given in Annex A.

3.3 The Health Council of the Netherlands

Not evaluated.

4 Monitoring

4.1 Environmental exposure monitoring

Since exposure to the emission of coal gasification implies exposure to a complex mixture, 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 coal gasification, concentrations of single components (benzo(a)pyrene or other polycyclic aromatic hydrocarbons), total hydrocarbons, coal tar pitch volatiles, and total amount or mass of particles, have been used to estimate exposure. These exposure markers are chosen because of their association with cancer development.

4.2 Biological exposure monitoring

Not specified.

5 Manufacture and uses

5.1 Manufacture

The information given below is abstracted from the IARC monographs.[1,3]

Several coal gasification systems have been developed, which can be classified by the heating value of the gas produced, and by the type of gasification reactor. The majority of the gasification systems consists of four operations: coal pretreatment, coal gasification, raw gas cleaning, and gas beneficiation. In this report, only the genotoxicity and carcinogenicity of exposure during coal gasification (step two) is evaluated.

Generally, any coal can be gasified if properly pretreated. Pretreatment operations include drying, partial oxidation, crushing, sizing, and briquetting of fines for feed to fixed bed gasifiers. The coal feed is pulverized for fluid or entrained bed gasifiers. After pretreatment, the coal enters the gasification reactor where it reacts with oxygen and steam to produce a combustible gas. Air is used as the oxygen source for making gas with a lower caloric value (so-called *low-Btu gas*, where Btu stands for British thermal units; one Btu is the heat required to raise the temperature of one pound of water by one degree Fahrenheit). Pure oxygen is used in making gas with higher value (*medium*- and *high-Btu gas*), as inert nitrogen in the air dilutes the heating value of the product. For gasification of coals, fixed bed, fluidised bed, and entrained flow reactors are used.[3] The choice of the appropriate process depends mainly on the fuel used and on the desired gas utilization. If the gas is utilised in a gas and steam turbine process, fluidised bed and entrained flow processes are particularly suitable, in which gasification occurs at high pressure (at least 25 – 30 bar). Entrained flow gasification takes place at considerably higher temperatures above the ash fusion point.

5.2 Identified uses

Syngas or synthesis gas is mainly used as fuel for electricity generation. In addition, the gas is used as intermediate resource in manufacturing of chemicals, such as chemical fertilizers.

6 Summary of toxicokinetics

6.1 Absorption, distribution and elimination

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

6.2 Toxicokinetics

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

7 Germ cell mutagenicity

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

7.1.1 Summary of genotoxicity tests in vitro

No studies are available on germ cells genotoxicity.

Mutagenicity

Cizmas et al. (2004) determined mutagenic activity of seven fractions of a MGP residue in *Salmonella typhimurium* strain TA98.[4] MGP residue was provided by a single site of the Electric Power Research Institute (Palo Alto, USA). The fractions were obtained by chromatographic fractionation of the MGP residue. The residue and its fractions differed in the presence and the composition of polycyclic aromatic hydrocarbons (PAH). Without metabolic activation, 4 of the 6 fractions tested showed mutagenic activity (see Table 1; fraction F6 not tested). In the presence of metabolic activation, mutagenic activity was observed in 6 of 7 fractions.

Table 1. Mutations.

Method	Cell type	Concentration range	Results	Remarks and reliability
Reverse mutation (Ames test) Cizmas et al. 2004[4]	*Salmonella typhimurium* strain TA98	MGP fractions: *Total PAH (µg/mg fraction):* F1 (197), F2 (295), F3 (185), F4 (72), F5 (20), F6 (12), and F7 (31) *Carcinogenic PAH (µg/mg fraction; sum of benz[a]anthracene, benzo[b]fluoranthene, benzo[k]fluoranthene, benzo(a)pyrene, chrysene, dibenzo[a,h]anthracene,and indeno[1,2,3-c,d]pyrene):* F1 (0.18), F2 (40.16), F3 (89,77), F4 (39.48), F5 (11.03), F6 (2.18) and F7 (0.56) Amount of fraction applied per plate: 0,05, 0,5 and 1,0 mg (solvent dimethyl sulphoxide served as negative control)	Positive (more than doubling of number of revertants/plate compared to solvent control): - without metabolic activation (S9): F2, F3, F4, F5 (F6 not tested) - with metabolic activation (S9): in 6 of the 7 fractions (dose-related)	Only one strain tested; no data on cytotoxicity; no positive controls used Reliability 2 (see Annex F)

Clastogenic and aneugenic effects

Currently, no publications are available that address in vitro clastogenic or aneugenic effects (chromosomal aberrations, formation micronuclei, sister chromatid exchanges) of coal gasification samples.

Conclusion on genotoxicity

The number of studies on mutagenic and genotoxic activities of coal gasification samples (*e.g.*, MGP) is limited. The results of an in vitro reverse mutation study indicate that MGP has mutagenic properties. No data are available that address in vitro clastogenic or aneugenic activities of whole coal gasification samples.

7.1.2 Summary of human data relevant for germ cell mutagenicity

No data available.

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

No in vivo studies are available, in which the mutagenic, clastogenic or aneugenic effects of coal gasification samples were tested.

DNA-adducts

In Table 2 results on DNA-adduct formation are summarized. These studies show that crude MGP or fractions of MGP cause a dose- related increase in DNA-adducts in the lung, the liver and the forestomach in mice, which were given MGP in various concentrations in the diet. Analyses of the MGP showed the presence of several types of PAH, among which PAHs with well-known genotoxic and carcinogenic potential. Animal experiments indicate that not only the well-known carcinogenic PAH, but also other constituents in MGP may have induced part of the DNA-adducts. Since it is unknown to which extent the detected DNA adducts interfere with DNA replication or are subject to DNA repair activities, the mere presence of DNA adducts cannot be taken as evidence for mutagenicity.

1 **Table 2**. Formation of DNA-adducts in animals exposed to MGP.

Study design	**Data on exposure**	**Results**	**Remarks and reliability (**Annex F)
Oral administration in diet for 28 days; male B6C3F1 mice; N = 8/group Culp and Beland 1994[5]	0, 0.1, 0.25, 0.5, 1 or 2% MGP in diet (corresponds with 0 to 52.5 mg MGP/day); B[a]P) served as positive control (applied in diet at doses of 2.5 - 50 mg/kg diet) DNA-adducts: ^{32}P-postlabeling assay	DNA-adduct formation increased with increasing dose, adducts/mg DNA): Lung: 22 up to > 6,776 Liver: 65 up to 3,121 Forestomach: 112 up to ± 1,792 Lower intake of diet found in animals given higher doses of MGP; body weights in higher dose groups were lower compared to no and low-dosed animals. Data are corrected for food consumption	Well-documented experimental set-up; proper use of controls; relevance for mode-of-action; well-performed study No statistical analyses Reliability 2
Oral administration using a gel diet system for 91 or 185 days; male and female B6C3F1 mice; N = 2 male and 2 females/group Weyand et al. 1994[6]	0, 0.05, 0.25 or 0.5% MGP in diet (corresponding with 0.5 g, 2,5 or 5 g MGP per kg diet); B[a]P) served as positive control DNA-adducts: ^{32}P-postlabeling technique	Dose-related increase in DNA-adduct formation in the lung and forestomach cells; adduct levels lung higher than in the forestomach.	Well-documented experimental set-up; proper use of controls; relevance for mode-of-action; well-performed study No statistical analyses Reliability 2
Oral administration using a gel diet system for 14 days; female A/J mice; N = 10/group Weyand et al. 1995[7]	Diets contained 0.25% MGP (corresponds to 5.9 mg MGP/day/ mouse); B[a]P as positive control DNA-adducts: ^{32}P-postlabeling assay combined with TLC and HPLC	MGP induced DNA adducts in isolated lung (± 1.8 pmol adducts/mg DNA) and to a lesser extent in forestomach cells (±0.15 pmol adducts/mg DNA)	Well-documented experimental set-up study (none-guideline study, not GLP); relevance for mode-of-action No statistical analyses; no negative controls Reliability 2

Study design	**Data on exposure**	**Results**	**Remarks and reliability (**Annex F)
Oral administration in basal gel diet for 14 days; female A/J mice; no data on group size Koganti et al. 2001[8]	0.25% MGP in diet (corresponds with 2.5 g MGP per kg diet); ethylene chloride soil extracts served as positive control DNA-adducts: ^{32}P-postlabeling assay	DNA adduct formation found in lung cells In MGP samples various PAH were found. No statistical analyses performed	Well-documented experimental set-up study (none-guideline study, not GLP); proper use of controls; relevance for mode-of-action; well-performed study Reliability 2
Single dermal application (topical; skin area 4 cm^2; at back of mouse); female ICR mice; N = 3/group Cizmas et al. 2004[4]	Crude MGP residue and seven MGP fractions, doses applied 0.48, 1.2, or 3.0 mg/mouse 7H-benzo[c]fluorene (PAH component) served as positive control DNA-adducts: ^{32}P-postlabeling assay (cells were harvested 24 hours after dermal application)	A dose-related increase in amount of DNA adducts found in isolated lung and skin (application site) cells Larger effects found in skin cells than in lung cells	Well-documented experimental set-up (none-guideline study, not GLP); proper use of controls; relevance for mode-of-action; well-performed study Reliability 2

7.2 Comparison with the CLP-criteria

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

In addition, substances may be categorized in 1B if there are "*positive results from in vivo somatic cell mutagenicity tests in mammals, in combination with some evidence that the substance has potential to cause mutations to germ cells*". The latter may be

based on a) "*supporting evidence from mutagenicity or genotoxicity tests in germ cells in vivo*", or b) "*by demonstrating the ability of the substance or its metabolites to interact with the genetic material of germ cells*" (Annex D). Currently, no in vivo mutagenicity or other genotoxicity tests have been performed on coal gasification samples.

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

7.3 Conclusion on classification and labelling for germ cell mutagenicity

Based on the available data, the Committee recommends classifying exposure during coal gasification as a germ cell mutagen in category 2 ("*Substances which cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans*").

In addition, the committee concludes that the mutagenic components which can be formed during coal gasification may act by a stochastic genotoxic mechanism.

8 Carcinogenicity

8.1 Summary and relevance of the provided information on carcinogenicity

8.1.1 Observations in humans

Meta-analysis

Bosetti et al. (2006) performed a meta-analysis to investigate the possible association between jobs with expected high polycyclic aromatic hydrocarbon exposure, including coal gasification workers, and the risk for certain cancer types.[15] The analysis included data from 5 cohort studies in the coal gasification industry (Doll et al. 1972, Manz 1980, Hansen et al. 1986, Gustavsson and Reuterwall 1990, Berger and Manz 1992).[16-20] Details of the meta-analysis and the five cohort studies are given in Annex B. The meta-analysis revealed a statistically significant increase in cancer mortality risk estimates for lung, respiratory tract, bladder and urinary tract cancer, in those working in coal gasification.

Uncertainties and limitations. In the meta-analyses, a certain degree of heterogeneity between studies was found. This is not surprising to the committee, because the exposure circumstances in different coal gasification facilities may vary. In addition, the committee noted that no description was given on how the authors assessed the quality of the studies, and to what degree each study contributed to the pooled relative risk estimate. The committee considers the study by Manz (1980) of low quality due to limited reporting.[20] Moreover, the committee noted that polycyclic aromatic hydrocarbon exposure was mainly based on job title; only in the study by Gustavsson and Reuterwall, some polycyclic aromatic hydrocarbon exposure measurements were made.[18] Furthermore, no sensitivity analyses were performed to account for type of study design, and for smoking habits. In most cohort studies data on smoking habits were not collected or reported. Overall, these uncertainties and limitations weaken the conclusion made in the meta-analysis.

Prospective cohort studies

Annex B describes three cohort studies with a prospective design. One is not considered by the committee due to limited reporting. Kawai et al. (1967) and Doll et al. (1972) found a statistically significant positive association between coal gasification work and lung cancer mortality.[17,21] The small study by Kawai et al. (1967) showed also that in the age group of 45 to 56 years, workers with more than 20 years of employment had a statistically significant higher lung cancer death rate than workers from the same age group with 10 to 19 years of employment.

Uncertainties and limitations. In none of the studies adjustments were made for smoking habits.

Retrospective cohort studies

Part of the retrospective cohort studies were limited in design or reporting (annex B), including the study by Manz (1980), which was included in the meta-analysis by Bosetti et al. (2006).[20] Therefore, these were not considered by the committee. In three studies a statistically significant positive association was found between exposure during coal gasification and, in particular, lung cancer mortality. Martin et al. (2000) reported an association only in the group of workers with the highest exposure levels.[22] Hansen et al. (1986) did not find an association when years of employment or latency were taken into account.[19] In addition, Gustavsson and Reuterwall (1990) did not find any association between exposure during coal gasification and cancer mortality.[18] In this study, exposure levels to benzo(a)pyrene in the Swedish gas production company at the top oven were reported to range between 0.007 and 33 µg/m^3 (1964), and between 0.021 and 1.29 µg/m^3 (1965).[18] The authors remark that these exposure levels are of the same magnitude as in American plants. Begraca et al. (1991) reported also on exposure levels.[23] Coal tar pitch volatiles during coal gasification ranged from 1.2 to 22,480 mg/m^3; mean average personal exposure to polycyclic aromatic hydrocarbon was 0.03 mg/m^3.[23] However, the documentation is too limited to conclude whether these exposure levels could have induced an excess of lung cancer in gas workers. *Uncertainties and limitations*. Most studies did not account for tobacco smoking, whereas this may seriously influence the outcome of lung cancer and bladder cancer risk estimates. However, Gustavsson and Reuterwall (1990) reported that the percentage of smokers among coal gasification workers and people living in large cities did not differ, and, therefore, suggested that smoking habits did not influence the outcomes for total mortality.[18] Martin et al. (2000) suggested that tobacco smoking had no or only a weak effect on cancer risk estimates, because smoking status is often related to socio-economic status, and the reference group was a reflection of the workers group.[22] Berger and Manz (1992) performed a subanalysis for stomach, colon and rectum cancer, comparing data from smokers with non-smokers (gas furnace workers).[16] For stomach cancer, a positive association was found for smokers, but not for non-smokers, whereas for colon and rectum cancer this was the other way around. The authors noted the imprecision of the risk estimates for colon and rectum cancer, because of the low frequencies of the observed and expected cases. Overall, the committee concludes that smoking status may have influenced the outcomes to a minor degree.

Conclusion observations in humans

Several cohort studies showed some evidence of a positive association between occupational exposure during coal gasification and lung cancer mortality, despite the variation in working and exposure conditions among the various coal gasification facilities. Also cancer at other sites of the body, such as in the bladder and stomach, have been reported. These data indicate that exposure to emissions of coal gasification is likely to result in cancer at first site of contact (the lungs), and that it may result in development of cancer at distant sites. The observed associations are most likely influenced to a minor degree by confounding factors, such as smoking. In conclusion, the committee is of the opinion that there is sufficient evidence of an association between occupational exposure during coal gasification and increased cancer mortality, in particular lung cancer mortality.

8.1.2 Animal carcinogenicity studies

In animal experiments various routes of exposure were used (see annex C). None of these studies met the current OECD guidelines for assessing carcinogenicity. At least two animal studies are of sufficient quality to be evaluated, of which a description is given below.

The first is the German inhalation study by Rittinghausen et al. (1997).[12] As shown in annex C, female mice developed lung tumours (squamous cell carcinomas) due to inhalation of coal gasification aerosol samples, or after consuming diets to which tar/pitch condensation products (from coal gasification sites) were included. No description or analytical data on the aerosols were reported, but the aerosols are considered to be related to exposure during coal gasification. No data were presented on general toxicity, and on the development of tumours at other sites in the body.
In the second study, Culp et al. (1998) fed female mice diets containing coal tar, which was obtained from coal gasification plant sites.[11] In the highest exposure groups, histopathologic analyses revealed that these mice developed tumours in the lungs (adenomas and/or carcinomas), the liver (adenomas and/or carcinomas), the forestomach (papillomas and/or carcinomas), and in the small intestines (adenocarcinomas). The authors also noted that in these groups the survival rate was very low and that the animals had on average lower body weights and food intake compared to the control group. Mice, which were given coal tar mixed from seven plant sites showed statistically significant dose-related increase in number of tumour bearing animals. Considering small intestinal tumours, the authors noted that this finding has similarities with the same mouse strain infected with the fungicide caplan.
Although other animal studies are of low quality, they give some support that coal tar or MGP, obtained from coal gasification sites, may induce tumours in the lungs, forestomach, and in the liver of mice (Weynand et al. 1995, Rodriguez et al. 1997).[7,13]

Based on the inhalation study by Rittinghaussen et al. (1997) and the oral study by Culp et al. (1998), the committee concludes that there is sufficient evidence that exposure to coal gasification samples causes cancer in mice.

8.2 Comparison with the CLP-criteria

Several cohort studies among workers in coal gasification processes show a positive association between exposure during coal gasification and cancer-related mortality, in particular lung cancer mortality. Other types of cancer observed include liver, stomach and skin cancer. Support for the carcinogenic properties of coal gasification samples comes from animal studies. Mice, which were chronically exposed to coal tar products of coal gasification by the diet or by inhalation, developed cancer at several sites of the body, such as in the lungs, the liver and the forestomach. Based on these findings and according to the CLP criteria, exposure during coal gasification should be classified as "*known to be carcinogenic to humans*", which corresponds to classification in category 1A.

8.3 Conclusion on classification and labelling for carcinogenicity

The committee concludes that occupational exposure during coal gasification is carcinogenic to humans, and recommends classifying the exposure in category 1A ("*Known to have carcinogenic potential for humans*").

References

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Annexes

A IARC evaluation and conclusion

B Details epidemiological studies

C Details animal carcinogenicity studies

D Classification criteria on germ cell mutagenicity

E Classification system on carcinogenicity

F Reliability testing of animal and in vitro studies

G Reliability testing of epidemiological studies

A IARC evaluation and conclusion

Occupational exposures during coal gasification are carcinogenic to humans (Group 1).

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Summary of Data Reported and Evaluation.

Exposure data

Coal gasification is a process by which coal is reacted with oxygen, steam and carbon dioxide by incomplete combustion to release fuel, tars, oils, phenols, heavy hydrocarbons and gas products. In addition to polycyclic aromatic hydrocarbons, workers in coal gasification may be exposed to many compounds, including asbestos, silica, amines, arsenic, cadmium, lead, nickel, vanadium, hydrocarbons, sulfur dioxide, sulfuric acid and aldehydes. Workers in the coal gasification industry are potentially exposed to polycyclic aromatic hydrocarbon, asbestos, silica, amines, arsenic, cadmium, lead, nickel, vanadium, hydrocarbons, sulfur dioxide, sulfuric acid and aldehydes.

Human carcinogenicity data

Two cohort studies of coal-gasification workers in the United Kingdom (Doll et al., 1972) and Germany (Berger & Manz, 1992), and a case–control study nested within a cohort of French gas- and electricity-production workers (Martin et al., 2000). In all studies an excess of lung cancer in association with coal gasification was found, which was not likely to be explained by other factors. There was evidence supporting a lung-cancer excess in a historical record-linkage study from the United Kingdom (Kennaway & Kennaway, 1947), in two smaller cohorts (Kawai et al., 1967; Hansen et al.,1986), and a large but inadequately reported Chinese study (Wu, 1988). In addition to lung cancer, the study from the United Kingdom (Doll et al., 1972) showed an excess of bladder cancer, and the German study (Berger & Manz, 1992) showed an excess of cancers of the stomach and colon-rectum.

Animal carcinogenicity data

Crude coal-tars from gas works were shown to induce skin papillomas and carcinomas in mice and rabbits after skin application. Manufactured gas plant residues (MGP) were shown to be carcinogenic in mice after exposure by the feed and after intraperitoneal injection. In these studies, several carcinomas were found, including hepatocellular

adenomas, alveolar/bronchiolar adenomas, forestomach papillomas, small intestine adenocarcinomas, as well as haemangiosarcomas and histiocytic sarcomas.

Other relevant data

There is strong evidence from experiments for a genotoxic mode of action for coal gasification samples. Although there are no human studies, it is highly likely that genotoxicity is the mechanism relevant to the carcinogenic hazards from exposures to emissions of coal gasification.

Evaluation

There is sufficient evidence in humans for the carcinogenicity of coal gasification. Coal gasification causes cancer of the lung. There is sufficient evidence in experimental animals for the carcinogenicity of coal-tars from gas-works and manufactured gas plant residues. There is strong evidence of a genotoxic mechanism for coal gasification samples based on experimental studies. Although there are no human studies, it is highly likely that genotoxicity is the mechanism for the carcinogenic effects of coal-gasification emissions, predominantly due to the presence of mutagenic polycyclic aromatic hydrocarbons.

Overall evaluation

Occupational exposures during coal gasification are carcinogenic to humans

(Group 1).

Previous evaluations:

Coal gasification was considered by previous IARC Working Groups in 1983, 1987, and 2005 (IARC, 1984, 1987, 2010).

B Details epidemiological studies

Association between occupational exposure to emissions of coal gasification and cancer development.

Study design and population	**Data on exposure and health assessment**	**Results**	**Remarks and reliability** (Annex G)
Meta-analysis			
5 cohort studies of coal gasification workers (with potential PAH exposure) Bosetti et al. 2006[15] Details of the individual cohort studies are shown in the list below (indicated as [A])	*Search period*: Up to December 2005 *Inclusion criteria*: workers in industries with high PAH exposure; cohort design; mortality or incidence data on cancer risk (the lungs, the respiratory tract, the bladder, the urinary tract) *Quality assessment individual studies*: not performed or reported *Meta-analysis*: pooled relative risk (RR; calculated as a weighted average of the SMRs, using the inverse of the variance as weight), fixed-effects model, chi-square test for heterogeneity	*Outcome:* positive association between coal gasification work and cancer in the lungs, the respiratory tract, the bladder and the urinary tract *Order:* standardized mortality ratio (SMR), observed/expected no. of cases, pooled RR (95% confidence intervals), p=value for heterogeneity *Lung cancer (4 cohorts)* SMR, 2.14, 188/87.7, 2.29 (1.98-2.64), p<0.0001 *Respiratory tract cancers (5 cohorts)* SMR, 2.40, 251/104.7, 2.58 (2.28-2.92), p<0.0001 *Bladder cancer (2 cohorts)* SMR, 2.38, 12/5, 2.39 (1.36-4.21), p=0.77 *Urinary tract cancers (3 cohorts)* SMR, 2.99, 18/6.02, 3.27 (2.06-5.19), p=0.17	Appropriate design No sensitivity analysis performed; data on smoking habits missing; no quality assessment performed on the individual studies Reliability 2
Prospective cohort studies			
Prospective cohort study; Gas generator plant at a steel	Exposure based on years of work:	*Outcome*: positive association found for lung cancer mortality; positive	Appropriate study design, adequate

plant, Japan; follow-up 1953-1965 (up to 12 years); N = 504 gas generator workers, N = 25,760 controls (workers in the same industry but not exposed to tar fumes); participants followed until age of 55 year Note: gas generator plant was closed in 1953 Kawai et al. 1967[21]	1) <10 years (short) 2) 10-19 years (mid) 3) ≥20 years (high) Information on lung cancer mortality based on death records; age-specific mortality was computed; statistical analyses by Poisson distribution	association found for years of employment; no associations found for other cancer at other sites of the body Standardized mortality ratio (obs/exp) of lung cancer: - all: 0.44 (6/0.135), p<0.001 - short: 0.18 (1/0.056), p=0.05 - mid: 0.35 (2/0.057), p=0.001 - long: 1.36 (3/0.022), p<0.001 All lung cancer cases were observed in the age group of 45-54 years Years of employment (age group 45-56 years old), death rate/100,000 population: 10-19 yrs: 496, 3 death cases, 604.5 persons at risk > 20 yrs or more: 2,688, 5 death cases, 186 persons at riskp p=0.022 No other cancer significantly affected	selection of study subjects Small study; possibility of serious bias (e.g., smoking habits) not taken into account Reliability 2
Prospective cohort study; coal carbonizing plants for making gas (4 locations), the UK; follow-up 1953-1965 (up to 12 years); N (A) = 2,444 coal carbonizing process workers, N (C1) = 579 process and maintenance workers in chemical and by-product plant; controls, death rates in male population England & Wales [A]Doll et al. 1972[17]	No data on exposure levels; length of exposure rated as regular, intermittent, or minimal/no exposure Information on cancer mortality based on death certificate; statistical analyses by Poisson analysis	*Outcome*: positive association for lung and bladder cancer mortality Standardized cancer mortality ratio (obs/exp (standardized annual death rates per 1,000 men)): *Coal workers (A)* - lung: 1.79 (3.82/2.13), p=0.001, 99 deaths - bladder: 2.35 (0.4/0.17), p=0.03, 10 deaths - skin and scrotum: 6.00 (0.12/0.02), p=0.0, 3 deaths - other cancer: 1.06 (2.70/2.55), 70 death	Appropriate study design; adequate selection of study subjects Limited documentation; possibility of serious bias, such as smoking habits, not taken into account Reliability 2

		Maintenance workers (C1) - lung: 0.75 (1.59/2.13), 11 deaths - bladder: 0.76 (0.13/0.17), 1 death - skin and scrotum: 0,00 (0.00/0.02), 0 deaths - other cancer: 0.94 (2.39/2.55), 17 deaths No subgroup analysis on duration of exposure	
Prospective cohort study; public utility, the USA; follow-up 1946-1961 (15 years); N = 1,031 gas plant workers (full cohort = 23,571 workers) Christian 1962[24]	No data on exposure levels Workers were observed for lung cancer development	*Outcome*: data do not allow a conclusion During follow-up, 125 lung cancer cases were observed, of which 123 cases were heavy smokers. This corresponds with 35.4 cases per year per 100,000 population (full cohort) *Gas plant workers*: - 23 cases/1,031 workers - 149 cases per 100,000 man-year observation (no other data presented)	No clear criteria in the selection study subjects; possibility of serious bias, such as smoking habits not taken into account; no statistical analyses performed Reliability 3
Retrospective cohort studies			
Retrospective cohort study; coal gas production company, Sweden; data retrieved from 1966-1988 (mortality) and 1966-1983 (cancer incidence); N = 295 workers employed for at least one year between 1965 and June 1972, when the coal gasification stopped; reference rates for mortality were based on mortality all man in 'greater Stockholm' or 'employed in Stockholm' [A]Gustavsson and Reuterwall 1990[18]	Exposure to B[a]P (top oven, area sampling) measured: 1964: 0.007-33 µg/m^3 1965: 0.021-1.29 µg/m^3 Workers were divided into departments (coke ovens, steam and generator central, coke department, byproduct workers, workshop and maintenance workers, outside workers, sample preparation), or by employment period	*Outcome*: no associations found Standardized Mortality Ratio (exp/obs, 95% confidence interval), expected based on 'employed in Stockholm' *Overall:* - all malignant tumours: 1,14 (22 /19.3, 0.71-1.72) - lung cancer: 0.82 (4/4.85, 0.22-2.11) *Employment period (years):* All malignant tumours 1-29 y: 1.03 (17/16.6, 0.6-1.64)	Well-documented study; study subjects adequately selected Limited number of participants; limited number of cases; possibility of serious bias not taken into account Authors report that the percentage daily

	Expected numbers of deaths based on local death rates among occupationally active men, expected numbers of cancer based on national statistics	≥ 30 y: 1.43 (8/5.6, 0.62-2.82) Lung cancer 1-29 y: 0.00 (0/1.3, 0–2.79) ≥ 30 y: 1.41 (2/1.4, 0.17-5.09) *Department:* Coke oven department: - All malignant tumours: 1.43 (5 /3.5) - Lung cancer: 0 (0/0.9) Steam and generator department: - all malignant tumours: 2.22 (2/0.95) - lung cancer: 0 (0/0.2) Coke department: - malignant tumours: 2.11 (6/2.8) - lung cancer: 2.84 (2/0.7)	smokers among coal gas workers (52%) were comparable with daily smokers in large cities. Therefore, they stated that excess of causes did not seem to be caused by smoking habits. Reliability 2
Retrospective cohort study; Hamburg coke gas plant, Germany; data retrieved for the period 1953-1989; N = 4,908 male workers employed for ≥ 10 years (in the period 1900 to 1989) [A]Berger and Manz 1992[16]	No data on exposure levels *Subcohorts based on job titles*: (I) gas furnace workers (exposed to high concentrations of coal tar gas, in particular PAH and different heterocyclics; 789 workers) (II) workers in other parts of the plant occasionally exposed to several chemicals, 3,401 workers) (III) white-collar workers (no exposure, 718 workers) Mortality and cause of death from company and personal medical records; Internal control = white-collar workers, external controls =	*Outcome*: positive association for cancer mortality (all cancers, lung cancer, stomach cancer) in gas furnace workers; non-smokers had no excess risk in stomach cancer mortality Standardized mortality ratio (obs/exp, 95% confidence interval) *Subcohort I* - all cancers: 1.86 (190/102.2, 1.61-2.14) - lung cancer: 2.88 (78/27.1, 2.28-3.59) - stomach cancer: 1.77 (31/1.5, 1.20-2.51) - colon and rectum cancer: 1.84 (13/7.1, 0.98-3.15) *Subcohort II* - all cancers: 0.96 (384/399.6, 0.87-1.06) - lung cancer: 0.96 (102/106.3, 0.78-1.17) - stomach cancer: 1.13 (72/63.7, 0.88-1.42)	Well-documented study; study subjects adequately selected; serious possibility for bias was taken into account (smoking habits and health worker effect) Reliability 2

	calendar period-, age-, and cause-specific death rates of males for Germany (from 1952-1989); statistical analyses by likelihood-ratio-test, chi-square test for homogeneity, confidence intervals by Poisson distribution; smoking habits taken into account	- colon and rectum cancer: 1.70 (48/ 28.3, 1.25-2.25) *Subcohort III* - all cancers: 0.56(59/104.9, 0.43-0.73) - lung cancer: 0.45 (12/26.2, 0.23-0.79) - stomach cancer: 0.57 (10/17.5, 0.27-1.05) - colon and rectum cancer: 0.92 (7/7.6, 0.37-1.90) *Smoking in subcohort I* - stomach cancer: no: 1.40 (3/2.15, 0.29-4.09), N=103 yes: 2.56 (22/8.61, 1.60-3.87, N=546 - colon and rectum cancer: no: 4.35 (4/0.92, 1.18-1,113), N=103 yes: 1.68 (8/4.76, 0.73-3.31), N=546	
Case control survey nested in a retrospective cohort study; national electricity and gas company, France; data retrieved from 1978 – 1989; 1,400,00 person-years based on male workers employed between 1978 – 1989 for at least one year; for each case four age-matches controls were randomly selected Martin et al. 2000[22]	No data on exposure levels; MATEX job exposure matrix was used, which is based on occupational groups. The matrix includes quantitative levels of exposure and exposure times. Lung cancer mortality identified by social security fund of company; for each case of lung cancer 4 age-matched controls from cohort were randomly selected; statistical analyses by conditional logistic regression models,	*Outcome*: only positive association found for lung cancer mortality in the highest exposed group A total 310 lung cancer cases were registered (mean age at time of diagnosis was 49.9 years, which was identical to that of the controls) Odds ratio (cases/controls, 95% confidence interval), coal gas production: *Overall (adjusted: no or yes)*: - no: 1.89 (26/12, 0.93-3.86) - yes: 1.64 (-/-, 0.80-3.40) *Cumulative exposure (percentiles, adjusted):* - not exposed: 1.00 (1,176/291, -) - <25th: 1.02 (7/2, 0.21-4.94)	Well-documented study; data were adjusted for serious bias, such as socioeconomic situation, and exposure to asbestos, PCBs, and polychlorinated biphenyls. Data on smoking habits were not available. Authors remark that smoking habits often are related to socioeconomic status, and therefore expect

	trend odds ratio's	- 25th-50th: 1.59 (7/3, 0.39-6.49) - 50th-75th: 0.55 (7/1, 0.07-4.57) - ≥ 75th: 3.87 (5/6, 1.15-12.9) Trend odd ratio: 1.10 (1.01-1.21)	that this confounding factor is weak or absent Reliability 1
Retrospective cohort study; Coal gasification plant, Kosovo; data retrieved from 1971-1986; study performed in 1986; N = 622 male workers (ever been employed through 1980); N = 442 reference population (open-pit lignite miners) Begraca et al. 1991[23]	Exposure data collected several days between 1981-1985: - area exposure was highly variable (range coal tar pitch volatile, 1.2 - 22,480 mg/m^3) - mean personal exposure (mg/m^3, range): benzene, 0.16 (<0.02-20.0); total hydrocarbons, 0.42 (<0.02 - 43.0); PAH, 0.03 (<0.002 -0.62); total particles, 0.22 (<0.01 - 10.0) - there was extensive surface contamination (no details given) Data based on employment and medical records of periodical occupational medical checks; only skin cancer was addressed; Average age: 34.2 years; average duration of experience: 10 years	*Outcome*: data do not allow a conclusion Incidence of skin cancer (rate, age adjusted): - gas workers: 1.9/1,000 (13 cases) - reference population: 1.5/1,000 (7 cases)	Limited documented study; small study; limited data on statistical methodology Data on smoking habits reported (28% in workers, 31% in reference group), but unclear whether these are taken into account in the analysis Reliability 3
Cohort; Denmark; 47 male workers employed > 1 year any time between 1911-1970; 141 non-exposed age-matched controls, selected from population registers; period of follow-up, no data	No data on exposure levels Mortality all causes, all cancers, and lung cancer	*Outcome*: positive association for lung cancer and general cancer mortality; no association with year of employment or latency Standardized mortality ratio (SMR) (95% confidence interval),	Small study, appropriate design No data on smoking habits or other confounding

		cases/controls *Lung cancer* SMR 8.9 (-), 7/6 Odds ratio 3.94, p=0.01 Other cancers SMR - (-), 7/8 Odds ratio, 2.91, p=0.02	factors Reliability 2
Retrospective mortality study; gas industry, the UK; N = 18,275 death certificates from England and Wales analysed for the years 1921-1932; annual total data for cases in women used for comparison Kennaway and Kennaway 1936[25]	No data on exposure levels; job history was based on death certificates Death certificates revealed 8,808 cases of lung cancer mortality and 9,472 cases of larynx cancer mortality	*Outcome*: data do not allow a conclusion Gas stokers and coke-oven chargers (estimated population 12,818) Standardized cancer mortality ratio (obs/exp): - lung: 3,42 (37/10.8) - larynx: 1,86 (20/10.7)	Appropriate study design, but limited reporting and analyses No statistical analyses performed; no data on smoking habits or other possible confounders Reliability 3
Retrospective cohort study; six coal gas plants, China; data retrieved from 1971-1981; N = 3,107 workers; reference population were workers in a steel rolling mill Wu et al. 1988[26]	No data on exposure levels Death cases identified among workers who were employed in 1971, and who died during the next 10 years	*Outcome*: data do not allow a conclusion Standardized Risk Ratios (confidence interval): - all causes: 1.29 (1.16-1.44), 234 deaths - all cancer: 1.73 (1.46-2.02), 109 deaths - lung cancer: 3.66 (2.36-5.43)	Data from secondary source, and listed as short summary: IARC 2012[3] No other data available Reliability 4
Cohort; Germany; 5.405 workers in one company; period of employment: 1953-1977; period of follow-up: no data [A]Manz (1980)[20]	No data on exposure levels Mortality	*Outcome*: data do not allow a conclusion Standardized mortality ratio (SMR) (95% confidence interval) *Respiratory tract cancer* SMR 3.7, 63 death cases *Urinary tract cancer* SMR 6.1, 6 death cases	Data obtained from secondary source: Bosetti et al. (2006)[15] No other data available Reliability 4

[A] Data of the study used in meta-analysis by Bosetti et al. (2006).[15]

C Details animal carcinogenicity studies

Cancer development in animals, which are exposed to waste products of the coal gasification process.

Animal species	Data on exposure and effect endpoints Xpo = exposure period; Xpe = exposure + observation period	Results	Remarks and reliability (Annex F)
Inhalation studies			
Female Crl:[WI]BR Wistar rats; N = 72/group Rittinghausen et al. 1997[12] Germany	Tar/pitch condensation aerosol (source unknown) of several B[a]P concentrations: 0 (clean air), 20 µg B[a]P /m^3, 50 µg B[a]P /m^3, or 125 µg B[a]P/m^3 *Exposure scenario 1:* 17 h/day, 5 days/week for 30 monts; Xpo = 10 months; Xpe = 30 months *Exposure scenario 2:* Exposure: 18 h/day, 5 days/week for 30 months; Xpo = 20 months; Xpe = 30 months Histopathological examination on lung lesions	Number of tumour bearing animals (in order of increasing exposure) *Exposure scenario 1:* - Pulmonary cystic keratinizing squamous cell carcinoma: 0/72, 0/72, 23/72*, 38/72* - Pulmonary keratinizing squamous cell carcinoma: 0/72, 1/72, 4/72, 3/72 - Total number of pulmonary squamous cell carcinomas: 0, 1/72, 27/72*, 41/72* *Exposure scenario 2:* - Pulmonary cystic keratinizing squamous cell carcinoma: 0/72, 19/72*, 63/72*, 62/72* - Pulmonary keratinizing squamous cell carcinoma: 0/72, 4/72, 5/72, 4/72 - Total number of pulmonary squamous cell carcinomas: 0, 23/72*, 68/72*, 66/72* * statistically different from control, p<0.001	Sufficient number of animals; sufficient duration of exposure Histopathological examination limited to the lungs; no data on: non-carcinogenic effects, number of tumours per anima; early mortality, trends in food consumption and body weight Reliability 2
Oral administration			
Female B6C3F1 mice; N = 48/group Culp et al. 1998[11] The USA	Coal tar (from coal gasification plant waste sites) added to the diet: - *Mixture 1*: composite of coal tar from seven sites (0.1% in diet corresponds	*Percentage survival whole treatment period (in order of increasing exposure):* *Mixture 1:* 65, 71, 69, 63, 21, 0, 0 *Mixture 2:* 65, 65, 65, 15 In highest dose groups significant decrease in food consumption. Also lower	Well-documented study; data included food consumption, body weight, organ weights and percentage of survival; sufficient

	with 2.2 ppm B[a]P); 0 (solvent, control), 0.01, 0.03, 0.1, 0.3, 0.6 and 1.0% in diet* - *Mixture 2*: composite of coal tar from two of the seven sites + one site with known high level of B[a]P content in coal tar (0.1% in diet corresponds with 3.7 ppm B[a]P): 0 (solvent, control), 0.03, 0.1 and 0.3% in diet - *Positive control*: B[a]P only * Food intake is estimated at 0.35g/day; average body weigt estimated to be 25 gram. Doses in diet correspond to approximately 1.4, 4.2, 14, 42, 84 and 420 mg B[a]P/kg bw/day Exposure on daily basis for 2 years; Xpe = 2 years, Xpo = 2 years Gross pathology and histopathology performed on the liver, lungs, small intestines, stomach, tongue and esophagus Full histopathology performed (except in mixture 1 group, 0.03%)	body and organ weight reported. *Number of tumour bearing animals* (in order of increasing exposure; * p< 0.05) *Mixture 1 (all exposure levels):* - Liver hepatocellular adenomas and/or carcinomas: 0/47, 4/48, 2/46, 3/48, 14/45*, 1/42, 5/43 - Lung (alveolar/bronchiolar) adenomas and/or carcinomas: 2/47, 3/48, 4/48, 4/48, 27/47, 25/47*, 21/45* - Forestomach papillomas and/or carcinomas: 0/47, 2/47, 6/45, 3/47, 14/46*, 15/45*, 6/41 - Small intestine adenocarcinomas: 0/47, 0/46, 0/45, 0/47, 0/42, 22/36*, 36/41* - Haemangiosarcomas: 1/48, 0/48, 1/48, 1/48, 11/48*, 17/48*, 1/45 - Histiocytic sarcomas: 1/48, 0/48, 0/48, 1/48, 7/48, 5/48, 0/45 - Sarcomas: 1/48, 4/48, 3/48, 2/48, 7/48, 1/48, 2/45 For all tumour types a dose significant trend was observed (p = 0.003 – 0.00001) *Mixture 2 (0.03%, 0.3% and 0.6%):* - Liver hepatocellular adenomas and/or carcinomas: 7/47, 4/47, 10/45* - Lung (alveolar/bronchiolar) adenomas and/or carcinomas: 4/48, 10/48*, 23/47* - Forestomach papillomas and/or carcinomas: 3/47, 2/47, 13/44* - Small intestine adenocarcinomas: 0/47, 0/47, 1/37 - Haemangiosarcomas: 1/48, 4/48, 17/48* - Histiocytic sarcomas: 3/48, 2/48, 11/48* - Sarcomas: 0/48, 4/48, 5/48 Not tested for dose related trends	number of animals per group No data on general toxicity; no data on coal tar consumption expressed as mg/kg bw/day; only female mice tested Reliability 2
Male and female B6C3F1 mice; N = 12/sex/group	0.0% (control) or 0.5% MGP* residue in basal gel diet; 0.005% B[a]P in diet served	No signs of acute toxicity or early mortality. Mean body weight in highest dosed group was lower compared to non-exposed	Number of animals too low for statistical robustness of the

	as positive control	animals.	outcome; exposure duration too short for tumour development; only one dose of MGP tested Reliability 3
Weyand et al. 1994[6] The USA	* Intake of 0.5% MGP: B[α]P content in diet = 1,560 mg/kg bw; food intake = 5.7 g/d/mouse (females). Based on average body weight of 25g during the study, MGP intake is estimated at 1,140 mg B[a]P/kg bw/day (for males: 1,480 mg/kg bw/day) Exposure on daily base for 185 days; Xpo and Xpe = 185 days; All organs histopathologicaly examined for gross lesions	*Number of tumour bearing animals* (in order of negative control, positive control and 0.5% MGP): - Forestomach, squamous-cell carcinoma: Male, 0/10, 0/10, 1/10; Female, no data; No correlation with exposure to MG Preneoplastic lesions: low and sporadic incidence, no correlation with exposure to MGP	
Female A/J mice; N = 30/group Weyand et al. 1995[7] The USA	0.0% (control), 0.10% or 0.25% MGP* residue in basal gel diet; 11 and 67 mg B[a]P per mouse served as positive control (administered by a single intraperitoneal injection) * Based on an average body weight of 25 g during the study, the exposures correlate to 0, 100 and 236 mg B[a]P/kg bw/day Exposure on daily base for 260 days; Xpo and Xpe = 260 days Histopatholic examination of the lungs and stomach on tumour development	Mice fed gel diet without MGP (control group) consumed less food and had lower body weights (authors did not have an explanation for this observation). Mortality rates ranged from 3 to 30% in control, MGP fed, and B[a]P exposed animal groups. Number of tumour bearing animals (in order of increasing exposure): - lung tumours: 4/21, 19/27*, 29/29* (B[a]P: 14/27*), * p<0.05 - forestomach tumours: 0/21, 0/27, 0/29 (B[a]P: 27/27*), * p<0.05 Number of tumours per mouse (multiplicity; in order of increasing exposure): - lung tumours: 0.19±0.09, 1.19±0.21*, 12.17±0.14* (B[a]P: 0.59±0.12), * p<0.05 - forestomach tumours: 0, 0, 0 (B[a]P: 4.22±0.41*), * p<0.05	Duration of study too short for maximum tumour development; limited histopathologival examination; tumour types not specified; in negative control group early mortality was noted Study not reliable Reliability 3

Dermal application

Male Syrian hamsters; N =	MGP residue applied at doses of 50% and 100%	No tumours in cheek pouch (only diffuse epithelial hyperplasia at 32 weeks)	Limited experimental set-up: only cheek pouch

4/group Brandon et al. 2009[10] The USA	solution in mineral oil; mineral oil served as negative control; 2% B[a]P and 0.5% DMBA served as positive controls (applied in mineral oil) 200 µL applied topically into the right cheek pouch Exposure 3 times per week: Xpo and Xpe 12, 16, 20, 28 and 32 weeks; Histopathologic examination of the right cheek pouch		examined; small number of animals; no data on general toxicity Reliability 3

Intraperitoneal injection

Male and female $B_6C_3F_1$ mice (infant, 15 days old); N = 30/group Rodriguez et al. 1997[13] The USA	Single injection of: - MGP-4*, 1,140 mg/kg bw - MGP-M7*, 285, 570 and 1,140 mg/kg bw - B[a]P served as positive control * MGP-4 represents coal tar from a single site, MGP-M7 is a residue composite of 7 sites Xpo: 26, 39 and 52 weeks Histopathologic examination on the lung, liver and forestomach tissues	No forestomach tumour found in any group. Few pulmonary tumours were observed, but no correlation with exposure to MGP. Liver tumours (data presented are from week 52; in order of corn oil only (control), MGP-4, MGP-M7 low, medium and high, B[a]P): *Number of tumour bearing animals*: Males: 3/63, 12/28, 4/34, 8/32, 17/29, 19/24 Females: no treatment related tumours *Number of tumours per mouse*: Males: 1.0, 1.7, 1.2, 1.4, 1.8, 2.5 Females: no treatment related tumours	Irrelevant route of exposure for humans; no statistical analyses performed; no whole body histopathological examination; no data on general toxicity Reliability 3

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D Classification criteria 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.[9]

3.5.1. Definitions and general considerations

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

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

3.5.2. Classification criteria for substances

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

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

3.5.2.3 Specific considerations for classification of substances as germ cell mutagens

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

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

Table 3.5.1 Hazard categories for germ cell mutagens

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

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

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

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

— mouse spot test;
— mammalian erythrocyte micronucleus test.

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

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

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

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

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

3.5.3 Classification criteria for mixtures

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

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

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

	Concentration limits triggering classification of a mixture as:

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

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

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

3.5.3.2.1. Classification of mixtures will be based on the available test data for the individual ingredients of the mixture using concentration limits for the ingredients classified as germ cell mutagens. On a case-by-case basis, test data on mixtures may be used for classification when demonstrating effects that have not been established from the evaluation based on the individual ingredients. In such cases, the test results for the mixture as a whole must be shown to be conclusive taking into account dose and other factors such as duration, observations, sensitivity and statistical analysis of germ cell mutagenicity test systems. Adequate documentation supporting the classification shall be retained and made available for review upon request.

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

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

3.5.4. Hazard communication

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

Table 3.5.3 Label elements of germ cell mutagenicity

Classification	Category 1A or Category 1B	Category 2
GHS Pictograms		
Signal word	Danger	Warning
Hazard Statement	H340: May cause genetic defects (state route of exposure if it is conclusively proven that no other routes of exposure	H341: Suspected of causing genetic defects (state route of exposure if it is conclusively proven that no other

	cause the hazard)	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 system on carcinogenicity

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

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

[a] See Guideline to the classification of carcinogenic compounds, the Health Council (2010).[27]

[b] See Section 3.6 (Carcinogenicity) of Regulation No. 1272/2008 of the European Parliament and of the council on classification, labelling and packaging of substances.[9]

F Reliability testing of animal and in vitro studies

To assess the reliability of animal and in vitro studies, the Committee uses the criteria set by Klimisch et al. 1997.[28] A summary of the criteria of the reliability scores is given below. Only studies with a reliability score of 1 or 2 are considered in assessing genotoxicity and carcinogenicity.

Reliability 1 (reliable without restriction)

For example, guideline study (OECD, etc.); comparable to guideline study; test procedure according to national standards (DIN, etc.).

Reliability 2 (reliable with restrictions)

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

Reliability 3 (not reliable)

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

Reliability 4 (not assignable)

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

G Reliability testing of epidemiological studies

To assess the reliability of epidemiological studies, the Committee uses the criteria set by Money et al.(2013).[29] 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).[30]

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.

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The Health Council and interests

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