Committee for Risk Assessment

RAC

Opinion on scientific evaluation of occupational exposure limits for

cobalt and inorganic cobalt compounds

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OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON THE EVALUATION OF THE OCCUPATIONAL EXPOSURE LIMITS (OELs) FOR COBALT AND INORGANIC COBALT COMPOUNDS

Commission request

The Commission asked the advice of RAC to assess the scientific relevance of occupational exposure limits for some carcinogenic chemical substances, in support of the preparation of proposals for amendment of Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens mutagens or reprotoxic substances at work (CMRD)[1].

I PROCESS FOR ADOPTION OF THE OPINION

Following the above request from the European Commission RAC, was requested to provide an opinion on the evaluation of the scientific relevance of occupational exposure limits (OELs) for cobalt and inorganic cobalt compounds with a deadline of 23 December 2022.

Chemical name(s): cobalt and inorganic cobalt compounds

In support of the Commission's request, ECHA prepared a scientific report concerning occupational limit values for cobalt and inorganic cobalt compounds at the workplace. This scientific report was made available on 11 April 2022 and interested parties were invited to submit comments by 10 June 2022.

In the preparatory phase of drafting this report, ECHA launched a call for evidence on 20 August 2021 to invite interested parties to submit comments and evidence on the subject by 19 November 2021.

RAC developed its opinion on the basis of the scientific report submitted by ECHA. During the preparation of the opinion, the scientific report was further amended as an Annex to the RAC opinion to ensure alignment.

The RAC opinion includes a recommendation to the Advisory Committee on Safety and Health at Work (ACSH) in line with the relevant Occupational Safety and Health legislative procedures.

II ADOPTION OF THE OPINION OF THE RAC

Rapporteurs, appointed by RAC: **Tiina Santonen and Ruth Moeller**.

The opinion was adopted by **consensus** on **1 December 2022**.

RAC Opinion of the assessment of the scientific relevance of OELs for cobalt and inorganic cobalt compounds

RECOMMENDATION

The draft opinion of RAC on the assessment of the scientific relevance of Occupational Exposure Limits (OELs) for **cobalt and inorganic cobalt compounds** is set out in the table below and in the following summary of the evaluation.

The limit values are derived from human and animal studies based on inflammatory effects and are recommended as OELs (8-h TWA) for the inhalable and respirable fraction, respectively.

SUMMARY TABLE

The table presents the outcome of the RAC evaluation to derive limit values for the inhalation route and the evaluation for dermal exposure and a skin notation.

Derived Limit Values[1]

OEL as 8-hour TWA[2]:	0.0005 mg Co/m^3 (0.5 µg Co/m^3; respirable fraction) 0.001 mg Co/m^3 (1 µg Co/m^3; inhalable fraction)
STEL:	not relevant
BGV:	Females: 2 µg Co/L urine Males: 0.7 µg Co/L urine
BLV:	not established

Notations

Notations:	"Skin sensitisation" and "Respiratory sensitisation"

[1] The naming conventions of limit values and notations used here follow the 'Methodology for the Derivation of Occupational Exposure Limits' (SCOEL 2013; version 7) and the Joint ECHA/RAC – SCOEL Task Force report (2017b). [https://echa.europa.eu/documents/10162/13579/jtf_opinion_task_2_en.pdf/db8a9a3a-4aa7-601b-bb53-81a5eef93145].

[2] The proposed OEL is based on a mode of action-based threshold for the carcinogenicity of cobalt compounds.

RAC OPINION

Background

This draft opinion concerns cobalt and inorganic cobalt compounds (see section 1 of Annex 1).

This evaluation takes previous reviews into account, in particular:

- AGS (2017). Begründung zu Cobalt und Verbindungen in TRGS910. Ausschuss für Gefahrstoffe – AGS-Geschäftsführung – BAuA.
- RAC (2020). Committee for Risk Assessment (RAC) Committee for Socio-economic Analysis (SEAC). Opinion on an Annex XV dossier proposing restrictions on: cobalt sulphate, cobalt dichloride, cobalt dinitrate, cobalt carbonate and cobalt di(acetate).
- RAC (2016). RAC agreement: Establishing a reference dose response relationship for carcinogenicity of five cobalt salts.
- RAC (2017). RAC Opinion proposing harmonised classification and labelling at EU level of cobalt.
- ANSES (2014) and (2018). Reports on OEL, BLV and BGV evaluations.
- ATSDR (2004). Toxicological Profile for Cobalt.
- DFG (2007, 2012, 2016, 2019). Cobalt and cobalt compounds. MAK Value documentation, BAT Value documentation and Air Monitoring methods.
- US National Toxicology Program (NTP) (2016). Report on Carcinogens. Monograph on cobalt and cobalt compounds that release cobalt ions *in vivo*.
- IARC (2006) and summary article (Karagas et al. 2022) on IARC 131 conclusions on cobalt carcinogenicity (ahead of Monograph Volume 131).

Key conclusions of the evaluation

- Workers are often exposed to a mixture of cobalt compounds. Because individual cobalt species cannot be separately monitored in mixed exposure scenarios, RAC recommends that the limits should be applied to all cobalt inorganic compounds.
- Lung cancer observed in the animal studies and non-cancer respiratory effects observed in exposed workers are the main critical toxic endpoints of cobalt metal and its inorganic compounds. Other toxic effects of cobalt and its salts include respiratory and skin sensitizing properties and reproductive toxicity.
- The available evidence from humans does not clearly show an increased risk of cancer among hard-metal workers or workers in cobalt salt manufacturing. However, a definite conclusion cannot be drawn from the human data due to several important limitations.
- The mechanism of action of cobalt carcinogenicity in the lungs is likely to involve multiple mechanisms, including oxidative stress, induction of HIF-1*a* and chronic inflammation, which are known to result in secondary genotoxicity.
- There is multiple evidence of the thresholded mechanisms of action of cobalt and chronic lung inflammation is likely to play a crucial role in the genotoxicity and carcinogenicity of cobalt. The threshold for lung inflammation is therefore the basis for the recommended OEL. RAC considers that when the OEL is derived from inflammatory lung effects, the the risk of cancer is substantially reduced at exposure levels below the level of the recommended OEL.

- Thresholds for chronic inflammatory lung effects of the respirable fraction of 0.5 µg/m^3 and of the inhalable fraction of 1 µg/m^3 were derived in a weight-of-evidence approach based on data from subchronic and chronic animal studies on cobalt sulphate hexa/heptahydrate, supported by the animal data from cobalt metal, as well as based on human data on the local respiratory effects of cobalt. These values are recommended to be used as OELs for cobalt and its inorganic compounds.
- Irritation, effects on lung function and respiratory sensitization have been observed in humans at distinct levels considering the two exposure settings: (i) production and use of cobalt and its substances and (ii) hard-metal industry. The human evidence is limited but may suggest that interstitial lung disease (ILD) and fibrosis are unlikely to occur in the concentration range below 100 µg/m^3, whereas occupational asthma, upper respiratory tract irritation and decrease in lung function may develop at lower concentrations (<50 µg/m^3).
- The dose-response data for non-cancer lung effects in humans is derived from Nemery et al. (1992) from diamond polishing industry without hard-metal and tungsten co-exposure, showing symptoms and mild but statistically significant decreases in lung function at inhalation exposure levels of 15 µg/m^3 with a NOAEC of 5 µg/m^3. This data was used to derive an OEL of 1 µg/m^3 for the inhalable fraction.
- The data from the hard-metal industry also show lung effects at dose levels <50 µg/m^3, with even a few studies suggesting respiratory tract symptoms (irritation, cough, phlegm, wheezing) in workers at low exposure levels of 2-5 µg/m^3.
- The above mentioned limits (0.5 µg Co/m^3 respirable fraction; 1 µg Co/m^3 inhalable fraction) can be applied also for cobalt oxide. Cobalt(II)oxide does not currently have an harmonised classification as a carcinogen in the EU, but has been self-classified as Cat 1B carcinogen under CLP, and was also recently classified by IARC as "possibly carcinogenic to humans" (Group 2B). Considering the available carcinogenicity and mechanistic data, the proposed OELs should be applied also to cobalt(II)oxide and cobalt dihydroxide.
- Poorly soluble cobalt compounds (e.g. tricobalt tetroxide, cobalt sulfide or cobalt dihydrate) have shown lower bioavailability and toxicity and have not consistently shown genotoxicity when compared to cobalt metal and its soluble salts. These are not classified as carcinogens either. Long-term toxicity data on these substances however are limited, which prevents their full assessment and the derivation of a separate OEL. However, the OELs proposed are expected to also protect workers from the potential hazards of poorly soluble cobalt compounds. The same considerations apply to complex inorganic cobalt compounds (e.g. pigments).
- Besides the main effects of lung inflammation, genotoxicity and carcinogenicity, cobalt can cause respiratory and skin sensitisation as well as reproductive toxicity. The proposed OEL is likely to protect from these effects.
- A DNEL of 4 µg/m^3 can be derived for male fertility effects based on animal data.
- The current data do not allow for the setting of a NOEC for asthma. Cobalt-induced asthma seems to be uncommon nowadays and the limit values recommended above are likely to reduce the risk of respiratory sensitisation as well.
- After oral exposure, cobalt salts are reported to have caused cardiac effects. However, evidence of such effects in workers is limited.
- Biomonitoring can be applied to assess the exposure to inorganic cobalt compounds.

A BGV is recommended on the basis of available data on levels in the general population. No BLV is established.

Carcinogenicity and mode of action (see section 7.7 and 8.1 of Annex 1 for a full discussion)

Cobalt metal and several cobalt compounds are carcinogenic and have a harmonised classification as Carc 1B under the CLP Regulation. IARC classified cobalt metal and soluble cobalt (II) salts as "possibly carcinogenic to humans" (Group 2B) in 2006. Recently, IARC updated the classification of cobalt metal and soluble cobalt(II) salts as probably carcinogenic to humans (Group 2A) on the basis of sufficient evidence in experimental animals and strong mechanistic evidence in human primary cells. Cobalt(II)oxide was classified as possibly carcinogenic to humans (Group 2B) on the basis of sufficient evidence in experimental animals. Cobalt(II, III)oxide (tricobalt tetraoxide), cobalt(II)sulfide, and other cobalt(II) compounds were each evaluated as not classifiable as to their carcinogenicity to humans due to inadequate evidence (Group 3). The evaluation did not consider hard-metal or cobalt alloyed with other metals (Karagas, 2022).

Lung carcinogenicity

Evidence for the lung carcinogenicity of cobalt metal and inorganic cobalt compounds comes from the available studies in animals and these have been evaluated earlier by RAC (RAC, 2016, 2017 and 2020). In RAC (2017), RAC evaluated the carcinogenicity of cobalt including its mode of action, leading to a Carc. 1B classification on the basis of evidence from animal experiments showing lung carcinogenicity after inhalation exposure. In the other assessments by the Committee(RAC, 2016, 2020), the focus was on soluble cobalt salts. The soluble cobalt sulphate hexa/heptahydrate (exposure was to heptahydrate but chemical analysis showed that most of the substance was in the form of hexahydrate) increased the incidence of alveolar/bronchiolar adenoma and/or carcinoma both in Fischer 344 rats and in B6C3F1 mice. Cobalt metal caused clear increases in the alveolar adenomas and carcinomas in NTP 2-year inhalation carcinogenicity studies, both in F344/NTac rats and B6C3F1/N mice in both sexes.

These studies provide robust evidence on the carcinogenicity of cobalt metal and its salts. Less information is available on cobalt oxides. However, intratracheal installation of cobalt(II)oxide induced increased incidences of lung neoplasms, including alveolar/ bronchiolar adenoma, benign squamous epithelial neoplasm, or alveolar/ bronchiolar carcinoma combined in rats, being statistically significant in males.

Human epidemiological data have not clearly shown an increased cancer risk in occupationally exposed workers and no further evidence has been published since the last RAC evaluation (RAC, 2020). As summarized before, some epidemiological studies have shown significantly increased risk for cancer in the lungs (Hogstedt and Alexandersson, 1990; Moulin et al., 1998, Lasfarguez et al., 1994; Wild et al., 2000) or trachea, bronchus or tongue (Lasfargues et al., 1994; Sauni et al., 2017) in workers occupationally exposed to cobalt in hard-metal production and in cobalt manufacturing. However, the available studies have limitations hampering definite conclusions, i.e. no adjustment for confounding factors due to smoking or exposure to other carcinogens and no quantitative exposure analysis. In those studies which reported an association of exposure to cobalt with lung cancer, standardised mortality ratios (SMR) were reported in the range of 1.4 to 2 or even above for higher exposure categories or longer exposure durations. The causality due to confounding is debatable. These risk estimates however would not contradict the animal-derived exposure-risk relationship (ERR), if we assume working life exposures at levels up to which significant and non-carcinogenic lung effects (interstitial lung diseases and fibrosis) are unlikely to occur (i.e. were not observed in hard-metal workers based on epidemiological studies, ≤ 100 µg/m^3).

RAC (2020) considered two epidemiological studies published more recently. The Sauni et al. (2017) evaluated the cancer incidence among 995 male workers employed in a Finnish cobalt plant for at least a year between 1968 and 2004, and the only cancer type with increased incidence was tongue cancer. However, because of the small size of the study, RAC concluded that the results have limited value. Marsh et al. (2017) reported a large international occupational epidemiological investigation of 32,354 hard-metal workers

from three companies and 17 manufacturing sites. The study showed no evidence of elevated lung cancer mortality risk among cobalt exposed hard-metal workers who had worked at least 1 year in hard-metal production (22 506 persons, 544 845 person-years of follow-up) (SMR 1.10 (95% CI 0.97 – 1.23)) and no dose-response with cumulative or mean cobalt exposure was seen. However, even the exposure levels of the highest exposure group were not high and at such levels it would require high statistical power to detect excess risks based on animal studies. It is also noted that the data indicate that the lung cancer risk estimates (Annex 1, Table 18) might be too high as there was positive confounding due to smoking, and furthermore the RR calculations were not based on an entirely unexposed reference population, but instead, on a population whose average exposure was below 2 µg Co/m^3. In this study, the exposure intensity to cobalt showed a median of 6 µg Co/m^3, a ratio mean of 13 µg Co/m^3 (calculated as the sum of cumulative exposure divided by sum of duration of exposure across all workers with known work history). The exposure range was from 1 to 300 µg Co/m^3, the highest category had a cumulative exposure of > 0.1275 mg/m^3-years (corresponding to > 3.2 µg/m^3 for 40 years, inhalable fraction) and the two highest categories were slightly below or above a mean exposure intensity of 11 µg/m^3.

The animal data-based ERR (see RAC, 2020; Annex 1, chapter 9.1; and section on cancer risk assessment below) predicts an excess cancer risk (ExCR) for the exposure (inhalable) of 11 µg/m^3 of $1.5*10^{-3}$ and for an exposure of 40 µg/m^3 (lower limit + 10% of range result) of $2.6*10^{-2}$ (40 years exposure, considering an inhalable/respirable ratio of 50% for this calculation). The detection of such excess risks in an epidemiological study is challenging and high statistical power is required. The baseline cumulative lung cancer incidence in the European population until the age of 75 years is in the range of 5-10% in males with decreasing trend, nowadays (statistics for 2020, https://gco.iarc.fr) 5.4×10^{-2} for men, and 3.7×10^{-2} for both sexes combined. Accordingly, the predicted relative risk (RR) for the above animal-data derived ExCR would be calculated as 1.10 (males) or 1.14 (combined sexes) for the exposure of 11 µg Co/m^3. The RR at 40 µg/m^3 would be 1.38 (males) and 1.56 (combined sexes), accordingly, which exceeds the RR and SMR of the Marsh et al. high exposure category (but still within the 95 CI).

While such rough comparison of absolute life-time lung cancer risks in the general population with the absolute life time predicted risks based on animal data (assuming 40 years workplace exposure and cohort follow-up for a lifetime) suggests that the animal ERR may overestimate cancer risks, no direct comparison can be easily done due to several differences:

i. The animal ERR relates to respirable particles while in Marsh et al. (2017) the relative risks refer to inhalable cobalt particles.
ii. The animal dose response assumes 40 years of exposure, while in the hard-metal follow-up cohort much shorter exposures (overall one third 1-4 years, one third 5-19 years, one third at least 20 years) were reported.
iii. Also, the ERR calculates risk for the entire lifetime while the epidemiological difference relates only to the person-years in each age category experienced so far in the cohort. In total, 40% of the cohort members were aged ≤ 55 years at the end of the follow-up and 76% were still alive, with a mean follow-up of 24 years.
iv. Furthermore, the animal ERR calculates excess lung cancer incidence risk, while Marsh et al. (2017) derived lung cancer mortality risks, which are expected to be somewhat lower than lung cancer cumulative incidences (e.g. EU 2020, 4.27% vs 5.4% cumulative lung cancer incidence vs mortality, males).
v. In addition, there are uncertainties with the assumptions on the ratio of respirable/inhalable particles, as well as the actual exposures and respiratory protective equipment worn by workers.

As concluded by RAC (RAC, 2020), these human epidemiological data do not allow either identifying a carcinogenicity threshold to be identified for cobalt exposure, or quantitative

modification of the dose-response derived from the animal data at levels of exposure experienced by the hard-metal workers followed.

In the view of RAC, the human data are considered overall to be too limited to draw conclusions regarding the carcinogenicity of cobalt and inorganic compounds. Furthermore, there is no indication that humans are more sensitive compared to animals and overall the animal and human data are not in contradiction.

Upper respiratory tract carcinogenicity

Neither epidemiological nor animal studies have provided evidence of upper respiratory tract tumours. Although exposure to cobalt sulphate hexa/heptahydrate did not result in the increase in tumours in the upper respiratory tract in cancer bioassays in rats and mice (NTP, 1998), the result indicated that both may develop pre-malignant lesions, including hyperplasia, metaplasia and atrophy in epithelial cells of the nose, and metaplasia of the squamous epithelium of the larynx suggesting a potential for carcinogenicity in the upper respiratory tract. However, as discussed in RAC (2020), the upper respiratory tract seems to be more than one order of magnitude less sensitive for the carcinogenic effects of soluble Co salts when compared to the lower respiratory tract.

Similarly, also metallic cobalt caused hyperplasia, metaplasia and athropy but not tumours in the nose of mice and rats in chronic inhalation studies.

Systemic carcinogenicity

Carcinogenicity studies with soluble cobalt salts have not shown clear evidence of systemic cancers (RAC, 2016). However, the concern for systemic carcinogenicity has mainly been raised from the studies with cobalt metal, in which increased incidences of systemic cancers were seen in rats (but not in mice), the main tumour types that increased in rats after exposure to cobalt dust were pheochromocytomas and pancreatic cancers (RAC, 2017). As discussed earlier (RAC, 2020) there are, however, indications that these effects might not be relevant at dose levels not causing lung damage. Increased incidence of pheochromocytomas at high doses has been linked to lung damage associated hypoxia and cobalt promotion of a hypoxia-like state even with normal molecular oxygen pressure by stabilising hypoxia-inducible factor (HIF-1*α*), which is a major regulator of the adaptation of cancer cells to hypoxia. The same phenomenon has been also observed with insoluble nickel metal. Similar mechanisms have been suggested also to apply in case of pancreatic islet tumours seen to be increased in cobalt metal exposed rats but not in mice or in animals exposed to soluble cobalt salts.

Mode of action of genotoxicity and carcinogenicity

Mechanisms of genotoxicity and carcinogenicity of cobalt compounds have been discussed already earlier by RAC (2016, 2017 and 2020). There is evidence supporting the role of oxidative stress, stabilization of HIF-1*α* and inflammation in the genotoxicity and carcinogenicity of cobalt metal and its soluble salts (see Annex 1, and RAC, 2016, 2017, 2020). Since the last RAC opinion (RAC, 2020), the mechanisms have been further studied in a series of recent publications (Derr et al 2022, Viegas et al., 2022; van den Brule et al., 2022, Verougstraete et al., 2022 and Burzlaff et al., 2022) which aimed to group different cobalt compounds according to their solubility in biological fluids, and their ability to cause persistent lung inflammation, oxidative stress, and stabilization of HIF-1*α*. These studies indicated the ability of cobalt compounds with high bioaccessibility in biological fluids (e.g. metal, cobalt salts like sulfate and oxide) to induce oxidative stress, stablize HIF-1*α*, inflammation and cytotoxicity, as well as acute toxicity and inflammation in lungs after acute exposure, whereas compounds (like tricobalt tetraoxide, cobalt sulfide) with poor solubility in biological fluids indicated low cytotoxicity and acute toxicity *in vivo* and no oxidative stress inducation or HIF-1*α* activation *in vitro* or *in vivo*. Danzeisen et al. (2022) interpreted the MoA and its Key Events (KE) for carcinogenicity for biosoluble cobalt compounds involving accumulation of Co ion in tissue (KE1), formation of ROS, hypoxia and cytotoxicity (KE2), inflammation with edema and epithelial damage (KE3) and hyperplasia (KE4). A mutagenicity MoA was not considered by Danzeisen et al. since

available evidence was considered to show that cobalt is not directly mutagenic. Following this evaluation, industry self-classified reactive low soluble cobalt compounds (cobalt carbonate, oxide, hydroxide, dihydroxide) as Carc 1B based on their Co^{2+} release and biological activity in the MoA studies (CI, 2022 submitted comments). Since poorly soluble compounds including tricobalt tetraoxide, cobalt sulphide, cobalt hydroxide oxide and cobalt lithium dioxide, were not triggering the hypothesized lung tumour MoA due to poor Co^{2+} release, it was proposed that they should be grouped and considered separately from "reactive" cobalt compounds (Danzeisen et al., 2022; CI, 2022 submitted comments).

Although RAC agrees that there is data to support the plausibility of a ROS, hypoxia and inflammation-based MoA, the available data is not sufficient to exclude the possible role of other (threshold or non-threshold) mechanisms in the carcinogenicity of cobalt, including mutagenicity, epigenetic changes, alterations in DNA repair and immunosuppression. RAC further notes uncertainties related to *in vitro – in vivo* correlation of the bioaccessibility in biological fluids, the role of delayed release of cobalt after long retention in the lung *in vivo* and particle related toxicity. Finally there is a lack of toxicity data on poorly soluble cobalt compounds as no subchronic and chronic toxicity and carcinogenicity data are currently available.

Chronic non-cancer lung effects and Limit Values for inhalable and respirable particles

Animal data

In animals studies, concerning the respirable fraction, cobalt metal and cobalt sulphate hexa/heptahydrate have caused inflammation in the nose and lungs, alveolar proteinosis, hyperplasia/metaplasia and also fibrosis after subacute-chronic exposure in both mice and rats. No NOAEC for these effects has been identified, but the lowest LOEAC of 0.3 mg/m^3 was observed in a 2-year chronic toxicity/carcinogenicity NTP study (1998) with cobalt sulphate heptahydrate. The chemical analysis revealed that the substance in the exposure chamber was mostly in the form of cobalt sulphate hexahydrate. Taking this into account, the LOAEC of 0.3 mg/m^3 corresponds to 0.067 mg Co/m^3.

For cobalt metal a LOAEC of 0.625 mg Co/m^3 was observed in the 90-days inhalation toxicity study (NTP, 2014). In a 2-years chronic toxicity/carcinogenicity study (Bucher et al., 1999) the lowest dose tested and representing a LOAEC was 1.25 mg Co/m^3.

In its previous opinion on restricting soluble cobalt salts, RAC (2020) concluded: *"RAC acknowledges that chronic inflammation is likely to play a role in the mode of action of cobalt-caused genotoxicity and cancer. An estimated threshold level for chronic pulmonary inflammation of 0.5 µg/m^3 (respirable fraction) is derived using animal data".*

This previously derived limit value of 0.5 µg Co/m³ (respirable fraction) for chronic lung inflammation for soluble cobalt salts was based on the data on **cobalt sulphate hexa/heptahydrate** using the LOAEC of 0.3 mg/m³, corresponding to 0.067 mg Co/m³, and conversion of the point of departure into a worker equivalent dose of 0.034 mg/m³ (0.067 mg/m³ * 6/8 hours * 6.7/10 m³) and by applying assessment factors of 2.5 for the remaining interspecies differences, 5 for worker intraspecies differences, and 5 for the dose-response including LOAEC-NOAEC extrapolation and severity.

For **metallic cobalt**, if a LOAEC of 0.625 mg Co/m^3 from the 90-days study is taken as a starting point and the same assessment factors are applied, complemented by an additional factor of 2 for extrapolation from subchronic to chronic exposure, a threshold of 2.5 µg/m^3 for inflammatory effects can be derived. However, this extrapolation is highly uncertain. No NOAECs were identified in the subacute, subchronic and chronic NTP studies. In the 2-year study on cobalt sulphate hexa/heptahydrate, incidences of alveolar granulomatous inflammation, metaplasia and interstital fibrosis were virtally 100% in all dose groups (96% in the low dose) with increasing severity with dose. According to NTP, inflammation was much more severe and occuring at lower concentrations in chronic than

in pre-chronic studies, proteinosis was moderate to marked and not observed in pre-chronic studies, and the occurence and extent of interstital fibrosis (a rather slowly developing lesion) in essentially all animals was not predicted based on the 13-weeks study. The chronic NTP study on cobalt metal applied too high dose levels resulting in a higher LOAEC than after sub-chronic exposures, with 100% inflammatory and fibrotic lung lesions and up to > 80% lung tumor rate in the low dose (84% in male mice). Considering the increase in incidence and severity of lung lesions with exposure duration study with cobalt metal is considered unsuitable for the extrapolation of a limit value in the view of RAC.

RAC takes note of NIOSH (1981) and a review of toxicological literature on **Cobalt dust** (2002, prepared for the National Institute of Environmental Health Sciences North Carolina), providing a reference to an older subchronic study (Popov 1977, Popov et al., 1977) in turn, reporting signs of respiratory irritation at 5-500 µg/m^3 and mild general toxicity effects at 1 µg/m^3. However, RAC recognises the uncertainties e.g. concerning the Co levels in exposure chambers, and their reliability. It should be noted that the lowest level claimed in this study was >500 times lower than the lowest level used in NTP studies.

Thresholds for **low or poorly soluble cobalt compounds** may be higher than thresholds derived for soluble cobalt metal and salts. However, only some acute-subacute data is available for one representative: In a 28-days inhalation study in rats, insoluble cobalt trioxide caused only mild neutrophilic accumulation and increase in inflammatory markers in BAL at the dose level of 15 mg Co/kg with a NOAEC being 3.75 mg Co/m^3 (Burzlaff et al., 2022). The substance showed also low acute toxicity with only a transient inflammatory response resolving soon after the exposure, whereas exposure to soluble cobalt metal and compounds caused persistent inflammatory effects (Viegas et al., 2022). These poorly soluble cobalt compounds have not been tested for subchronic and chronic toxicity/carcinogenicity and therefore no information is available on delayed release and toxicity of cobalt after long retention in the lung *in vivo.* They have currently not been classified for carcinogenicity or reproductive toxicity (also IARC placed them to group 3 due to inadequate evidence).

To conclude on the above, the NTP studies used rather high-dose levels for subchronic and chronic testing and inflammatory and fibrosis incidences were virtually 100% at the low doses, although it is recognized that the severity of the findings at the lowest doses with cobalt sulphate was only minimal to mild. Based on this, thresholds for cobalt metal and soluble salts derived using LOAEC levels as a starting point come with significant uncertainties. In particular, extrapolations for cobalt metal based on the LOAEC derived from the sub-chronic NTP study to chronic exposures is considered too uncertain to be used as a starting point for OEL setting.

Therefore, RAC considers the animal data in a weight-of-evidence approach together with the human epidemiological data on non-neoplastic respiratory effects.

Human data

In the context of this OEL assessment for cobalt and inorganic compounds, RAC considers three occupational exposure settings:

1. the production and use of cobalt and compounds;
2. the production and use of hard-metal and;
3. the polishing of diamonds.

Exposure to cobalt compounds is an established cause of obstructive lung disease/asthma, called cobalt-asthma, while exposure to cobalt-containing hard-metal is an established cause of parenchymal lung disease, interstitial pneumonitis, and progressive pulmonary fibrosis, called "hard-metal disease". In the hard-metal industry workers are co-exposed to cobalt and tungsten carbide, and although cobalt is considered as the main causative agent for this disease, tungsten carbide has been suggested to potentiate its effects resulting in synergism.

Cases of this parenchymal lung disease have also been reported in diamond polishing workers which have not been exposed to tungsten carbide, confirming a causal role for cobalt in the pathogenesis of hard-metal disease, which has been also called "cobalt-lung". Pathogenesis of this disease is not fully clear and individual susceptibility factors have been suggested to play a significant role in its pathogenesis (Nemery et al., 2001). The prominent role of individual susceptibility factors have made it difficult to identify dose-response relationships for the disease (Nemery et al., 2001).

Very few studies are available on exposure of workers to cobalt or cobalt compounds other than hard-metal. Interstitial lung diseases and fibrosis have not been associated with concentrations < 0.1 mg/m^3. Swennen et al. (1993) reported respiratory effects linked to asthma and effects on lung function at 0.125 mg/m³ (GeoMean 8-h TWA, range 1-7800 µg/m^3; exposure duration 8 years, range 0.3-39 years) in a cross-sectional study among 82 exposed workers of a cobalt production plant. The authors report that no lung abnormalities were detected on the chest radiographs and the results suggest that exposure to high airborne concentrations of Co alone is not sufficient to cause pulmonary fibrosis. RAC however notes that cobalt-lung is a rather rare disease with individual susceptibilities suggested as contributing to its development. Verougstraete et al. (2004) performed a longitudinal analysis in the same plant (N=122, male) and observed that cobalturia[3] contributed significantly to deterioration of FEV1 over the years but only in association with smoking. According to the authors, a slight detoriation was estimated by the best fit model for exposures entailing a cobalturia of 10, 20, or 40 µg/g creatinine roughly estimated equivalent to a time-weighted average exposure at 10, 20 or 40 µg/m^3. This is the only available longitudinal study from the cobalt industry.

In a Finnish cobalt salt manufacturing plant, Linna et al. (2003) did not see hard-metal disease and effects on lung function at an average cumulative exposure level of 1 mg/m³-years (~0.045 mg/m³ average exposure based on average exposure duration 22 years, corresponding to 0.025 mg/m^3 when considering 40 years exposure) but increased incidence of occupational asthma, chronic bronchitis (non significant) were observed. RAC notes that workers also had a cumulative exposure to 400 µg/m^3 years of nickel compounds and 19400 µg/m^3 total dust, and furthermore to irritative gases. Roto et al. (1980) concluded, based on their earlier study in this cobalt salt manufacturing plant, that cobalt asthma may occur already at exposure levels of < 0.1 mg/m^3. Subsequently, Sauni et al. (2010) made an evaluation of the asthma cases diagnosed in the same plant and concluded that exposure to cobalt sulphates in the department with average exposures of 0.03 mg/m³ (range 0.01-0.1 mg/m³) still resulted in an asthma incidence density (number of new cases per person-years) of 0.005. These data suggests that interstitial lung disease and fibrosis is unlikely in the concentration range below 100 µg/m^3, but occupational asthma may develop at lower concentrations (< 50 µg/m^3).

However, studies on diamond-polishing workers also need to be considered. Cobalt-containing diamond polishing discs were used for some time until cobalt-lung disease was discovered in these workers who did not experience tungsten carbide co-exposure. The proportion of cobalt in bonded diamond tools is much higher, i.e. up to 90%, than in hard-metal (5-25%), thus diamond polishing dusts consists largely of cobalt and may contain to some extent diamond dust (Nemery, 2001). In addition to those cases of severe parenchymal lung disease in diamond polishers, milder respiratory effects, including irritation and decreases in lung function have been described in diamond polishers.

The most important diamond-polishing study under consideration is Nemery (1992), who reported increased prevalance of respiratory symptoms (irritation and cough) and small

[3] 'Cobalturia' is often chosen as an indicator (measuring urinary cobalt concentration as µg/gcreat) for biological monitoring programs in occupational exposure to cobalt dusts.

but significant effects on lung function at the highest exposure group of 10.2 µg/m^3 (area-sampling) to 15.1 µg/m^3 (personal sampling) or 20.5 µg Co/g$_{creatinine}$ (n=194 exposed, 59 non-exposed workers). A NOAEC of 1.6 µg/m^3 (area-sampling) to 5.1 µg/m^3 (personal sampling) was suggested from this study. Irritation of eyes, nose, and throat and cough, and the fraction of these symptoms related to work, were significantly increased in the high-exposure group. The group also had significantly reduced lung function compared to controls and the low exposure group assessed by FVC (forced vital capacity), FEV1 (forced expiratory volume in 1 second), MMEF (forced expiratory flow between 25% and 75% of the FVC), and mean PEF (peak expiratory flow rate).

The study does not report the employment or exposure duration in years. The authors report a mean age (years ± SD) of male (m) and female (f) workers in the three exposure categories with 28.2±9.5 y (m) / 21.1±3.0 y (f) in the control category, 32.1±10.9 y (m) / 25.9±10.5 y (f) in the low exposure category, and 32.8±11.1 y (m) / 25.4±7.1 y (f) in the high exposure category. Less women than men participated (22%, 9%, 21% in the control, low and high exposure group, respectively). Thus, the majority of workers had an average age of about 30 years suggesting that the average exposure duration was only up to 10-15 years when assuming as a worst case a continuous employment history. It is possible thus, that longer working life exposure, or exposure of older, or otherwise more susceptible workers, could lead to a higher risk for developing lung dysfunction, more severe symptoms, or respiratory effects at even lower exposures (< 5-10 µg/m^3). On the other hand, it is noted that effects on lung function observed at the LOAEC of 15 µg/m^3 were mild with an unknown clinical relevance and acute irritative symptoms are considered to be more related to the concentration than to the cumulative exposure. An additional aspect to note is that the relationship between these symptoms and lung function findings observed in the Nemery et al (1992) study and the severe cobalt-caused parenchymal lung disease is unclear.

ATSDR (2004) in its Toxicological Profile for cobalt chose the dose of 5.1 µg/m^3 for decreased ventilatory function in exposed workers as PoD to derive a chronic inhalation Minimal Risk level, because this study in diamond polishers was considered well-conducted, it examined a human population and identified a NOAEL, neither of which occurred in the animal NTP studies.

Also ANSES (2015) considered diamond polishing workplaces (free of tungsten co-exposure) as relevant for OEL setting for cobalt and concluded "*The field data of Nemery et al. (1992) and Lison et al. (1994) thus enabled to recommend a BLV of 5 µg.g-1 of creatinine on the basis of exposure to cobalt compounds, excluding hard metals, at 2.5 µg.m-3 (8h-OEL recommended by the OEL Committee). This value must not be applied to exposure to cobalt when associated with tungsten carbide*".

Furthermore, diamond polishing workplaces were considered by IARC in its recent (2022) evaluation of cobalt carcinogenicity, which excluded hard-metal related tungsten co-exposure.

Also RAC (2020) previously considered this estimate suitable for deriving a limit value for the inhalable fraction for soluble cobalt salts. In its opinion on the restriction of soluble cobalt salts, RAC (2020) concluded: *The data by Nemery et al., 1992 suggests that at levels below 5 µg Co/m³ there is no effect on lung function in exposed workers. Based on this, a limit value of 1 µg Co/m³ for the inhalable fraction can be set by using an assessment factor (AF) of 5 for inter-individual differences. Although, the current data do not allow setting of a NOEC for asthma, based on the data available from three Member States and from an industry survey, asthma caused by cobalt seems to be uncommon nowadays. It is agreed by RAC that the limit value given above is likely to reduce the risk of respiratory sensitisation as well.*

RAC reiterates this conclusion. Indeed, the Nemery study is a well conducted human study and provides a dose-response relationship between lung function indices and cobalt exposure. RAC considers this study as particularly suitable for cobalt limit value derivation for the following reasons as reported by the authors:

- The study provides a dose-effect relationship between ventilatory function indices and cobalt exposure.
- Cobalt exposure was reliably measured by personal, static, and biomonitoring measurements, correlating very well with each other.
- Based on measurements very close to the discs (1 cm), only traces and no other relevant exposures were apparent.
- Workers were not exposed to hard-metal and tungsten carbide.
- A dust-related decrease in lung function can be excluded as well for two reasons. First of all, dust exposure was very low and not higher than in control workshops as reported by the authors. In addition workers were very young (20-30 years of age) and general dust-related decreases in lung function appear usually only after longer term (tens of years) exposure. The workplaces (with exception) were described as rather clean and the authors acknowledge a type of "healthy workshop" effect. The workshops of this survey therefore were characterised by apparently good hygiene practice, and this allowed the detection and attribution of lung function effects to low cobalt exposure as the plausible cause.
- RAC further stresses that according to the authors no clinically manifest cases of hard-metal disease/cobalt-lung were discovered in this survey. According to the author, the selection of the workshops was not based on previous lung disease cases in these workplaces.

RAC also notes that the LOAEC of 15.1 µg/m^3 derived from Nemery et al. on lung function indices in diamond polishers is rather close to the LOAEC of 30 µg/m^3 derived from Sauni et al. on clinically relevant manifested asthma in cobalt manufacturing, i.e. only a factor of 2 between the LOAECs.

To conclude, RAC considers this study to have a high value for limit value derivation and cannot identify any reason to cluster it with the epidemiological evidence on hard-metal exposure, or to consider that the effects are caused by some (unknown) synergism unrelated to the assessment of cobalt metal and its compounds.

When considering hard-metal work settings, more data is available for occupational exposure to cobalt but with concomittant exposure to hard-metal and thus tungsten carbide.

Kusaka et al. (1986) reported hard-metal asthma related to mean TWA exposures of <0.05 mg/m^3.

Meyer-Bisch (1989) in their cross-sectional survey reported chest radiographs suggestive of more abundant parenchmal diseases in 433 French exposed workers with current mean airborne levels of 30-272 µg/m^3 and an average exposure duration of 14 years, compared to unexposed and the difference was maintained after correction for smoking habits. Mean urinary levels were 10-100 µg Co/g$_{creatinine}$. No information on the past exposure levels in the factories were provided and no dose-response was reported.

The pooled mortality follow-up for lung cancer and non-malignant respiratory disease (NMRD) among 32 354 hard metal workers (Marsh et al. 2017) found no evidence that cobalt exposure at levels of 1-300 µg/m^3 (ratio mean of 13 µg/m^3 and median of 6 µg/m^3) increased mortality risks for lung cancer or NMRD.

Other hard-metal studies exist, even if few, reporting effects at similar low exposures of 10 µg/m^3 or less as reported by Nemery in diamond polishers:

Sprince et al. (1988) reported a prevalence of Interstial Lung Disease (ILD) of 0.7% in 1039 hard metal workers. The risk was significantly increased when comparing those with an average life-time exposure of at least 100 µg/m^3 with those with less than 100 µg/m^3, but not when those with an average life-time exposure of at least 50 µg/m^3 were compared with those with exposure less than 50 µg/m^3. However, 3/7 cases were never exposed

above 0.05 mg/m^3, their individual life time average exposure was estimated 3, 4, and 7 µg/m^3.

Kennedy et al. (1995) reported a cross-sectional study in 118 saw 'filers' in British Columbia lumber mills and reported respiratory symptoms (phlegm, cough, wheeze) at average levels of 5 µg/m^3 (personal sampling, no direct non-exposed control). However, control of other confounding exposures (e.g. chromium) was not made and may have contributed to the results.

Alexandersson & Bergman (1978) and Alexandersson (1979) reported in their cross-sectional studies increased prevalence of respiratory tract irritation at exposures starting from as low as 2 µg/m^3, ventilatory lung function impairment at 60 µg/m^3 with trends for impairment at 13 µg/m^3 (FVC) and 8 µg/m^3 (FEV, MMF). However, no dose response for irritative symptoms were observed. Effects on lung function may have been caused by higher past exposures.

RAC notes that specifically designed epidemiological studies on hard-metal disease prevalence or incidence are rare. Furthermore, the literature suggests that the disease lacks a clear dose-response and time-dependency, while individual susceptibilities are suggested to contribute to its development.

RAC proposal for the limit values for respirable and inhalable particles:

RAC has carefully evaluated the available evidence, including animal and human data on exposure to cobalt metal and salts as well as hard-metal and diamond polishing dust, and the following considerations:

- severity of effects in animal studies reporting respiratory irritation, inflammation and fibrosis at considerably high incidences (100%), at all doses levels, and with increasing dose-dependent severity with a LOAEC at the lowest dose of 0.067 mg Co/m^3 for **cobalt sulphate hexa/heptahydrate** (chronic; NTP, 1998),
- acknowledging significant inherent uncertainties when extrapolating inflammatory thresholds based on an animal LOAEC for cobalt metal-induced respiratory tract effects (no NOAECs were identified in the subacute, subchronic and chronic NTP studies), resulting in a conclusion that for **cobalt metal,** the available subchronic and chronic animal studies are too uncertain for limit value extrapolation,
- acknowledging the mode of action suggesting a key role for chronic inflammation in cobalt-induced carcinogenicity,
- acknowledging Nemery et al. (1992) study on diamond polishers as well conducted and highly relevant key study providing an NOAEC for low cobalt exposures without co-exposure to hard-metal and tungsten carbide,
- acknowledging other epidemiological workplace reports cited above (Sprince et al., 1988; Kennedy et al., 1995; Alexandersson & Bergman, 1978; Alexandersson, 1979) which suggest evidence of respiratory tract symptoms in hard-metal workers at low exposures ≤ 5-10 µg/m^3 (i.e. 2-5 µg/m^3), although these studies are not considered sufficient for dose-response analysis due to the related uncertainties (e.g. lack of dose response, role of past and confounding exposures),
- lung effects in workers were observed at similar low exposure levels for the use of cobalt in hard-metal industries and in other cobalt exposures (Nemery et al., 1992; Veroughstraete et al., 2004; Sauni et al., 2010).

In a weight of-evidence assessment and based on these considerations, RAC reiterates its recommendation:

Limit value of 0.5 µg/m^3, **respirable fraction**, derived from animal data (NTP, 1998): 0.067 mg/m^3 (LOAEC) * 6/8 hours * 6.7/10 m^3 / 2.5 (interspecies differences) / 5 (intraspecies differences) / 5 (severity LOAEC-NOAEC)

Limit value of 1 µg/m^3, **inhalable fraction**, derived from human data (Nemery et al. 1992): 0.0051 mg/m^3 (NOAEC) / 5 (intraspecies differences) = 0.001 mg/m^3

These limit values are recommended by RAC as OEL (8-h TWA) for the inhalable and respirable fraction, respectively.

This threshold of 0.5 µg/m^3, respirable fraction, based on lung inflammation, is used as a breakpoint in the cancer dose-response curve derived based on the same study (see below "cancer risk assessment").

RAC recognises that using MPPD[4] models can result in a higher respirable threshold (2 µg/m^3 if the same AFs are applied) than the default approach for animal to human extrapolation. However, human data suggests that such a value would not be conservative enough especially if applied for the respirable fraction of cobalt metal.

RAC also notes that the ratio between inhalable and respirable dust varies according to the processes involved and specific exposure scenarios (Wippich et al., 2022) and that it is not possible to give any universal value. This means that it is not possible to try to extrapolate the limit value for inhalable fraction from the limit value derived for respirable fraction. In addition, in order to protect both from non-cancer respiratory tract effects (affecting also upper respiratory tract) and lung cancer, it is generally advisable to measure both fractions unless there is some existing information on the ratio for specific tasks.

RAC considered whether the proposed thresholds should also apply to poorly soluble compounds and other cobalt comounds including complex substances and compounds with different counter ions. Some have no confirmed hazard but most have been at least self-classified by industry for one or several of the CMR properties. For these substances, not only sub-chronic and chronic animal toxicity data are essentially lacking, also specific human data are not available. In the reported observational studies, workers were either exposed to several cobalt compounds and mixtures during employment or to hard-metal exposure. Thus, RAC notes that in most exposure settings, workers are exposed to mixtures of cobalt compounds. Since the monitoring of exposure is based on analytical methods detecting total cobalt mass without speciation, individual cobalt species cannot be separately monitored in mixed exposure scenarios. Therefore, **RAC recommends the limits should be applied to all inorganic cobalt compounds.**

As regards poorly soluble cobalt compounds specifically, it is further noted that available scientific knowledge does not allow to extrapolate higher thresholds based on distinct bioavailabilities, e.g. as measured in artificial lung fluids. Concerning the MoA hypothesis, the recent *in vivo* acute-subacute inhalation studies were conducted with one substance tricobalt tetraoxide (micro-sized) as a representative of the "poorly soluble" cobalt substance group (see above). RAC considers that the identification of a distinct threshold for these substances is not possible due to insufficient data.

For the **hard-metal exposure scenario**, **RAC considers the limit values as derived are also protective**. The human data on hard-metal industry suggests respiratory tract symptoms (irritation, phleg, cough, wheeze) at low exposures ≤ 5-10 µg/m^3 (i.e. 2-5 µg/m^3, Kenndey et al. 1995, Alexandersson & Bergman, 1978; Alexandersson, 1979). Although based on the available evidence the risk of parenchymal lung disease (cobalt lung) in hard metal exposure is likely to be low at these levels, the scarcity of specifically designed epidemiological studies providing dose-response information as well as the contribution of individual susceptibilities introduces some uncertainties.

At the proposed OEL, no measurement difficulties are foreseen (see Annex 1, chapter 6.1 for analytical methods):

[4] 'Multiple Path Particle Dosimitry' model - can be used for estimating human and laboratory animal inhalation particle dosimetry.

With current air measurement techniques it is possible to achieve cobalt levels well below 10% of the proposed OELs for the inhalable and respirable fractions. It is recommended to use ICP with AES or MS detectors as analytichal technique allowing to reach a LOQ lower than 10% of the OEL, i.e. 0.083 µg/m^3 for a 480 l sample using the NIOSH 7300 and 7301 sampling methods (NIOSH, 2003a and 2003b) or 0.029 µg/m^3 for a 1200 l sample using IFA7808 (IFA 2021).

Workplace exposure data reported in Annex 1 (chapter 5.3), and provided by industry and Member States, relate to various exposure scenarios for cobalt metal and inorganic compounds. For data provided by industry, the highest exposures relate to packaging and handling of powders with P90 from 149-1093 µg/m^3, while the exposures are the lowest when cobal metal and inorganic compounds are used in fermentation processes, humidity indicator cards or rubber adhesion agents production and use with P90 ≤ 2 µg/m^3. P90 estimates are typically above 100 µg/m^3 (median/mean > 10 µg/m^3).

Data reported by Member States to ECHA in the context of the cobalt restriction in 2020 show median values typically around ≥ 10 µg/m^3 and P90 ≤ 100 µg/m^3. Several recent publications also report cobalt levels, e.g. (a) P75 in Italian settings of 2 µg/m^3 (GeoMean 0.33 µg/m^3), (b) P95 measured by Finnish Institute of Occupational Health of 155 µg/m^3 (median of 0.35 µg/m^3 for the period 2016-2019, n=231, personal measurements typically made outside RPE) and (c) mean in Austrian settings of 20 µg/m^3 (1985-2012).

Based on the workplace exposures reported, the recommended OELs (8-h TWA) are considered effective in reducing exposures in various industry settings in Europe.

Cancer Risk Assessment (see section 9.1 of of Annex 1 for full discussion).

RAC notes the importance of inflammatory mechanisms in the development of cancer. Thresholds derived for chronic inflammation can be anticipated to protect from the genotoxicity caused by these mechanisms and result at least in a lowering of the cancer risk.

Therefore, the level of 0.5 µg Co/m³ (respirable fraction) derived from the studies with cobalt sulphate hexa/heptahydrate was already used as a breakpoint in the dose-response of cobalt salt carcinogenicity in the RAC opinion on the restriction of cobalt salts (RAC, 2020). Based on this breakpoint, RAC had used the so-called 'hockey-stick' model to derive a dose-response for the carcinogenicity of cobalt salts.

RAC reiterates this approach and derives the sublinear dose-response below and above the breakpoint as follows:

Concentrations > 0.5 µg/m^3: ExCR = 1.06 x exposure level (mg Co/m^3, respirable fraction) - 0.0005

Concentrations ≤ 0.5 µg/m^3: ExCR = 0.105 x exposure level (mg Co/m^3), respirable fraction

The starting point for the dose-response modelling was the $BMDL_{10}$ of 0.414 mg/m^3 as cobalt sulphate hexa/heptahydrate (0.093 mg/m^3 as cobalt) based on lung tumours (adenoma or carcinoma) in a rat inhalation carcinogenicity study (NTP, 1998). This BMDL refers to an exposure scheme of 6h/d, 5d/week, and for 105 weeks life time.

For the workplace, a **$BMDL_{10(worker)}$ of 0.095 mg/m^3** is derived by RAC: 0.093 mg Co/m^3 * 6/8 hours * 6.7/10 m^3 * 52/48 weeks/year * 75/40 years.

It should be noted that a dose-response of cobalt metal may differ from the dose-response of cobalt sulphate hexa/heptahydrate. No BMDL level has been published for cobalt metal carcinogenicity. However, RAC considers overall that the two substances show a

comparable lung tumour response although the dose range tested and the tumour incidences, are distinct. When combining the dose responses as net tumor incidence of both NTP studies on cobalt sulphate hexa/heptahydrate (0.067, 0.22, 0.67 mg Co/m^3) and cobalt metal (1.25, 2.5, 5 mg Co/m^3), into single dose responses, it is apparent that the trend from the low dose range administered as cobalt sulphate continues with a saturation of tumor induction at higher cobalt metal doses. No sublinearity or threshold is evident with a somewhat steeper dose-response for the cobalt sulphate hexa/heptahydrate. The cobalt metal study showed a tumor rate of 84% (52% net) in the low dose of 1.25 mg/m^3 in male mice. The study employed too high doses apparently. A BMD_{10} or TD_{10} is extrapolated far outside the tested dose range. RAC considers these data not suitable for extrapolation of cancer risks in the low dose range. The cobalt sulphate hexa/heptahydrate study employed lower dose levels and achieved moderate tumor responses (0%, 6%, 30%, 30% for control, low, mid and high dose, adenoma or carcinoma) in female rats, and a BMD_{10} or TD_{10} can be derived by interpolation.

Concerning hard-metal related cobalt exposure, RAC considers that the bioavailablity of cobalt released from hard-metal is rather comparable to soluble cobalt species including cobalt metal. Furthermore as indicated above, the animal-derived dose-response does not contradict the epidemiological evidence obtained from the hard-metal industry. The epidemiological evidence at lower dose levels of cobalt in hard-metal industries rather suggests an enhancement of cobalt hard-metal associated lung effects by the presence of tungsten carbide.

RAC conclusions on the lung carcinogenicity dose response for different cobalt compounds

Overall, the cobalt sulphate hexa/heptahydrate NTP study (1998) is considered suitable and appropriate to serve the point of departure (PoD) for the cancer dose-response for cobalt including soluble cobalt salts and cobalt metal. Potency differences due to distinct bioavailability of the cobalt metal is considered a minor uncertainty in the approach taken by RAC.

The PoD and cancer dose-response derived from the cobalt sulphate hexa/heptahydrate animal study is also considered applicable for cobalt cancer risk assessment for hard-metal industry.

In the hockey-stick model, the default assumption is that the risk of cancer is reduced by a factor of ten at the breakpoint level. It is acknowledged that this is a default approach in the absence of scientific data to reliably quantify the remaining risk at the levels below the estimated breakpoint.

Since inflammation and secondary genotoxicity were considered to significantly contribute to and enhance the cancer risk, RAC already earlier recommended (RAC, 2020) that the exposure levels should be controlled below the inflammatory threshold.

Considering also human data, and the exposure settings considered in this scientific opinion on OEL derivation, RAC recommends to consider the inflammatory threshold value of 1 µg/m^3 for inhalable and 0.5 µg/m^3 for respirable fraction to protect from lung inflammation and secondary genotoxicity (resulting in higher lung cancer risk) of cobalt metal and inorganic compounds.

RAC notes that there are still remaining uncertainties related to the possible other mechanisms of action, and related to the dose-response of these inflammatory and genotoxic effects *in vivo*.

Toxicity to reproduction (see section 7.8 of Annex 1 for full discussion)

Cobalt metal and inorganic cobalt compounds show reproductive toxicity, including significant effects on male reproductive system and fertility. Thus, several cobalt and inorganic compounds have a harmonised classification as Repr. 1B (H360F), i.e. cobalt, cobalt dichloride, cobalt sulphate, cobalt dinitrate, cobalt carbonate (see table 5 of Annex

1) or have been notified by industry as Repr. 1B (H360, e.g. cobalt oxide, dihydroxide, hydroxide oxide) or Repr. 1A (H360, cobalt sulphide).

Effects of cobalt and inorganic compounds on reproduction toxicity, including fertility and development, have been investigated in several repeated dose and reproduction studies mainly on cobalt metal, cobalt sulphate heptahydrate, but also on cobalt dichloride, tricobalt tetraoxide and cobalt sulphide (see Annex 1, table 30). Except for one older study on developmental effects in pregnant women, no human data have been identified.

Fertility

After a 3-months exposure, cobalt metal and cobalt sulphate hexa/heptahydrate showed significant effects on the male reproductive system including reproductive tissue weights, testicular atrophy, spermatid and epididymal spermatozoa counts, sperm motility, and histopathological findings in both testis and epididymis. The lowest LOAEC for Cobalt metal was 1.25 mg/m^3 (NTP, 2014) based on reduced sperm motility in rats. The study identified a NOAEC of 0.625 mg Co/m^3. Cobalt sulphate hexa/heptahydrate was tested earlier by NTP (Bucher 1991) with a LOAEC identified at this concentration in mice of 0.67 mg Co/m^3 (3 mg/m^3 for the sulphate hexa/heptahydrate) for reduced sperm motility as the most sensitive effect. Reproductive data were not analysed at lower concentrations in this study.

The corresponding chronic NTP studies identified higher effect levels for male fertility, while the most sensitive effect (sperm motility) identified in subchronic studies was not analysed in the chronic studies.

RAC calculates a **$DNEL_{fertility}$ of 4 µg Co/m^3** by applying assessment factors of 2 for sub-chronic to chronic exposure, 2.5 for interspecies differences, 5 for intraspecies differences, and 3 for dose-response (LOAEC-NOAEC extrapolation) based on the 3-months NTP study with cobalt sulphate hexa/heptahydrate in mice (Bucher, 1981) and a LOAEC of 0.67 mg/m^3 corresponding to 0.34 mg/m^3 worker equivalent concentration (0.67 mg Co/m^3 * 6/8 hours * 6.7/10 m^3).

Development

Cobalt substances have also been assessed for developmental toxicity. No relevant human studies are available. In animals, several studies have been conducted, including developmental toxicity studies in rats, mice, and rabbits, with different design and duration (e.g. only organogenesis period, or until end of pregnancy, or late pregnancy including lactation period), dominant lethal tests, subchronic exposure of males with mating untreated females, and reproductive toxicity screening studies. Most of these studies were conducted with cobalt dichloride and cobalt sulphate heptahydrate and were published in the literature. All had deficiencies and limitations. However the effects reported included reduced fetal weight, growth and skeletal retardation, resorptions, and pup mortality. The effect levels varied, but in general developmental effects were seen at higher doses than those causing fertility effects (see above). LOAELs reported were as low as 5.4 mg Co/kg bw/d (Domingo et al., 1985, cobalt dichloride) and NOAELs as high as 24.8 mg/kg bw/d (Paternain 1988, cobalt dichloride). Thus DNELs for development would be higher than the DNEL calculated for fertility.

In summary, the lowest reproductive DNEL of 4 µg/m^3 is derived for male fertility and this DNEL exceeds the inflammatory threshold for the respirable fraction and the limit value for the inhalable faction.

It is concluded that the **OELs** proposed based on lung effects are also **protective for toxic effects on reproduction and fertility**.

Biological Monitoring (see section 6.2 of Annex 1 for full discussion)

Exposure to cobalt can be biomonitored by measuring cobalt in urine. Also, blood cobalt analysis has been used earlier. For example the MAK Commission had an EKA value for blood cobalt, which was, however, withdrawn in their latest update (DFG, 2012). This is

because the levels of cobalt in blood are about 10 times lower than in urine, and it is therefore a less sensitive and reliable biomonitoring method than urine analysis. Also, non-invasiveness of the sampling is considered important.

It is noted that cobalt (at low concentrations) is an essential element (vitamin B12) (Annex 1, 5.1). Background urinary cobalt levels have been reported in the literature from several countries:

Studies in the European general population indicated that urinary cobalt level were significantly higher in females than males:

- In the Belgian population, the 95th percentile was 1.0 µg/L for males and females combined, with mean urinary cobalt level significantly higher in females than males (GM 0.182 µg/L vs. 0.124 µg/L) (Hoet et al. 2013).
- Similarly, 95th percentiles in UK and Italian populations were 1.04 and 2.24 µg/L, respectively (Morton et al., 2014, Aprea et al., 2018). In both countries, females showed higher levels than males.
- In Finland, a reference limit for occupationally non-exposed population has been set as 1.4 µg/L based on the 95th percentile measured in a Finnish non-occupationally exposed population (n=118) (FIOH, 2012).
- The most comprehensive European study, Fréry et al. (2011), reported a 95th percentile of 1.13 µg/g creatinine (~1.3 µg/L) for the French population (n=1991), females showing higher levels than males (1.951 µg/L vs 0.697 µg/L, respectively).

In the USA (2015-2016), in 20+ years old adults, 95th percentile urinary cobalt level was 1.41 µg/L, females showing higher levels than males (1.82 vs 1.08 µg/L, respectively) (NHANES, 2019).

Since all studies report similar findings, the data of Fréry et al. (2011) are considered as representative for the European general population. Consequently, a **BGV of 2 µg/L and 0.7 µg/L** for **females and males**, respectively, is considered by RAC.

There are analytical methods available to measure cobalt in urine that are able to reach concentrations well below the background levels. The analytical methods for cobalt in urine are based on Voltammetry and Electrothermal Atomic Absorption Spectrometry (ET-AAS) (Heinrich and Angerer, 1984), Flame Atomic Absorption Spectrometry (F-AAS) (DFG, 1985), and Inductively coupled plasma mass spectrometry (ICP-MS) (Goullé et al., 2005). These analytical methods only allow the determination of the total cobalt levels. There is no method to allow the distinction between different inorganic cobalt compounds in biological fluids.

Since there is some accumulation of cobalt over the course of the workweek, biomonitoring samples are recommended to be taken post-shift at the end of the work-week.

Several studies report correlations between air cobalt levels in the workplace and urinary cobalt levels. These have been used to set e.g. the German EKA levels for cobalt (DFG, 2019) that are as follows:

Table: EKA correlations derived by DFG (2019)

Cobalt in air (mg/m^3)	**Cobalt in urine (µg/L)**
0.005	3
0.010	6
0.025	15
0.050	30
0.100	60
0.500	300

It should be noted that these EKA correlations are mainly based on the data from the hard-metal industry and may result in lower (i.e. more conservative) predicted U-Co levels at specific air levels than the use of data from soluble salts. ANSES, on the other hand, used

data from Nemery et al. (1992) (Co metal) and Lison et al. (1994) (soluble cobalt salts) and recommended a BLV of 5 µg/g creatinine (~5.7 µg/L), which was calculated to correspond to the French OEL of 2.5 µg/m^3.

It should be noted that most correlation equations published in literature are based on measured data of air concentrations and usually clearly above 20 µg/m^3. Therefore, the estimation of urinary levels corresponding to air levels of 1 µg/m^3 and below, using these correlation equations includes uncertainties. Equations used by the German MAK Commission in their EKA calculations (MAK, 2019) result in urinary cobalt levels close to or even below the general population reference limits when applied for 1 µg/m^3 air levels.

Using the correlation equation published by Lison et al. (1994), the air level of 1 µg/m^3 can be calculated to correspond to a urinary cobalt level of 2.75 µg/g creatinine (~3 µg/L) and the air level of 0.5 µg/m^3 can be calculated to correspond to 1.78 µg/g creatinine (~2 µg/L). In all cases, the levels are very close to the population background levels. This means that individual background levels caused by exposure from other sources may complicate the interpretation of the results at these levels and simple comparison of individual samples to general population reference limits (which are usually based on 95th percentiles observed in non-occupationally exposed population) may not be enough to detect these exposures. On the other hand, **urinary levels clearly exceeding general population reference limits (1-2 µg/L) and the recommended BGV are likely to indicate an occupational exposure to the air levels of ≥1 µg/m^3**, although dermal contamination (and hand-to-mouth exposure) may also contribute to total urinary cobalt levels. Such exceedance should result in the identification of the exposure sources and to improvement of risk management measures at workplaces. It should be noted that urinary Co levels indicate only the recent exposure and may vary according to the daily/weekly tasks.

A **Biological Limit Value (BLV) is not given** because the air levels corresponding to the proposed OELs are likely to result in urinary levels which are very close to these 95th percentiles of the general population.

Summary of Derived Limit Values

OEL – 8-h TWA

Limit values for respirable and inhalable particles are derived based on chronic inflammatory lung effects of cobalt compounds. It is agreed by RAC that the following limit values are likely to reduce the risk of respiratory sensitisation as well:

- Respirable fraction: 0.5 µg Co/m^3
- Inhalable faction: 1 µg Co/m^3

The calculated value for reproduction toxicity is 4 µg/m^3 (respirable fraction). At higher limit values, effects on male reproduction system and fertility cannot be ruled out.

Short Term Limit Value (STEL)

No separate short-term limit value for protection from acute toxicity and irritation is considered necessary. Histopathological lung lesions and inflammatory response in BAL was observed for cobalt sulphate heptahydrate after acute exposure of Fischer rats with 10 mg/m^3 and 30 mg/m^3, with an NOAEC determined at 1 mg/m^3. LC_{50} was < 50 mg/m^3 for cobalt metal powder and cobalt metal dihydroxide, and above 5000 mg/m^3 for poorly soluble cobalt compounds.

Biological Guidance and Limit Values

- Biological Guidance Value (BGV)

Studies in the EU general population indicate that the 95th percentile levels for cobalt in urine are usually between 1.0 µg/L and 2.24 µg/L, for males and females (combined). However when analysed separately, females show higher levels than males.

Based on the data by Fréry et al. (2011; most comprehensive European study), a value of 2 µg Co/L urine for females and a value of 0.7 µg Co/L urine for males is proposed as BGV unless there is specific national data supporting the use of other values.

- Biological Limit Value (BLV)

A BLV is not given because the air levels corresponding the proposed OELs are likely to result in urinary levels which are very close to these 95th percentiles of the general population.

Notations

Exposure to cobalt compounds at workplaces may result in contact sensitisation and, although uncommon nowadays, in sensitisation of the respiratory tract. Cobalt metal and several cobalt compunds have a harmonised classification as skin sensitiser and respiratory sensitiser. Therefore, "skin sensitisation" and "respiratory sensitisation" notations are warranted.

Although dermal contamination and the ingestion route (due to hands-to-mouth contact) may also contribute to total systemic Co levels, data on systemic bioavailability following dermal contact is scarce. Therefore no "skin" notation is recommended.

ATTACHMENTS

Annex 1: gives the detailed scientific grounds for the opinion ('ECHA scientific report').

Annex 2: provides the comments received on the ECHA scientific report, and the responses provided by ECHA and RAC (excluding confidential information).