Committee for Risk Assessment

RAC

Opinion on scientific evaluation of occupational exposure limits for

Nickel and its compounds

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Adopted

9 March 2018

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

Commission request

The Commission, in view of the preparation of the third and fourth proposals for an amendment of Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work (CMD), and in line with the 2017 Commission Communication '*Safer and Healthier Work for All - Modernisation of the EU Occupational Safety and Health Legislation and Policy*'[1], asked the advice of the Committee for Risk Assessment (RAC) to assess the scientific relevance of occupational exposure limits for some carcinogenic chemical substances.

Therefore, the Commission made a request (8 March 2017[2]) in accordance with Article 77 (3)(c) of the REACH Regulation, to evaluate, in accordance Directive 2004/37/EC, the following chemical compounds: 4,4'-methylenebis[2-chloroaniline] (MOCA), arsenic acid and its inorganic salts, nickel and its compounds, acrylonitrile and benzene.

I PROCESS FOR ADOPTION OF THE OPINION

Following the above request from the European Commission, the Executive Director of ECHA in the mandate of 12 May 2017[3], requested RAC to draw up an opinion on the evaluation of the scientific relevance of occupational exposure limits (OELs) for nickel and its compounds with a deadline of 26 March 2018.

Chemical name(s): Nickel and its compounds

In addition to nickel metal, this opinion covers principally the inorganic nickel compounds (see sections 1.1 and 1.2 and of the Background Document for full identification)**.**

In support of the Commission's request, ECHA prepared a proposal concerning occupational limit values for nickel and its compounds at the workplace. This proposal was made publically available[4] on **10 October 2017** and interested parties were invited to submit comments by **7 November 2017**.

RAC developed its opinion on the basis of the proposal submitted by ECHA. During the preparation of the opinion, the ECHA proposal was further developed as a Background

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[1] http://ec.europa.eu/social/main.jsp?langId=en&catId=148&newsId=2709&furtherNews=yes

[2] https://echa.europa.eu/documents/10162/13641/ec_note_to_echa_oels_en.pdf/f72342ef-7361-0d7c-70a1-e77243bdc5c1

[3] https://echa.europa.eu/documents/10162/13641/rac_mandate_for_oels_for_nickel_en.pdf/647788e7-24d2-ff4f-93a0-7d87fdfae28a

[4] https://echa.europa.eu/echas-executive-director-requests-to-the-committees-previous-consultations

Document to ensure alignment. In addition, stakeholders were able to provide comments on the RAC opinion during the evaluation process.

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 and in the format used by SCOEL.

II ADOPTION OF THE OPINION OF THE RAC

Rapporteurs, appointed by RAC: **Tiina Santonen** and **Lina Dunauskiene**

The opinion was adopted by **consensus** on **09 March 2018.**

RAC Opinion of the assessment of the scientific relevance of OELs for nickel and its compounds

RECOMMENDATION

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

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[5]

OEL as 8-hour TWA[6]:	0.005 mg/m^3 for respirable dust 0.03 mg/m^3 for inhalable dust
STEL:	not established
BLV:	not established
BGV:	not established

Carcinogenicity Classification/categorisation

CLP Harmonised classification for carcinogenicity	Nickel and nickel powder: suspected human carcinogen (Carc. 2) Nickel compounds – various, mainly inorganic: known human carcinogen (Carc. 1A)
SCOEL Categorisation of carcinogens[7])	Group C (SCOEL/SUM/85 June 2011[8])

Notations

Notations:	'Sensitisation'

[5] 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].

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

[7] See Appendix 1 of the Background Document for details on the "SCOEL classification of carcinogens".

[8] https://circabc.europa.eu/sd/a/0ad09fb3-de34-4dfd-8a63-460338f69b0e/SUM%20085%20Nickel%20and%20Nickel%20Compounds.pdf

RAC OPINION

Background

This opinion concerns **nickel and its compounds**; this includes the metal nickel and nickel powder as well as a wide range of inorganic nickel compounds (See section 1 of the Background Document).

This evaluation, takes previous reviews into account, in particular:

- the REACH lead registrant's updated Chemical Safety Report, NiPERA (2017),
- the Scientific Opinion of the EFSA CONTAM Panel, EFSA (2015),
- the report from the German Scientific Committee AGS (2017) and
- the recommendation of the Scientific Committee on Occupational Exposure Limits, SCOEL (2011).

In addition, the Background Document prepared by ECHA extensively reviewed recent primary literature in critical areas such as genotoxicity and carcinogenicity which were subsequently taken into account by RAC. Account has also been taken of the comments provided by interested parties during the public consultation.

Key conclusions of the evaluation

- The main hazard of nickel compounds is their carcinogenicity in the respiratory tract. In animal tests, carcinogenic effects have been demonstrated only with poorly soluble nickel species. In humans, exposure to mixed nickel compounds have resulted in increased lung cancer risk and in some studies cancer risk has correlated best with the exposure to soluble nickel. In addition, an increased risk for nasal cancer has been demonstrated in humans.
- Metallic nickel has not shown clear carcinogenic effects in relevant animal studies using physiological routes of exposure or in epidemiological studies in humans.
- Differences in lung clearance and local cellular uptake between different nickel species are assumed to explain the variability in their carcinogenic potency.
- In humans, exposure to nickel is often to a mixture of soluble and poorly soluble nickel compounds.
- Nickel compounds are not directly mutagenic but have been shown to induce genotoxic effects via different indirect mechanisms.
- Chronic inflammation is also likely to play a significant role in nickel-induced carcinogenicity together with indirect genotoxicity.

- The available information on the mechanisms of genotoxicity and cancer support a mode-of-action based threshold [9]for carcinogenic effects.
- The proposed OEL therefore relies on a mode of action-based threshold for the carcinogenicity of nickel compounds. In addition to the mechanistic data reviewed by RAC, data on the lack of genotoxicity in animals at inhalation doses below the levels causing inflammation and cytotoxicity support this conclusion.
- At exposures below the proposed limit value, no significant residual cancer risk is expected for workers.
- In addition, nickel is a well-known skin sensitizer. It can also cause respiratory tract sensitization although such sensitization caused specifically by nickel is rather uncommon.
- Nickel compounds have also been shown to exert reproductive effects (effects on both fertility and developmental) in animal studies. The OELs proposed here are also considered to be protective for reproductive effects.

Carcinogenicity and mode of action (see sections 7.9 & 7.6.3 of the ECHA Background Document for full discussion)

The carcinogenicity of nickel compounds has been demonstrated both in animals and in humans. In animals, poorly soluble nickel compounds (nickel subsulfide and nickel oxide) have caused lung cancer starting at dose levels of 0.11 or 0.5 mg Ni/m^3, respectively. Soluble nickel sulfate, on the other hand, did not show any increase in tumour frequencies in animal tests at doses of 0.6 to 2.2 mg Ni/m^3.

In humans, epidemiological evidence shows dose-related carcinogenic potential (for lung and nasal cancer) of mixed exposure to both water soluble nickel compounds and insoluble oxidic and sulfidic nickel species. There is some variation in the epidemiological estimates on whether exposure to soluble or non-soluble nickel is the main contributor to the increased risk of respiratory tract cancer (see Chapter 7.7.1 in ECHA proposal). For example, the Kristiansand cohort (Andersen et al., 1996, Grimsrud et al., 2002, 2003), providing the most comprehensive dose-response data, indicate soluble nickel as the main contributor for cancer. In this cohort a statistically significant increase in the risk of lung cancer (Odds Ratio = 2.5) was observed at cumulative dose of 1.6 mg/m^3 soluble Ni (meaning 3.2 mg/m^3 after correction for sampler efficiency, see ECHA background document, section 8.2). However, there are no cohorts available that were exclusively exposed to a single nickel species. For example, in the Kristiansand cohort, it can be estimated that total Ni (soluble+oxidic+sulfidic Ni) concentration was on average 4.5 times that of soluble Ni (see section 8.2 of the ECHA background document). Oller et al (2014) analysed the lung cancer risks in different epidemiological cohorts at exposure levels of either above or below 0.2 mg/m^3 for sulfidic nickel and above or below 0.1 mg/m^3 for soluble nickel and above or below 2 mg/m^3 for oxidic nickel. The authors concluded that if

[9] Joint Task Force ECHA Committee for Risk Assessment (RAC) and Scientific Committee on Occupational Exposure Limits (SCOEL) on scientific aspects and methodologies related to the exposure of chemicals at the workplace. Task 2. 6 December, 2017, https://echa.europa.eu/documents/10162/13579/jtf_opinion_task_2_en.pdf/db8a9a3a-4aa7-601b-bb53-81a5eef93145

sulfidic nickel exposure drops below 0.2 mg Ni/m^3 (inhalable fraction), soluble nickel below 0.1 mg Ni/m^3 and oxidic nickel below 2 mg/m^3 (inhalable fraction) there is no cohort with a significantly increased lung cancer risk.

Nickel metal has not shown lung carcinogenicity in relevant *in vivo* animal studies using physiological routes of exposure or in epidemiological studies in humans. The difference in the carcinogenic potency between different nickel species is likely to be related to the differences in the uptake of the nickel particles into the cells. The systemic cancers (pheochromocytomas) observed in nickel metal carcinogenicity studies in rats are assumed to be secondary to lung toxicity and/or to the induction of hypoxia-inducible transcription factor (HIF-1).

The mechanisms of nickel-induced cancer are multifactorial. A key point is that nickel has not shown clear direct mutagenicity. In bacterial mutagenicity tests nickel compounds have been negative (see further chapter 7.6.3 of the ECHA background document). Weakly positive findings observed in some *in vitro* mammalian cell studies are suggested to be due to other genetic events, such as chromosomal aberrations and DNA methylation, rather than point mutations (Klein et al., 1994, Lee et al., 1995). In vivo, Mayer et al (1998) showed that nickel subsulfide is not able to induce mutations in lacZ and lacI transgenic mice after high dose short term inhalation exposure. Lack of the direct interaction with DNA is supported by the fact that nickel has only a weak affinity for DNA but it has a high affinity (>10^7 fold higher) for chromatin proteins, particularly histones and protamines (Costa et al. 1994; Kasprzak et al. 2003b; Oller et al. 1997).

Both soluble and insoluble nickel compounds can give rise to DNA breaks, DNA-protein crosslinks and chromosomal damage both in vivo and in vitro (for individual studies, see ECHA background document chapter 7.6.3). According to the current knowledge, the observed genotoxic effects are mediated by the following mechanisms (ECHA background document, chapter 7.9.3): 1) interference with cellular redox regulation and induction of oxidative stress; 2) inhibition of DNA repair systems and 3) disregulation of signalling pathways and alteration of the epigenetic landscape. In addition to these, local inflammation and cytotoxicity in the respiratory tract is likely to contribute to respiratory tract carcinogenicity by increasing the formation of reactive oxygen species and indirect genotoxicity (Kawanishi, 2002; Efremenko et al., 2014 and 2017). In vivo inhalation studies by Efremenko et al (2014, 2017) in rats show that transcriptional pathways affected by nickel subsulfide and nickel sulfate primarily reflect responses to toxicity, including inflammatory and proliferative signalling. In the case of nickel subsulfide indications on the activation of the pathways related to DNA damage were seen only at the two highest dose level (0.11, and 0.44 mg Ni/m^3) with a NOAEL of 0.06 mg Ni/m^3 after 1 month exposure and BMD10 for the activation of inflammatory pathways was 0.06 mg Ni/m^3 whereas for oxidative stress pathways it was 0.11 mg Ni/m^3. These results give confidence for an indirect genotoxic mode of action driven by chronic toxicity, inflammation and proliferation, leading to misreplication and the threshold based on inflammatory and cytotoxic effects.

Even though nickel subsulfide and nickel sulfate seem to cause local inflammation and cytotoxicity at similar exposure levels, the higher carcinogenic potency of subsulfide in animal studies at these levels has been explained by its lower clearance rate and higher intracellular uptake in lungs (see figure 1 in the ECHA Background Document). Efremenko et al (2017) estimated that similar inhaled Ni concentrations translate to about 2-3-times higher lung burdens for nickel subsulfide than for nickel sulfate.

Cancer Risk Assessment and Derived Limit Values (see section 8 of the ECHA background document for full discussion)

Nickel oxide and nickel subsulfide have caused lung cancer in animals, and human epidemiological data show increased risk for lung and sinonasal cancer in nickel exposed workers. No induction of cancer has been observed in other organs. As it is explained above, nickel compounds are not directly genotoxic and exert only weak affinity to DNA in contrast to a high affinity to proteins.

Based on the available evidence on the mode of action, nickel compounds are considered as genotoxic carcinogens for which it is possible to identify a mode-of-action based threshold. Inflammatory and cytotoxic effects in the lungs are considered critical for the carcinogenic process leading to misreplication and secondary genotoxicity. Therefore, the threshold will be based on these effects.

Limit value for respirable particles

In the 2 year inhalation toxicity study in rats with nickel sulfate, a NOAEC of 0.027 (≈0.03) mg Ni/m^3 for inflammatory effects was observed (no lung tumours were observed with nickel sulfate at any dose). For less soluble nickel subsulfide and nickel oxide, no NOAEC is available from long term (2 y) inhalation studies, but LOAECs of 0.11 and 0.5 mg/ Ni/m^3, respectively, were identified in NTP (1996a,b,c) studies for inflammatory effects, lung fibrosis and lung cancer.

Since in all these studies, the particle size was in the respirable range, the limit value derived on the basis of these studies then applies specifically to respirable particles.

A NOAEC of 0.03 mg Ni/m^3 is taken as a starting point for nickel sulfate. For nickel subsulfide and nickel oxide, LOAECs of 0.11 mg Ni/m^3 and 0.5 mg Ni/m^3 are taken as starting points. Since these levels represent LOAECs, an Assessment Factor of 3 is used to derive NAECs. This results in NAECs of 0.04 and 0.17 mg/m^3 for nickel subsulfide and nickel oxide, respectively (Table 1). Although no NOAEC was identified for lung inflammation in the 2 year inhalation study for nickel subsulfide in rats, in a 13 week rat inhalation study a NOAEC of 0.04 mg Ni/m^3 has been identified (Benson et al., 2002). Higher levels (0.11 mg Ni/m^3) resulted in lung inflammation and DNA strand breaks. This can be considered to provide support for the calculated NAEC level of 0.04 mg/m^3 for Ni subsulfide.

For extrapolation to humans, the lead REACH registrant's updated approach for the calculation of human exposure concentration (HEC) is used (NIPERA, 2017). This is based on a multiple-path particle deposition model (MPPD, Asgharian et al., 1999), which was used to predict the deposition of particles in the alveolar and tracheo-bronchial region. The MPPD model is validated for human and rat lung deposition and clearance of spherical particles. It is considered to provide reliable estimates on the total, regional and airway specific lung doses. It takes into account particle characteristics, breathing frequency and pattern, exposure concentration and duration. The present calculation is an update of the earlier HEC calculations published by Oller and Oeberdoerster (2010). Since it was assumed that the alveolar retained dose is the main determinant when considering long term toxicity (including lung cancer) caused by nickel compounds, retained doses were also calculated on the basis of retention T½ for nickel particles with different solubility in animal studies. Calculated deposited and retained doses and further information on the parameters are given in Table 39 in the ECHA background document. The ratio of retained

doses (rat/human) was used to calculate respirable HECs for different nickel species, which are presented in Table 1.

Table 1:

	Respirable HEC (mg Ni/m^3) based on inflammatory effects			
	Ni metal	Ni oxide	Ni subsulfide	Ni sulfate
Observed LOAEC	0.1	0.5	0.11	
Observed NOAEC	-	-	-	0.03
Derived NAEC	0.03	0.17	0.04	
Calculated HEC	0.02	0.03	0.03	0.03

The use of retained doses instead of deposited doses results in the same or lower (i.e. more conservative) HECs. This gives additional confidence for using HECs based on retained doses for OEL setting.

Assessment factors (AF) were applied as follows:

- Since the HEC calculation already takes into account the possible differences in toxicokinetics, there is no need for a further AF for such differences. Regarding the AF for the toxicodynamic part of interspecies extrapolation, the rat is generally the most sensitive species for local lung effects of poorly soluble particulates (Oberdoerster 1995, Mauderly 1997), which is supported by the difference seen in long term inhalation effects of nickel subsulfide between mice and rats. However, this general data on particle effects may not be enough to support the conclusion that humans are less sensitive than rats to the lung toxicity and carcinogenicity of nickel. When considering non-malignant lung effects, humans have not shown clear fibrotic/pneumoconiotic changes in lungs after exposure to nickel (Muir et al., 1993, Berge and Skyberg (2003) or higher mortality to non-malignant lung diseases in epidemiological studies (for specific data see ECHA background document, section 8). Comparison of respirable doses resulting in similar cancer risks in rats and in humans in the Grimsrud et al (2002) cohort providing the highest risk estimates for the carcinogenicity of humans, does not indicate that humans are more sensitive than rats to the carcinogenic effects of nickel compounds (for details see "Sensitivity analysis of the OEL approach used for respiratory fraction" under section 8.2 in ECHA background document). This is further supported by the analyses of 13 cohorts by Oller et al (2014) showing that if sulfidic nickel exposure stays below 0.2 mg Ni/m^3 (inhalable fraction) and soluble nickel below 0.1 mg Ni/m^3 (inhalable fraction) and oxidic nickel below 2 mg/m^3 there is no human cohort with a significantly increased lung cancer risk. The respirable fraction is estimated to account for about 10-20% of the inhalable particles in these cohorts (see further

ECHA background document section 7.7.1). On the basis of these analyses, an AF of 1 is considered sufficient to cover also for toxicodynamic differences between rats and humans.

- For intraspecies variability an AF of 3 is applied. Although the OEL has been primarily based on animal data, RAC used human evidence to support the setting of an OEL. In the case of nickel compounds, the human epidemiological database is extensive and is considered to cover the variability expected in the worker population. The only remaining uncertainty is that human data is based on information regarding inhalable dust and the proportion of respirable particles (ca. 10-20% of inhalable dust) has been estimated on the basis of general information and limited specific data.
- Finally, an additional AF of 2 is applied for nickel compounds for the severity of the toxic endpoint (cancer). Although humans do not show similar steep dose-response for the carcinogenicity of nickel compounds as do rats in the case of nickel subsulfide, this provides an additional safety margin to the levels, which have shown inflammatory, genotoxic and carcinogenic effects in rats.

This results in a value of 0.005 mg Ni/m^3 for sulfidic, oxidic and soluble nickel compounds. For metallic nickel, which has not shown carcinogenic properties in modern inhalation carcinogenicity studies in animals or in epidemiological studies in humans, only an AF of 3 for intraspecies variability is applied. This results in an OEL of 0.0067 mg/m^3 (0.02/3), which is rounded as 0.005 mg/m^3.

Thus, a rounded value of **0.005 mg Ni/m^3 is recommended as an OEL for the respirable fraction of both nickel metal and nickel compounds[10]**.

It should be noted that exposure to nickel in occupational settings is almost in all cases to a mixture of different nickel species and therefore it is not practicable to give different values for different nickel compounds.

The proposed OEL assumes a mode of action-based threshold for the carcinogenicity of nickel compounds. In addition to the mechanistic data, the data on the lack of genotoxicity in animals at inhalation doses below the levels causing inflammation and cytotoxicity gives further support for this assumption (Benson et al., 2002; Efremenko et al., 2014, 2017). Uncertainties related to this approach are, therefore, considered to be very low; it is always difficult to definitively exclude some remaining risks at lower exposure levels.

At the proposed OEL, no measurement difficulties are foreseen (see ECHA background document chapter 6.1 for analytical methods). With current air measurement techniques it is possible to achieve levels at least down to 10% of the proposed OEL.

[10] The choice of 0.005 mg Ni/m^3 instead of 0.0067 mg/m^3 is in accordance with the general practise of OEL setting which usually uses the decimals of the integers 1, 2 or 5 ppm or mg/m^3, if scientific reasons do not suggest a more specific value (further see SCOEL key documentation from 2014). This avoids giving the wrong impression of precision in cases in which uncertainties related to the limitations of the database do not justify same.

Limit value for inhalable particles

Since nickel compounds have been shown to increase also the risk of sinonasal cancer in humans, an OEL for the inhalable fraction is also considered appropriate for the protection of workers. However, limited data is available on the dose-responses of the sinonasal effects of nickel compounds. As in the case of lung carcinogenicity, cytotoxicity and inflammation resulting in oxidative damage are considered critical in the generation of sinonasal tumours. Although in animal studies, inflammatory reactions have been observed, the animal data derived from studies using respirable particles is not considered appropriate for the setting of limit value for inhalable particles. According to epidemiological data from Norwegian refinery workers (Kristiansand cohort including 5300 workers, Andersen et al., 1996; Grimsrud et al., 2002, 2003) a statistically significant increase in cancer incidence for water soluble nickel is observed at a cumulative exposure of 1.6 mg/m³-years. Since the average exposure of the cohort was 13 years, this corresponds to an average exposure to 0.123 mg Ni/m^3. However, since workers can be potentially exposed for 40 years to nickel, this needs to be taken into account. In 40-years occupational exposure, 1.6 mg/m^3 x years corresponds an exposure level of 0.04 mg Ni/m^3. It should be noted that this conversion assumes that Haber's rule applies for cancer incidence and brings additional conservativeness to the assessment. In addition, Kristiansand cohort (Grimsrud et al., 2002, 2003) gives highest risk estimates for cancer when compared to the other epidemiological analyses. Thus, the use of Kristiansand cohort as a starting point can be considered as a conservative choice.

Assessment factors are then applied as follows:

- A standard Assessment Factor of 3 is used for the LOAEC to NOAEC extrapolation resulting in a value of 0.013 mg Ni/m^3.
- When a correction factor of 2 for recognised historical changes in sampler efficiency (see chapter 5.3.2 in ECHA background document) is applied, this results in an inhalable exposure value of 0.027 mg/m^3.
- Since the starting point represents the most conservative estimate on the cancer risk among several human cohorts including more than 100,000 workers and these epidemiological data are considered to adequately address the variability among workers, no additional Assessment Factor for interindividual variation is considered to be needed.

The LOAEL derived from the Kristiansand cohort is based on lung cancer incidence. This is considered, however, to be protective against sinonasal cancer as well since increased sinonasal cancer risk has not been observed at exposure levels which did not result in increased lung cancer incidence.

The value of 0.027 mg/m^3 is rounded as 0.03 mg/m^3 since as explained in the ECHA background documentation, a cumulative risk estimate of 1.6 mg/m³ x years for soluble Ni in the Kristiansand cohort underestimates true total Ni exposure, since it was not adjusted for the effect of other Ni species. Thus, **the value of 0.03 mg/m^3 is considered to be conservative and is proposed as an OEL for the inhalable fraction.**

This is to be measured according the International/ European Standard 481, which provides definitions of the inhalable, thoracic and respirable size fractions, and target specifications for sampling instruments to measure these fractions.

As the respirable fraction is estimated to account for 10-20% of the inhalable fraction, it can be also concluded that the derived values of 0.03 mg/m^3 for the inhalable and 0.005 mg/m^3 for the respirable fraction are in line with each other.

Since metallic nickel is very poorly soluble and has not been shown to cause effects in the upper respiratory tract, no separate value for the inhalable fraction of metallic nickel is considered necessary.

Toxicity to reproduction

Nickel compounds show reproductive toxicity, including effects on fertility and development in animal studies. The EFSA CONTAM panel (EFSA, 2015) has set a tolerable daily intake of 2.8 µg Ni/kg body weight (b.w.) per day for general population. This is derived from a lower 95 % confidence limit for a benchmark dose at 10 % extra risk (BMDL10) of 0.28 mg/kg b.w. for post-implantation fetal loss in rats by applying a 100-fold safety factor. If this is converted as occupational inhalation exposure occurring 5 days per week (instead of 7 days per week), it corresponds an air level of 27 µg Ni/m^3 (0.027 mg Ni/m^3) as 8 h TWA, which is in the same or higher level than the proposed OELs. **Thus, the OELs proposed here are considered also protective for reproductive effects.**

Respiratory sensitisation

There is no quantitative information on the risk of respiratory sensitisation to nickel. However, according to the current information, respiratory sensitization caused by nickel is relatively rare among workers and the cases described are often associated with exposure to other sensitizing compounds (e.g. chromium (VI) and cobalt). Therefore, at the level of the proposed OEL, the risk of respiratory sensitization is considered to be low.

Short term limit value (STEL)

The acute toxicity and irritancy of nickel metal and its compounds is generally low. Therefore, a STEL is not considered necessary. An important exception to this is nickel tetracarbonyl, which is an acutely toxic, organic nickel compound. For nickel carbonyl a STEL may need to be given separately.

Biological guidance and limit values

No EU-wide **biological guidance value** is given for nickel. 95th percentiles of the general population urinary nickel levels vary between 2.5-8.1 µg/l depending on the study and the population. Variation may reflect difference in the background environmental exposure in industrial, urban and rural areas. Therefore, it is recommended to set biological guidance values on the basis of the local/national data. In addition, since 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, it may be advisable to use pair samples (both pre-shift and post-shift samples are sampled from the same individual) when assessing potential exposure on the basis of urinary levels.

A **Biological limit value** is not given because of the uncertainties related to the correlations between air and urinary levels at these low air levels (see below) and 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.

Biological Monitoring (see section 6 of the ECHA background document for full discussion)

Nickel can be measured in the serum and the urine of exposed workers but urine analysis is usually preferred over serum. Nickel can be also found in the urine of the non-occupationally exposed population. German MAK Commission has earlier identified the 95th percentile in non-occupationally exposed populations of around 3 µg/l. This value was recommended by the SCOEL for a biological guidance value (BGV) for nickel. However, recent large population studies in France and Belgium show 95th -97.5th percentiles between 4.5-5.99 µg/l (Frery et al., 2010, Nisse et al., 2017 and Hoet et al., 2013). In the study by Kasper-Sonnenberg et al (2011) 95th percentile as high as 8.1 µg/l was reported for adult German females. Reported mean nickel levels in these population studies are usually between 1-2 µg/l (see table 18 in ECHA background document). In some studies, clear difference between urban and rural areas were seen.

There are also studies showing a correlation between air and urinary nickel levels from occupational settings. However, it must be noted that the exact nickel species have a significant impact on the urinary levels; for poorly soluble nickel compounds higher inhalation exposure is needed in order to achieve similar urinary levels as in the case of soluble nickel compounds. It has been calculated that in the case of nickel metal and sparingly soluble nickel compounds an 8 h TWA exposure to air of 0.1 mg Ni/m^3 results in end-of-the-shift/end of the work week urinary level of 15 µg/l. In the case of soluble nickel compounds, similar exposure in urinary levels of 70 µg/l. Using the published correlation equivalents, it can be estimated that exposure to nickel and its compounds at an air level of 0.005 mg Ni/m^3 as an 8 h TWA may result in urinary levels which are very close to the 95th percentile of the general population (levels only up to 5-10 µg/l). The proposed OEL for inhalable dust (0.03 mg Ni/m^3), on the other hand, may result in urinary levels of up to 10 µg/l in the case of poorly soluble dust and to levels of ≈20 µg/l in the case of soluble nickel compounds. However, since these correlation equations have been made on the basis of higher 8 TWA exposures, it should be noted that the extrapolation to these levels includes uncertainties since the associations may be weaker at these low levels. In addition, quite often in occupational settings the exposure is mixed exposure to both soluble and poorly soluble nickel compounds and it is difficult to decide whether the results should be interpreted on the basis of the data on soluble or insoluble compounds.

Notations

Systemic bioavailability of nickel following dermal contact to various nickel compounds is limited with a large part of the applied dose remaining on the skin surface or in the stratum corneum. **Therefore, no skin notation is proposed.**

Exposure to nickel compounds at workplaces may result in contact sensitisation and in rare cases also sensitisation of the respiratory tract. **Therefore, a sensitisation notation is warranted.**

ANNEX:

Annex 1 The Background Document gives the detailed scientific grounds for the opinion. The BD is prepared by the European Chemicals Agency (ECHA).

Annex 2 Comments received on the ECHA proposal, response to comments provided by the ECHA Dossier Submitter and RAC (excluding confidential information).