ANNEX 1

Background Document

in support of the Committee for Risk Assessment (RAC) for evaluation of limit values for nickel and its compounds in the workplace

Prepared by the European Chemicals Agency

ECHA/RAC/A77-0-0000001412-86-189/F

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Preamble

The Commission, in view of the preparation of the third and fourth proposals for 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 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.

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 at: 'https://echa.europa.eu/echas-executive-director-requests-to-the-committees-previous-consultations' on **10 October 2017** and interested parties were invited to submit comments by **7 November 2017**.

The Committee for Risk Assessment (RAC) developed its opinion on the basis of the proposal submitted by ECHA. During the preparation of the opinion on occupational limit values for nickel and its compounds, the ECHA proposal was further developed as the Background Document. In addition, stakeholders were able to provide comments on the RAC opinion during the evaluation process.

Following adoption of an opinion on 9 March 2018, recommending an Occupational Exposure Limit for nickel and its compounds by RAC, this Background Document was amended to align it appropriately with the view of RAC. It supports the opinion of the RAC and gives the detailed grounds for the opinion[3].

[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/10162/13579/interim_wponevaluation_oel_agreed_rac_42_en.pdf/021bc290-e26c-532f-eb3f-52527700e375

Table of Contents

Figures

Tables

Literature search

The background document on nickel and its compounds is based on recent reviews by other organisations, in particular the lead REACH registrant for nickel and inorganic compounds, NiPERA (2017), the Scientific Opinion of the EFSA CONTAM Panel (2015), the report from the German Scientific Committee AGS (2014) and the Recommendation from SCOEL (2011). However, reviews such as IARC (1990, 2012), the EU RAR (2008), the Danish EPA (2008) and ATSDR (2005) have also been included. This has been complemented by a review of the REACH registrations and a literature search of published papers from the last ten years.

1. Chemical Agent Identification and Physico-Chemical Properties

1.1 Nickel

Nickel is generally found as the divalent ion Ni^{2+} (Ni(II)) in different minerals and in combination with cobalt, copper, iron, and/or magnesium. It is a silvery-white, hard, ductile metal and one of only few elemental metals which are magnetic at room temperature. Nickel can exist in oxidation states –1, 0, +1, +2, +3, and +4, however the divalent ion (Ni^{2+} or Ni(II)) is the only one relevant under normal environmental conditions and is the most important for both organic and inorganic substances, but the trivalent form (Ni^{3+} or Ni(III)) may be generated by redox reactions in the cell (Huang et al 1993).

Nickel's identification and physico-chemical properties are described in the tables below:

Table 1: Substance identification

Substance name	CAS No,	EINECS/EC - list No.	Description	Molecular formula
Nickel	7440-02-0	231-111-4	a silvery-white, hard, ductile metal	Ni

Table 2: Physical and chemical properties

Substance name	EC/list number	Physical state	Density [g/cm³ at 20°C]	Melting point [°C]	Water Solubility
Nickel	231-111-4	solid metal powder	8.9	1455	insoluble

1.2 Nickel compounds

The nickel compounds considered in this proposal are generally those for which data are available and for which use at higher tonnages is known, mainly CLP classified substances for which data could be extracted from the REACH registration dossiers.

There are 59 nickel containing substances for which a harmonised classification is available (see section 2 and Appendix 3 for a full list) out of which 17 had been registered at the time of writing. There are another 36 substances, which have been self-classified and for which a registration is available. The list was amended by adding one substance, (931-895-4) for which a registration is available, but no classification, and by adding Nickel tetracarbonyl (236-669-2), for which no registration is available. The latter substance was added because it is an organoometallic compound with known high acute toxicity and its consideration in previous OEL setting for Nickel and its compounds. Therefore, the total number of nickel compounds (excluding nickel itself) considered is 54. The substance

identification and physico-chemical properties are described in tabulated summaries in Appendix 2.

1.2.1 Inorganic compounds

The inorganic compounds (35 substances) can be grouped according to their solubility in water: soluble compounds include nickel chloride, nickel sulphate, and nickel nitrate, and less-soluble compounds include nickel oxide and nickel subsulfide. Solubility may be important with regard to all relevant routes of exposure.

1.2.2 Organic compounds

The organic nickel compounds (20 substances) can be grouped by the chemical nature of the ligand. Especially carboxylates which are expected to dissociate to a significant degree in aqueous solution whereas some other complexes may be relatively stable in solution. Dissociation data are unfortunately not available.

For most organic compounds, nickel is present in an oxidation state of +2 with nickel tetracarbonyl as the only exception with nickel in an oxidation state of 0. Nickel tetracarbonyl is known to be the most toxic of all nickel compounds and it appears to be exceptionally toxic by inhalation as evidenced by a number of human poisoning accidents (NIPERA, 1996). It has been estimated to be lethal in man at atmospheric exposures of 30 ppm for 20 min (Doull, J et al, 1980). However, nickel as carbonyl has the oxidation state Ni^0 and is unlikely to express carcinogenic potential. Due to the high toxicity it is not relevant for long term exposure and not within the scope of the COM request of OEL setting.

2. EU Harmonised Classification and Labelling - CLP (EC) 1271/2008

Annex VI of the Regulation lists 54 entries for the classification of nickel and its compounds based on EC Regulation 1272/2008 on classification, labelling and packaging of substances and mixtures.

Nickel (and nickel powder) are classified as suspected human carcinogens (Carc. 2), as is nickel tetracabonyl; all other nickel compounds are classified as known human carcinogens (Carc. 1A). Nickel and all its compounds except for nickel tetracabonyl, are classified as skin sensitisers and of these compounds 31 are classified as respiratory sensitisers. 27 compounds are classified as repro tox (25 as 1B and 2 as 1A) and 27 compounds are classified as Mut 2.

Nickel and key compounds that are registered are listed in the table below: full details of all compounds are given in Appendix 3.

Table 3: EU classification: Summary of nickel and its compounds

Index No	International chemical ID	EC No	CAS No	Annex VI of CLP hazard class and category	Hazard statement code
028-002-00-7	nickel	231-111-4	7440-02-0	**Carc. 2** STOT RE 1 Skin Sens. 1	H351 H372** H317
028-002-01-4	Nickel powder : [particle diameter <1mm]	231-111-4	7440-02-0	**Carc. 2** STOT RE 1 Skin Sens. 1 Aquatic Chronic 3	H351 H372** H317 H412

Index No	International chemical ID	EC No	CAS No	Annex VI of CLP hazard class and category	Hazard statement code
028-003-00-2	nickel monoxide [1] nickel oxide [2] bunsenite [3]	215-215-7 [1] 234-323-5 [2]	1313-99-1 [1] 11099-02-8 [2] 34492-97-2 [3]	Carc. 1A STOT RE 1 Skin Sens. 1 Aquatic Chronic 4	H350i H372 ** H317 H413
028-006-00-9	nickel (II) sulfide [1] nickel sulfide [2] millerite [3]	240-841-2 [1] 234-349-7 [2]	16812-54-7 [1] 11113-75-0 [2] 1314-04-1 [3]	Carc. 1A Muta. 2 STOT RE 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H341 H372 ** H317 H400 H410
028-007-00-4	trinickel disulfide; nickel subsulfide [1] heazlewoodite [2]	234-829-6 [1]	12035-72-2 [1] 12035-71-1 [2]	Carc. 1A Muta. 2 STOT RE 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H341 H372 ** H317 H400 H410
028-008-00-X	nickel dihydroxide [1] nickel hydroxide [2]	235-008-5 [1] 234-348-1 [2]	12054-48-7 [1] 11113-74-9 [2]	Carc. 1A Muta. 2 Repr. 1B Acute Tox. 4 * Acute Tox. 4 * STOT RE 1 Skin Irrit. 2 Resp. Sens. 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H341 H360D *** H332 H302 H372 ** H315 H334 H317 H400 H410
028-009-00-5	nickel sulfate	232-104-9	7786-81-4	Carc. 1A Muta. 2 Repr. 1B Acute Tox. 4 * Acute Tox. 4 * STOT RE 1 Skin Irrit. 2 Resp. Sens. 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H341 H360D *** H332 H302 H372 ** H315 H334 H317 H400 H410
028-011-00-6	nickel dichloride	231-743-0	7718-54-9	Carc. 1A Muta. 2 Repr. 1B Acute Tox. 3 * Acute Tox. 3 * STOT RE 1 Skin Irrit. 2 Resp. Sens. 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H341 H360D *** H331 H301 H372 ** H315 H334 H317 H400 H410
028-012-00-1	nickel dinitrate [1] nitric acid, nickel salt [2]	236-068-5 [1] 238-076-4 [2]	13138-45-9 [1] 14216-75-2 [2]	Ox. Sol. 2 Carc. 1A Muta. 2 Repr. 1B Acute Tox. 4 * Acute Tox. 4 * STOT RE 1 Skin Irrit. 2 Eye Dam. 1 Resp. Sens. 1 Skin Sens. 1	H272 H350i H341 H360D *** H332 H372 ** H315 H318 H334 H317

Index No	International chemical ID	EC No	CAS No	Annex VI of CLP hazard class and category	Hazard statement code
				Aquatic Acute 1 Aquatic Chronic 1	H400 H410
028-013-00-7	nickel matte	273-749-6	69012-50-6	Carc. 1A STOT RE 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H372 ** H317 H400 H410
028-018-00-4	nickel bis(sulfamidate); nickel sulfamate	237-396-1	13770-89-3	Carc. 1A Muta. 2 Repr. 1B STOT RE 1 Resp. Sens. 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H341 H360D *** H372 ** H334 H317 H400 H410
028-022-00-6	nickel di(acetate) [1] nickel acetate [2]	206-761-7 [1] 239-086-1 [2]	373-02-4 [1] 14998-37-9 [2]	Carc. 1A Muta. 2 Repr. 1B Acute Tox. 4 * Acute Tox. 4 * STOT RE 1 Resp. Sens. 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H341 H360D *** H332 H302 H372 ** H334 H317 H400 H410
028-029-00-4	nickel difluoride [1] nickel dibromide [2] nickel diiodide [3] nickel potassium fluoride [4]	233-071-3 [1] 236-665-0 [2] 236-666-6 [3]	10028-18-9 [1] 13462-88-9 [2] 13462-90-3 [3] 11132-10-8 [4]	Carc. 1A Muta. 2 Repr. 1B STOT RE 1 Resp. Sens. 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H341 H360D *** H372 ** H334 H317 H400 H410
028-039-00-9	nickel oxalate [1] oxalic acid, nickel salt [2]	208-933-7 [1] 243-867-2 [2]	547-67-1 [1] 20543-06-0 [2]	Carc. 1A STOT RE 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H372 ** H317 H400 H410
028-057-00-7	dialuminium nickel tetraoxide [1] nickel titanium trioxide [2] nickel titanium oxide [3] nickel divanadium hexaoxide [4] cobalt dimolybdenum nickel octaoxide [5] nickel zirkonium trioxide [6] molybdenum nickel tetraoxide [7] nickel tungsten tetraoxide [8] olivine, nickel green [9] lithium nickel dioxide [10] molybdenum nickel oxide [11]	234-454-8 [1] 234-825-4 [2] 235-752-0 [3] 257-970-5 [4] 268-169-5 [5] 274-755-1 [6] 238-034-5 [7] 238-032-4 [8] 271-112-7 [9]	12004-35-2 [1] 12035-39-1 [2] 12653-76-8 [3] 52502-12-2 [4] 68016-03-5 [5] 70692-93-2 [6] 14177-55-0 [7] 14177-51-6 [8] 68515-84-4 [9] 12031-65-1 [10] 12673-58-4 [11]	Carc. 1A STOT RE 1 Skin Sens. 1	H350i H372 ** H317

Index No	International chemical ID	EC No	CAS No	Annex VI of CLP hazard class and category	Hazard statement code
028-058-00-2	cobalt lithium nickel oxide	442-750-5	-	Carc. 1A Acute Tox. 2 * STOT RE 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H330 H372 ** H317 H400 H410
607-288-00-2	Tetrasodium (c-(3-(1-(3-(e-6-dichloro-5-cyanopyrimidin-f-yl(methyl)amino)propyl)-1,6-dihydro-2-hydroxy-4-methyl-6-oxo-3-pyridylazo)-4-sulfonatophenylsulfamoyl)phthalocyanine-a,b,d-trisulfonato(6-))nickelato II, where a is 1 or 2 or 3 or 4,b is 8 or 9 or 10 or 11,c is 15 or 16 or 17 or 18, d is 22 or 23 or 24 or 25 and where e and f together are 2 and 4 or 4 and 2 respectively	410-160-7	148732-74-5	Eye Irrit. 2 Skin Sens. 1 Aquatic Chronic 3	H319 H317 H412
611-103-00-0	trisodium (1-(3-carboxylato-2-oxido-5-sulfonatophenylazo)-5-hydroxy-7-sulfonatonaphthalen-2-amido)nickel(II)	407-110-1		Eye Dam. 1 Skin Sens. 1 Aquatic Chronic 2	H318 H317 H411
611-122-00-4	hexasodium (di[N-(3-(4-[5-(5-amino-3-methyl-1-phenylpyrazol-4-yl-azo)-2,4-disulfo-anilino]-6-chloro-1,3,5-triazin-2-ylamino)phenyl)-sulfamoyl](di-sulfo)-phthalocyaninato)nickel	417-250-5	151436-99-6	Eye Dam. 1 Skin Sens. 1	H318 H317

3. Chemical Agent and Scope of Legislation - Regulated uses of nickel and its compounds in the EU

The uses of nickel and its compounds are currently not covered by an indicative or a binding occupational exposure limit (IOEL, BOEL). However some uses are already covered by regulation as described below.

3.1 Directive 98/24/EC and Directive 2004/37/EC

Nickel and its compounds are hazardous chemical agents in accordance with Article 2 (b) of Directive 98/24/EC and falls within the scope of this legislation.

Nickel compounds are also carcinogens or mutagens for humans in accordance with Article 2(a) and (b) of Directive 2004/37/EC and falls within the scope of this legislation.

3.2 REACH Registrations

There are 55 substances considered registered under REACH[4] for nickel (1) and nickel compounds (53). For 49 of these substances tonnage information is available as part of a REACH registration. These include, 35 substance with full registrations, and 14 substances only registered as an intermediate. Information on the registrations is available on the ECHA website[5]. Chemical Safety Reports are only available for those with a full registration.

The table below gives an overview of the type of registrations with tonnage for the 10 registered nickel substances in the highest quantities as used later in this proposal. The total tonnage reported for these 10 substances is representing about 98% of the overall tonnage reported for nickel compounds within registations; full details are in Appendix 4.

Table 4: REACH Registrations and tonnage

Substance(s)		Tonnage (tonnes/annum	
name	EC number	Full registration	intermediate use
Nickel	231-111-4	>100 000	
Slags, ferronickel-manufg.[6]	273-729-7	>100 000	
Matte, nickel[9]	273-749-6	>100 000	1000-10 000
Nickel monoxide	215-215-7	10 000-100 000	1000-10 000
Nickel sulphate	232-104-9	10 000-100 000	1000-10 000
Nickel dichloride	231-743-0	10 000-100 000	
Nickel sulphide	240-841-2	10 000-100 000	1000-10 000
Trinickel disulphide	234-829-6	100-1000	100-1000
Residues, copper-iron-lead-nickel matte, sulfuric acid-insol.	310-050-8	100-1000	10 000-100 000
[carbonato(2-)] tetrahydroxytrinickel	235-715-9	1000-10 000	100-1000

[4] Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC (OJ L 396 of 30 December 2006, p. 1; corrected by OJ L 136, 29.5.2007, p. 3)

[5] ECHA https://echa.europa.eu/information-on-chemicals/registered-substances

[6] use and exposure information is not provide in the respective registration

3.3 Authorised uses under Annex XIV of REACH

Nickel and its compounds are not listed in the Annex XIV of REACH ("Authorisation List"), therefore there are no authorised uses for nickel and its compounds.

3.4 Restricted uses under Annex XVII of REACH

Annex XVII of REACH entry 27[7] restricts the use of nickel and it compounds in jewellery (including watches) and articles intended to come into contact with the skin.

3.5 Plant Protection Products Regulation (EC)1107/2009

There are no plant protection products authorised under Regulation (EC) No 1107/2009 which are based on or include nickel or nickel compounds. Also, no maximum residue levels (MRLs) have been derived for pesticides including nickel and/or its compounds.

3.6 Human and Veterinary Medicinal Products Directives 2001/83/EC and 2004/28/EC respectively

Nickel and its compounds are not used in human medicine, however nickel gluconate and nickel sulphate are indicated for use in cases of nickel deficiency in several food producing species, (namely cattle, sheep, goats, pigs, chickens and rabbits as well as horses). However, no maximum residue levels (MRLs) are required and both compounds are included in Annex II of Council Regulation (EEC) No 2377/90, in accordance with Directive 2004/28/EC.

Nickel is used in medical implants such as joint prostheses, sutures, clips, and screws for fractured bones, in accordance with Council Directives 93/42/EEC and 90/385/EEC.

3.7 Biocidal Products Regulation (EU)528/2012

There have been no biocidal products authorised under Regulation (EU) No 528/2012 which are based on or include nickel or nickel compounds, nor has there been an active substance evaluation on nickel and related compounds.

4. Existing Occupational Exposure Limits

In various EU Member States as well as outside the EU OEL's for nickel and nickel compounds are established. These OEL's are presented in Table 5 and Table 6. The list should not be considered as exhaustive.

The table below covers limit values for nickel, inorganic soluble nickel compounds and inorganic insoluble nickel compounds. Please note that some Member States also have published OELs for individual nickel compounds such as nickel oxides or nickel sulphate. Values for these nickel compounds can be found at: http://www.dguv.de/ifa/gestis/gestis-internationale-grenzwerte-fuer-chemische-substanzen-limit-values-for-chemical-agents/index-2.jsp

[7] https://echa.europa.eu/documents/10162/7851171d-53e9-455a-8bb8-7ca22e89ad87

Table 5: Existing Occupational Exposure Limits (OELs) for nickel and nickel inorganic compounds compounds

Country / Organisation	Soluble inorganic Ni compound	Insoluble inorganic Ni compound	Nickel metal	Comments
	Level (mg/m³)[a]			
Austria	0.05 (I)	0.5 (I)	0.5	Ni metal incl alloys
Belgium	0.1	0.2	1	
Denmark	0,01	0.05		
Ireland	0.1	0.5		
Hungary	0.1			
Finland	0.05 (I) 0.01 (R)	0.05 (I) 0.01 (R)	0.01 (R)	
France (1)			1 (I)	
Germany	0.005* (R)	0.006* (R)	0.006 (R)	*Limit value is acceptable risk value (4: 10.000)
Latvia (1)			0.05	
Netherlands	0.1	0.1	0.1	Not legally applicable since 1/1/2007
Romania	0.1	0.1	0.1	Limit value for Nickel and its compunds (binding value)
Spain	0.1(I)	0.2 (I)	1	
Sweden			0.5	
Switzerland	0.05 (I)	0.05 (I)	0.05 (I)	
United kingdom	0.1 (MEL)	0.5 (MEL)	0.5 (MEL)	MRL: maximum exposure limit
US-NIOSH	0.015	0.015	0.015	
US-OSHA	1	1	1	

Notes:

[a] for 8-hours TWA (Time-Weight Average) unless otherwise noted.

(I) Inhalable compounds; (R): respirable compounds;

All values refer to 'total' nickel unless otherwise noted.

(1) No limit values published for nickel soluble or insoluble compounds as a group, but nickel for some individual nickel compounds available

Regarding organic nickel compounds, Ireland has a limit value for nickel organic compounds (1 mg/m³). Several countries have limit values for nickel tetracarbonyl, a (non-exhaustive) list with these limit values can be found in Table 6 below.

Table 6: Existing Occupational Exposure Limits (OELs) for nickel tetracarbonyl

Country / Organisation	Nickel tetracarbonyl				Comments
	TWA (8 hrs)		Short term		
	mg/m³	ppm	mg/m³	ppm	
Austria	0.35	0.05	0.14	0.02	TRK value (based on technical feasibility)
Belgium	0.12	0.05			As Ni
Denmark	0.007	0.001	0.014	0.002	
France	0.12	0.05			As Ni
Hungary	0.15				As Ni
Finland	0.007	0.001			
Ireland	0.12	0.05	0.24	0.1	As Ni
Latvia	0.0005				As Ni
Romania	0.05		0.1		Binding value
Spain	0.12	0.05			As Ni
Sweden	0.007	0.001			
Switzerland	0.35	0.05			
United kingdom			0.24	0.1	As Ni
US-NIOSH	0.007	0.001			
US-OSHA	0.007	0.001			

Biological limit values

Some Member States have also published biological limit values for nickel. The (non-exhaustive) table below shows the list of biological limit values.

Table 7: Biological limit values for nickel and its compounds

Country / Organisation	Soluble Ni compound	Ni metal and insoluble Ni compound	Nickel tetracarbonyl	Comments
Finland	0,2 µmol Ni /L urine (12 µg/L)	0,1 µmol/L urine (6 µg/L)		
Germany	Range of values starting from value of 25 µg Ni/l urine for an external concentration of 0.025 mg/m3 in air	Range of values starting from value of 15 µg Ni/l urine for an external concentration of 0.1 mg/m3 in air		EKA value (1)
Germany	3 µg Ni /L urine			BAR value (2)
Romania	15 µg Ni/L in urine	15 µg Ni/L in urine	15 µg Ni/L in urine	Binding value Sampling at the end of the shift
Romania			COHb 5% total Hb in blood	Binding value Sampling at the end of the shift
Canada	1.1 Ni/L blood			RV_{95}
Canada	4.4 Ni/L blood			RV_{95}

Notes:

(1) Exposure equivalents for carcinogenic substances, It shows correlation between internal and external exposure: see Tables 16 and 19

(2) Background level of a substance which is present concurrently at a particular time in a reference population of persons of working age who are not occupationally exposed to this substance

(3) 95th percentile of the measured pollutant concentration levels in the relevant matrix of the reference population.

5. Occurrence, Use and Occupational Exposure

5.1 Occurrence

Nickel is widely distributed in nature, forming about 0.008% of the earth's crust. The core of the earth contains 8.5% nickel, deep-sea nodules 1.5%; meteorites have been found to contain 5–50% nickel (EFSA 2015). Nickel is obtained through mining and it is estimated that there is about 140 million tonnes available in identified deposits.

Natural nickel is a mixture of five stable isotopes; nineteen other unstable isotopes are known. Although it can exist in several different oxidation states, the prevalent oxidation state under environmental conditions is Ni(II), nickel in the +2 valence state, primarily found combined with oxygen or sulphur as oxides or sulphides. Other valences (-1, +1, +3, and +4) are also encountered, though less frequently (Cempel 2005). Nickel forms simple binary compounds with non-metals, some that are practically insoluble in water including carbonate, sulphides (NiS and Ni_3S_2) and oxides (NiO, Ni_2O_3), and others that are soluble including chloride, sulphate and nitrate.

Nickel can be obtained from two main types of deposits with an estimated availability of 140 million tonnes based on identified sources. Firstly from the mineral garnierite (Ni-silicate) in nickel-rich laterite formed by weathering of ultramafic rocks in tropical climates (estimated availability 84 million tonnes). Garnierite is mainly mined in Australia, New Caledonia (France), Russia, Indonesia, Cuba and the Dominican Republic. Nickel also is mined from nickel-sulphid`e concentrations, mainly from pentlandite in igneous mafic rocks (estimated availability 56 million tonnes). Pentlandite is mainly mined in Canada, Russia, Australia and South Africa.

Sulphide deposits are easier and cheaper to mine and process with current techniques than lateritic ore deposits. However, extensive mining of sulphide deposits has meant that large scale high grade deposits of this type are being depleted at a faster rate than discovery. As such laterite deposits will account for a greater percentage of nickel production in the future.

Sulphide type nickel deposits are usually, although not always, found hundreds of metres underground resulting in an underground mining operation to extract them. Sulphide ores are much easier to process as they can be concentrated through physical separation by flotation. Laterite deposits are usually located closer to the surface, about 15 to 20m down, meaning they can be mined via open-cut methods. These deposits form where nickel sulphides have oxidised. The disadvantage of laterites is that it is more difficult to process the ore to retrieve the nickel, requiring the ore to be completely molten or dissolved, dramatically increasing processing costs. As such operations to mine laterite deposits must be of a magnitude larger than sulphide deposits to create the necessary economy of scale for the project to be financially viable.

The natural background levels of nickel in water are relatively low, in open ocean water 0.228– 0.693 µg/litre, in fresh water systems generally less than 2 µg/litre (WHO 2000).

Agricultural soils contain nickel at levels of 3–1000 mg/kg; in 78 forest floor samples from the north eastern United States of America, concentrations of 8.5–15 mg/kg were reported.

The nickel content is enriched in coal and crude oil. Nickel in coals ranges up to 300 mg/kg; most samples contain less than 100 mg/kg but there is a large variation by region. The nickel content of crude oils is in the range <1–80 mg/kg.

5.2 Production and Use Information

Before nickel in any form is put to use, it first has to be explored/mined, refined, fabricated and integrated into products for domestic use and for export. This occurs in the following countries within the EU:

Table 8: Nickel production

Exploration / Mining	Smelting	Refining	Chemicals
Finland	Finland	Finland	Finland
Greece	Greece	France	France
France (New Caledonia)	France (New Caledonia)	Norway	Belgium
Spain	Austria	United Kingdom	Germany
Sweden (exploration)			Poland
			Sweden

The EU uses approximately 700,000 tonnes of nickel per annum[8]: 387,200 tonnes in 2008 from mines, the rest recovered from recycled material, mainly stainless steel. Although the majority of nickel-containing scrap is recycled, the demand for nickel-containing materials is increasing around the world, and as a result there is not enough scrap to satisfy demand. Most nickel-containing products have long lives. The average life of nickel-containing products is in the range of 25-35 years and for some applications such as roofs and cladding this can go up to 100 years.

In addition to direct usage, nickel forms many useful compounds with non-metals, characteristically blue or green in colour, and often hydrated. Some examples of these compounds are associated with the uses described in the following sections.

Manufacture of alloys

About 90% of all new nickel sold each year in the EU goes into alloys, two-thirds of that going into the production of over 8 million tonnes of stainless steel (containing 8-12% nickel). This accounts for about 35% of all the stainless steel produced in the world.

Nickel is also used in alloys similar to stainless steel, but with a higher nickel content, in the chemical, petrochemical, energy and aerospace industries. Alloys of iron and nickel find many uses in electrical and electronics industries and other specialist engineering fields. Alloys of copper and nickel are used in coinage and marine engineering. There are about 3000 nickel-containing alloys in everyday use. Some typical alloys and their uses are (IARC 2012):

- Nickel–copper alloys (e.g. Monel alloys) are used for coinage (25% nickel, 75% copper), industrial plumbing (e.g. piping and valves), marine equipment, petrochemical equipment, heat exchangers, condenser tubes, pumps, electrodes for welding, architectural trim, thermocouples, desalination plants, ship propellers, etc.
- Nickel–chromium alloys (e.g. Nichrome) are used in many applications that require resistance to high temperatures such as heating elements, furnaces, jet engine parts, and reaction vessels
- Molybdenum-containing nickel alloys and nickel–iron–chromium alloys (e.g.
- Inconel) provide strength and corrosion resistance over a wide temperature range, and are used in nuclear and fossil-fuel steam generators, food-processing equipment, and chemical-processing and heat-treating equipment

[8] https://www.oma.on.ca/en/multimedialibrary/resources/NickelintheEuropeanUnionPDF.pdf

- Hastelloy alloys (which contain nickel, chromium, iron, and molybdenum) provide oxidation and corrosion resistance for use with acids and salts
- Nickel-based super-alloys provide high-temperature strength and creep, and stress resistance for use in gas-turbine engines

Although there are variations across alloys, their manufacture generally involves the following set of processes:

1. Melting: The raw materials are first melted together in an electric furnace. This step usually requires 8 to 12 hours of intense heat. When the melting is finished, the melt is cast into semi-finished forms.
2. Forming: Next, the semi-finished alloy goes through forming operations, beginning with hot rolling, in which the steel is heated and passed through huge rolls. Blooms and billets are formed into bar and wire, while slabs are formed into plate, strip, and sheet.
3. Heat treatment: After the alloy is formed, most types must go through annealing, which is a heat treatment in which the alloy is heated and cooled under controlled conditions to relieve internal stresses and soften the metal. Although the heating rate to reach the aging temperature does not affect the properties, the cooling rate does.
4. Descaling: Annealing causes a scale or build-up to form. The scale can be removed using several processes (such as pickling or electrocleaning).
5. Cutting: Cutting operations are usually necessary to obtain the desired blank shape or size to trim the part to final size. Mechanical cutting is accomplished by a variety of methods, including straight shearing using guillotine knives, circle shearing using circular knives horizontally and vertically positioned, sawing using high speed steel blades, blanking, and nibbling. Blanking uses metal punches and dies to punch out the shape by shearing. Nibbling is a process of cutting by blanking out a series of overlapping holes and is ideally suited for irregular shapes. Alloys can also be cut using flame cutting, which involves a flame-fired torch using oxygen and propane in conjunction with iron powder. Another cutting method is known as plasma jet cutting, in which an ionized gas column in conjunction with an electric arc through a small orifice makes the cut.
6. Finishing: Surface finish is an important specification for alloy products and is critical in applications where appearance is also important. A smooth surface as obtained by polishing also provides better corrosion resistance. On the other hand, rough finishes are often required for lubrication applications, as well as to facilitate further manufacturing steps. There are a variety of methods used for finishing. A dull finish is produced by hot rolling, annealing, and descaling. A bright finish is obtained by first hot rolling and then cold rolling on polished rolls. A highly reflective finish is produced by cold rolling in combination with annealing in a controlled atmosphere furnace, by grinding with abrasives, or by buffing a finely ground surface.

During the processes described above there are a number of opportunities for nickel exposure. Metal fumes are formed by evaporation, condensation and oxidation of metals in air. Furnace tenders, melters, casters, ladle-men, pourers and crane drivers are exposed to fumes from molten metal. Fettlers (finishers) are exposed to metal fumes and dusts from grinding, welding and flame-cutting operations.

Hard-wearing coatings – plating or electroforming

Nickel provides hard-wearing coatings for either decorative (“brushed nickel” and “chrome” finishes) or engineering purposes using surface technologies such as plating or electroforming. Surface treatment or finishing operations can be carried out using manual, mechanised or fully automated processes together with the application of different levels of risk management measures (RMM). Most surface technology is used on components or customised shapes, which means that it mainly takes place near where the customers are.

Thus there are few large stand lone surface technology operations. Overwhelmingly this industry consists of thousands of small or medium-sized firms or specialist units attached to larger companies that need such supplies. This means there is a wide range of operating conditions and RMM in use in the surface finishing industry. Surface technology operations are found in every significant manufacturing centre of the EU [9].

Electro- and electroless plating are coating technologies while electroforming is essentially a fabrication technique. In any nickel electrodeposition process, there are four main components: a container containing a nickel salt solution (electrolyte), a source of direct current, and 2 electrodes - the positive (cathode) on which the nickel is to be deposited, and the negative (anode) is normally a suitable form of nickel metal. There are many variations in the composition of the electrolytes used but all contain nickel in solution, usually in the form of nickel sulphate, nickel chloride or nickel sulphamate or a combination of these salts. Variations include nickel acetate, nickel ammonium sulphate and nickel sulphate hexahydrate. Successful plating requires careful control of the purity of the electrolyte (by precipitations and filtration) and of the operating variables e.g. pH, temperature, agitation and solution concentration levels of nickel and additives e.g. surfactants, fume suppressants. These in turn impact on exposure.

In electroplating plating, an additional nickel layer is applied, electrolytically, to an existing part (workpiece). The workpiece is immersed into a Watts nickel (or all-chloride, all-sulphate, sulphate-chloride) electrolyte solution at temperature between 40 and 60oC. The nickel anode dissolves into the electrolyte and are reduced to the nickel plate at the cathode (the workpiece).

Electroforming is an electroplating technology, in which a new piece (the electroform) is made using a mandrel (model or mould). The mandrel is submerged in a nickel solution (nickel sulphamate) through which an electrical current is passed at room or elevated (40 to 60 oC) temperatures. Finally, after hours or days, the mandrel is removed and separated from the electroform.

Electroless nickel plating uses a solution that plates a nickel phosphorous alloy via an autocatalytic reaction. The solution (nickel sulphate with a reducing agent) is routinely operated at a temperature of around 70 oC and the workpiece is immersed for up to an hour. The nickel content of the plating solution must be maintained at 80% nickel and this requires regular monitoring and chemical additions.

For all three processes, workpieces are dipped in the nickel-containing solution and other cleaning, strike and passivating process solutions held in tanks arranged sequentially in a ‘plating line’. Rinse tanks are situated between each processing tank, with workpieces being dipped in these so to wash off the processing solutions before the workpieces enter a different tank solution to avoid contamination. The washed Ni metal coating or surface would be dried in the final step of the finishing process. Activities maybe run largely from a control room in a highly automated plant or from a gantry or work station beside the process line when they are required to operate the process more directly. The workpieces are secured on a jig or loaded in a barrel to pass down through each plating line solution. The jig or barrel lifting equipment (hoist) can be operated from the shop floor by a hand held or hoist-mounted control panel or remotely from a control room. Dipping may be done manually for small jigs, small jobs or by small plating businesses.

Workers in electroplating shops may be exposed to Ni substances in the form of mists, dusts or powders from electrolytic solutions, nickel anodes, nickel plate or wastes during the plating operation, maintenance of solutions and plant or cleaning of the premises, equipment and plant. These present an inhalation risk. Skin contact with nickel plating

[9] https://www.oma.on.ca/en/multimedialibrary/resources/NickelintheEuropeanUnionPDF.pdf

solutions can occur for example when loading and unloading workpieces from the jigs and barrels and making-up, replenishing or destroying plating solutions.

Through use the bath solutions become depleted of plating and additive chemicals and therefore require replenishing or topping-up. Solution testing is carried out to aid bath composition, pH and surface tension regulation. Adding nickel powders/solutions to plating baths may result in spills or generate dusts or mists. By adding nickel plating chemicals as a solution (not a dry powder) and pumped into plating tanks rather than manually pouring excessive exposures can be avoided. Equally leaving containers open and failing to clean surrounding work surfaces (tables, etc.) at the end of each shift can increase the amount of nickel in the workplace and so chemical tanks and containers should be covered when not in use. When a plating solution becomes exhausted it needs to be properly destroyed or neutralised and disposed of before a fresh plating solution made up. This involves draining and removing residue liquid and sludge from dip tanks and disposing of them carefully as a chemical waste where appropriate.

Polishing the plated nickel workpiece on a vibratory or pedestal system can generate Ni dust. Current commercial Ni electroplating solutions usually contain brighteners and levellers and do not require the plate surface to be mechanically polished. Polishing may still be required after sulphamate plating. By switching to a plating solution that does not require the new plate to be polished eliminates this source of exposure

Jig plating requires the operators to mount the individual work pieces on the jig. This brings them in contact with plating solutions and nickel metal which has become plated onto the jig, leading to dermal exposure. Maintenance and repair and cleaning work is done to tanks and pumps need to be cleaned before use with a different chemical also present such dermal (and inhalation) exposure risks

Manufacture of batteries

Battery electrodes which use Ni substances are composite electrode structures where an ‘active mass’, containing Ni and other conductive materials, is supported by or encased in ‘current collector’ plates which are coated with nickel.

Nickel metal, $NiSO_4$ (probably with $NiCl_2$ when electroplating from a Watts nickel bath) and $Ni(OH)_2$ are used widely in the battery industry to make 4 types of electrodes. $Ni(NO_3)_2$ and nickel metal are used to make one type of electrode. ide (NiMH) alkaline batteries.

Table 9 shows the structure of these 5 main electrode types used in nickel/cadmium (NiCad) and nickel/metal hydride (NiMH) alkaline batteries.

Table 9: Nickel substances used in 5 electrode technologies

Electrode technology	Battery electrode structure		
	Active mass		Conductive substrate as current collector
	Positive	Negative	
Pocket plate	$Ni(OH)_2$ as a dry powder of $Ni(OH)_2/Co(OH)_2$ & other additives	$Cd(OH)_2$/ $Ni(OH)_2$	Ni electroplated steel strip
Foam/fibre	$Ni(OH)_2$ as a wet paste of $Ni(OH)_2$, $Co(OH)_2$ & other additives	$Cd(OH)_2$/ $Ni(OH)_2$	Ni foam & Ni fibres
Plastic Bonded	$Ni(OH)_2$ as a wet paste of $Ni(OH)_2$, $Co(OH)_2$ & other additives	$Cd(OH)_2$/ $Ni(OH)_2$	Ni electroplated steel strip
Sintered	$Ni(OH)_2$ as a $Ni(OH)_2/Co(OH)_2$ surface precipitate	*$Cd(OH)_2$/ $Ni(OH)_2$	Ni sintered steel perforated strip or Ni gauze

Notes:

$Ni(OH)_2/Co(OH)_2$	$Co(OH)_2$ co-precipitated with $Ni(OH)_2$ from a $CoSO_4/NiSO_4$ mixed solution
$Ni(OH)_2$, $Co(OH)_2$	$Co(OH)_2$ 'dopant' added to and mixed with $Ni(OH)_2$
*	Assumed

Nickel sulphate powder, $NiSO_46H_2O$, or solution is used to top up the (Watts nickel) plating solutions for nickel plating the iron or steel strips used in (pocket plate and plastic bound) electrode production. This uses a typical open electroplating line which can have LEV to provide ventilation at the plating bath. Foam electrodes are made by combining a pure, porous Ni metal substrate with the active mass and so no electroplating is involved in their production. Ni metal powder is used to sinter the steel strip used in the sintered electrode production.

The 'positive' active mass for pocket plate electrodes is produced in three stages. Firstly, nickel metal (as briquettes or squares, cut from bulk electrolytic nickel) is reacted with sulphuric acid to make $NiSO_4$ solution. There is some level of manual intervention at the reactor head when adding the metal to the acid. This takes place in a closed reactor, only open during the Ni metal addition. Sodium hydroxide solution is used to precipitate $Ni(OH)_2$ (together with $Co(OH)_2$) from a $NiSO_4/CoSO_4$ co-solution. It is assumed this is recovered in an enclosed filtration operation. This would appear to an 'on-site isolated intermediate' provided it is manufactured and used under strictly controlled conditions. The $Ni(OH)_2/Co(OH)_2$ is isolated and combined with other conducting additives to make the 'positive active mass'. This is shaped into tablets which are sandwiched between the Ni plated strips forming a roll of 'pocket plate' electrode in a continuous process. The electrodes are cut from the roll of pocket plate electrodes and assembled into a battery. A similar process is used to make $Ni(OH)_2/Co(OH)_2$ for application to the substrates of the foam, fibre and plastic bonded electrodes.

For the Ni sintered electrode, $Ni(NO_3)_2$ is prepared from the reaction between nickel metal and nitric acid (HNO_3). Additives including cobalt and cadmium are added to give a (multi-metal) $Ni(NO_3)_2$-based solution. The sintered nickel-coated (perforated steel or nickel gauze) strip is passed through this solution to 'coat' Ni and Co onto the strip. The $Ni(OH)_2$ is precipitated 'in situ' onto the strip by passing the 'coated' strip though sodium hydroxide, NaOH. Again, the $Ni(OH)_2$ is produced in the last stage of the production process and technically may not be classified as a 'non-isolated intermediate'.

Continuous automated production is used to make the electrodes and wind the finished electrode strip onto a spool. Exposure will depend on the time spent close to the plant and the level of containment and ventilation of this process. Since the plant is automated, it would seem unlikely that workers are stationed next to the plant for the full shift. However, it is possible that any breakages in the strip or blockages in the plant would require some level of manual intervention. Inhalation and dermal exposure would be higher for these tasks.

Catalysts

Nickel-containing catalysts for use at industrial sites are generally in the form of a nickel sulphide (NiS, or nickel subsulphide, N_3S_2, or a mixture of both), NiO or Ni metal. Nickel has strong catalytic properties (due to easy oxidative addition and ready access to multiple oxidation states) that serve the chemical and petrochemical industries. Ni-containing catalysts are generally supported and produced in shaped (tablets, pellets, droplets etc.) or powdered forms. These are dependent on small powder and chemical production facilities found in most EU countries with the large-scale production in Denmark, Finland, France, The Netherlands, and Sweden.

Use of nickel-containing finished catalysts usually occurs at a completely different industrial site from where it is made e.g. by a downstream user company, operating in a different industrial sector e.g. petrochemical, fine or bulk chemicals or food stuff. The catalysts are used in batch or continuous production in a closed industrial reactor. Pellet catalysts can typically be in continuous use for half a year up to several years before they

become exhausted and have to be replaced with fresh or regenerated catalysts. Droplet and powder supported catalysts and unsupported catalyst are used largely in batch production (unsupported catalysts can also be used in continuous production). Fresh catalyst is supplied more frequently in these processes. Entirely enclosed charging and discharging of catalyst into a reactor, generally involve piped transfer of catalyst from a supply tank and return of spent catalyst to a separate tank. Dust may become airborne when the pipes or hoses are manually connected and disconnected at the start and finish of transfer. Spent catalysts are recycled or disposed of as waste. During recycling, catalysts may be regenerated in place (in-situ) or often taken off-site to another plant (ex-situ).

Finished catalysts are usually delivered to commercial companies in bulk (e.g. road tanker) and loaded into the reactor via an enclosed transfer system. Alternatively, the finished catalyst is supplied in flow bins or drums and transferred to the reactor using a manually operated vacuum system. Workers do not come into contact with the Ni-containing catalyst during the catalysts working lifetime. At the end of the working lifetime of the catalyst, the spent catalyst is unloaded from the reactor to the bulk or individual containers by enclosed transfer.

In terms of exposure, the final shaped product is not regarded as dusty and generally no significant dust is generated during packing. However, formation of dust may arise due to abrasion of these pellets during processing, transfer and packaging operations. The pellets can be passed through de-dusting systems to remove dust, fine particles and other undesirable contaminants from the final catalyst stream, prior to packaging. Alternatively, the openings or dust emission points in processing plant can be ventilated.

Where powdered Ni-containing catalysts are produced, in general airborne exposures are likely to be higher than for the production of shaped catalysts. However airborne exposure concentrations during most of the production process prior to final catalyst packaging would be expected to be similar to those associated with producing shaped catalysts. Nickel salts and slurries used to prepare catalyst intermediates by impregnation etc. are prepared and used under wet conditions and catalysts are manufactured and used within closed reaction vessels and associated pipework e.g. during charging and discharging.

Cleaning and maintenance operations are typically less frequent and off shorter duration than routine operations. However, airborne exposure concentrations during cleaning and maintenance activities are likely to exceed those associated with routine operations, particularly where it is necessary to enter or work with vessels or pipework that have contained some form of powdered Ni. Higher exposures may also be experienced when clearing blockages in pipes and closed conveyors. Unsupported Ni-containing catalysts are generally handled with complete containment to prevent contact with air. In droplets the Ni-containing catalyst is held within an organic matrix and so any dust formation during handling should be negligible.

Exposure to airborne Ni is controlled during the loading/unloading and charging/ discharging of industrial reactors with pellets or powders. The transfer operations to and from reactor to container or vehicle use a hermetically sealed system, e.g. under vacuum, the potential for exposure is small and is largely be associated with switching between drums or other containers during loading/unloading. Due to the infrequency of the task, long term average exposure concentrations for workers at user sites may tend to be considerably less than shift average exposures exposure concentrations on production sites.

Use as intermediate

Under the REACH regulation, an intermediate is a substance that is manufactured for and consumed in or used for chemical processing in order to be transformed into another substance (REACH Article 3(15)). This can cover a wide variety of nickel compounds which are often used in the formation of other nickel compounds (and nickel).

Examples of intermediate uses are (IARC 2012):

- nickel hydroxide, nickel chloride, green nickel oxide and nickel nitrate hexahydrate used to manufacture catalysts
- nickel acetate, black nickel oxide and nickel sulphate hexahydrate used to manufacture catalysts and other nickel compounds
- nickel carbonate used in the manufacture of nickel catalysts, pigments, and other nickel compounds (including nickel oxide, nickel powder).

As can be seen, the main use as intermediate is in the manufacturing of catalysts. The processes for manufacturing catalysts and potential exposures during their manufacture and use are described below.

Catalyst pellets are usually impregnated onto alumina or silica supports, or are palletised after co-precipitation with other metal oxides. Supported catalyst droplets are essentially 'safe by design'. The Ni-containing catalyst is embedded inside an organic matrix. Consequently, Ni-containing dust formation during handling will be negligible. Other catalyst forms such as powdered supported (impregnated alumina or silica powder, or powder formed after co-precipitation with other metal oxides) and unsupported catalysts appear to be less commonly produced and used. Unsupported catalysts are often air sensitive and presumably become inactive on contact with air. Therefore, plants are designed to prevent air ingress into the system via breaches. Prevention of exposure to airborne dust when handling these materials, even during charging or discharging reaction vessels should be controlled by plant design as a closed process.

Finished NiO and Ni metal catalysts, ready to be used at industrial sites to catalyse commercial industrial processes, are generally made in three and four stages respectively.

- Preparation of a Ni-containing solutions or slurries {$NiCl_2$, $Ni(NO_3)_2$, & NiHydCarb/$Ni(OH)_2$} (as an intermediate or to make an intermediate)
- Generating Ni-containing intermediates in catalyst precursors by impregnation or precipitation of the nickel-containing intermediate into a catalyst support (catalyst precursor)
- calcining (the catalyst precursor) to give NiO-containing catalyst (for industrial use) or a catalyst precursor
- reduction of nickel NiO-containing catalyst precursor to give a Ni/NiO-containing catalyst (for industrial use)

Nickel sulphide based catalysts are made from a two stage production process, these being:

- regeneration (to NiO) and
- sulphiding (NiS/ N_3S)

The entire (generally batch) production process is largely automated and enclosed. As such, the plant is manned by a few (2 to 3, depending on the size of the plant) operators who spend their shift undertaking work outside on the plant (in the field) and remotely from a control room. Routine field (outside on the plant) tasks tend to be of short duration. These would include inspection rounds to check the correct material stream has been brought forward; take meter readings; manually load dry powder, solutions or slurries into charging hoppers, turning valves and aligning pipes, collecting samples, field testing samples, cleaning up spills and leaks and clearing blockages.

Lower levels of containment may be applied early in the process where nickel substances are being prepared as solutions or slurries. For operations involving powdered raw materials, intermediate or finished products (e.g. loading vessels, weighing, powdering/granulation, transfer, tableting, mixing) release of dust into the workplace would be prevented or controlled by enclosure or ventilation at open ports, providing

necessary access to or from a piece of machinery, conveyor systems or breaches in the plant.

Pigments

Metallic pigments provide an essential tool in the hands of the formulators and manufacturers of organic based coatings. The inherent visual properties of the various types of metallic pigments generally determine the applications in which they are used. Other types of pigment may be specified on the basis of properties other than just appearance, such as resistance to corrosion or chemical attack. Nickel pigments exhibit good corrosion resistance, attractive visual appearance, high electrical conductivity and ferromagnetism (Hart 2003).

Doted rutile pigments are manufactured by reacting finely divided metal oxides, hydroxides or carbonates in the solid state at a temperature of 1000 to 1200°C (OECD SIDS, 2002). The production is based on reactive anatase, or titanium dioxide hydrolysate containing sulfuric acid, and on the oxidation of trivalent antimony with oxygen in the form of nitric acid or air. For the production of C.I. Pigment Yellow 53 (nickel antimony titanium yellow rutile), nickel metal oxide, hydroxide or carbonate is used.

The reactions proceed more readily if the components are reactive, finely divided and intimately mixed. Adding mineralisers promotes solid-state reaction during calcination, which is performed either continuously in a rotary, annular or tunnel furnace, or batchwise in a directly fired car-bottom or rotary-hearth furnace. After calcination, the resulting clinker is wet-ground and any soluble salts are washed out. The product is dried either in a spray-drying tower, when low-dusting, free-flowing grades are required, or by standard means, which, however, necessitates subsequent grinding to a pigment powder.

Raw-material dust, and gases (e.g. SO_3 and NOx), emitted during the calcination step are removed from the flue gas by dust separators and alkaline flue scrubbers. The raw-material dust can be recycled. Soluble metal salts can be removed by neutral precipitation in the waste-water treatment plant, and suspended pigment particles can be mechanically separated from the water from washing and purification steps. Altogether, only a small amount of waste is produced with each tonne of product.

The finished C.I. Pigment Yellow 53 contains about 2 to 5 % nickel (II).

Nickel particulate materials are available in three quite distinct physical forms:

- Flakes
- Filamentary powders
- Spherical powders

all of which are suitable for use as pigments in organic-based systems. This means that they can be used not only in coating products such as paint and ink but also in filled elastomers, sealants and adhesives.

Nickel pigments can be used in 3 kinds of coatings:

- Decorative/functional coatings: decorative grades of nickel flakes are used to produce bright, fully metallic, coatings, stable in aqueous media and corrosion resistant.
- Electrically conducive coatings: to provide shielding for all types of electronics equipment in order to avoid radiofrequency (RFI) and electromagnetic (EMI) interference problems.
- Nickel-containing coatings for magnetic applications: as nickel is the only substance that is both strongly ferromagnetic at ambient temperatures and available in small particles suitable for us as pigments

Some other examples of nickel compounds that are used as pigments include nickel carbonate and nickel titanate.

Slags, ferronickel-manufacturing

Ferronickel production plants generate slag as by-product from smelting and refining of iron-containing nickel ores. The slag is used in many applications, for civil engineering construction (embankments, ballasts, granular bases and bricks), in high density aggregate, as abrasives in sandblasting (and possibly in electroplated abrasive tools). The slag can be recovered from various stages in the smelting process as electric furnace air cooled slag; electric furnace water cooled slag and air cooled converter slag. The nickel/iron alloy is generally produced as granules or ingots.

The drying and reduction of the nickel oxidised ores is conducted, firstly, in a series of rotary kilns. The calcined product of the rotary kilns is then fed into a series of electric arc furnaces that are supervised and operated on a highly automated basis. The feeding of the electric arc furnaces is carried out with cranes. The flow of the by-product of the furnaces (electric furnace slag) is manually controlled. The handling of the electric furnace slag stream is carried out through special installation. The refining of the melted product (ferronickel alloy) of the electric furnaces is conducted in OBM (Oxygen Bottom Maxhűtte) Converters. The refined final product (ferronickel alloy) is solidified as granules and ingots. The produced OBM Converter's Slag and refined ferronickel alloy is handled and stored.

Review of registration information

A review of the ECHA registration information identified the top 10 substances based on the number of registrations and quantities manufactured or imported. Eight are listed in the table below with the exposure estimates indicated for the most common uses (as described above). Where a use is described by a single exposure scenario a single exposure estimate is given. Where a use is described by a number of contributing scenarios/activities a range of exposure estimates is given. As can be seen quite often the contributing activity leading to the highest inhalation exposure is cleaning and maintenance (or cleaning and dust removal), and the activity leading to the highest dermal exposure is the raw material handling. The exposure estimates for two of the ten substances (slags ferronickel manufacturing and residues, copper-iron-lead-nickel matte, sulfuric acid-insol.) are not included as the use and exposure information is not provide in their respective registrations.

Table 10 : Exposure estimates for the most common uses of the 8 registered nickel substances in the highest quantities

Substance	Exposure estimates for the most common uses (A range indicates that the use is described by a number of contributing scenarios, with the * indicating the specific activity that leads to the highest exposure for that end-point)					
	Manufacture of alloys	**Electroplating and electroforming**	**Production of batteries**	**Use of catalyst**	**Use as intermediate** (in the manufacture of catalysts, nickel or nickel compounds)	**Pigment manufacture**
Nickel metal	Inhalation (mgNi/m3) Acute local 0.018-0.34* Long-term systemic and local 0.006-0.115* Dermal Long-term local (mgNi/cm2/day) 0.00003-0.0003** *PROC 0: Cleaning and maintenance **PROC 21: Packing, shipping and storage	Inhalation (mgNi/m3) Acute local 0.060-1.71* Long-term systemic and local 0.02-0.57* Dermal Long-term local (mgNi/cm2/day) 0.00001-0.00109* *PROC 0: Cleaning and maintenance	Inhalation (mgNi/m3) Acute local 0.0426-1.026* Long-term systemic and local 0.0142-0.0342* Dermal Long-term local (mgNi/cm2/day) 0.000003-0.00005 *PROC 0: Cleaning and maintenance	<u>*Powdered catalysts*</u> Inhalation (mgNi/m3) Acute local 0.04 Long-term systemic and local 0.01 Dermal Long-term local (mgNi/cm2/day) 0.0005 <u>*Shaped catalysts*</u> Inhalation (mgNi/m3) Acute local 0.06 Long-term systemic and local 0.02 Dermal Long-term local (mgNi/cm2/day) 0.0005	<u>*Powdered catalysts*</u> Inhalation (mgNi/m3) Acute local 0.16 Long-term systemic and local 0.04 Dermal: Long-term local (mgNi/cm2/day) 0.0005 <u>*Shaped catalysts*</u> Inhalation (mgNi/m3) Acute local 0.06 Long-term systemic and local 0.02 Dermal: Long-term local (mgNi/cm2/day) 0.0005	-
Matte nickel	-	-	-	-	Inhalation (µg/m³ $Ni(Ni_3S_2)$) Acute local: 1-2050* Long-term systemic and local 1-1363* Dermal Long-term local (µg Ni/cm2/day) <1 - 72* *Cleaning and maintenance	-
Nickel oxide	Inhalation, mg/m³ systemic, long-term 0.006-0.026* local, long-term 0.006-0.026* local, acute 0.011-0.051* Dermal, local, long-term 0.76-5.18* µg/cm² *Raw material handling (PROC 26)	-	-	<u>*Powdered catalysts*</u> Inhalation, mg/m³ systemic, long-term 0.01 local, long-term 0.01 local, acute 0.04 Dermal, local, long-term 5E-4 mg/cm² <u>*Shaped catalysts*</u>	<u>*Powdered catalysts*</u> Inhalation, mg/m³ systemic, long-term 0.035 local, long-term 0.035 local, acute 0.105 Dermal, local, long-term 5E-4 mg/cm² <u>*Shaped catalysts*</u> Inhalation, mg/m³ systemic, long-term 0.026 local, long-term 0.026	Inhalation, mg/m³ systemic, long-term 0.003-0.025* local, long-term 0.003-0.025* local, acute 0.007-0.037* Dermal, local, long-term 0.076-0.76* µg/cm²

				Inhalation, mg/m³ systemic, long-term 0.02 local, long-term 0.02 local, acute 0.06 Dermal, local, long-term 5E-4 mg/cm²	local, acute 0.022 Dermal, local, long-term 5E-4 mg/cm²	*Cleaning/removal of dust (PROC 26)
Nickel sulphate	-	Inhalation, mg/m³ systemic, long-term 0.003-0.025* systemic, acute 0.007-0.037* local, long-term 0.003-0.025* local, acute 0.007-0.037* Dermal, local, long-term 0.06-0.11** µg/cm² *CLEANING/REMOVAL OF DUST (PROC 26) **RAW MATERIAL HANDLING (LOW DUSTY MATERIALS) (PROC 26)	Inhalation, mg/m³ systemic, long-term 0.003-0.025* systemic, acute 0.007-0.037* local, long-term 0.003-0.025* local, acute 0.007-0.037* Dermal, local, long-term 0.06-0.11** µg/cm² *CLEANING/REMOVAL OF DUST (PROC 26) **RAW MATERIAL HANDLING (LOW DUSTY MATERIALS) (PROC 26)	-	Inhalation, mg/m³ systemic, long-term 0.011-0.025* systemic, acute 0.022-0.037* local, long-term 0.011-0.025* local, acute 0.022-0.037* Dermal, local, long-term 0.06-0.11** µg/cm² *CLEANING/REMOVAL OF DUST (PROC 26) **RAW MATERIAL HANDLING (LOW DUSTY MATERIALS) (PROC 26)	Inhalation, mg/m³ systemic, long-term 0.003-0.025* systemic, acute 0.007-0.037* local, long-term 0.003-0.025* local, acute 0.007-0.037* Dermal, local, long-term 0.06-0.11** µg/cm² *CLEANING/REMOVAL OF DUST (PROC 26) **AUTOMATED TRANSFER PROCESS (PROC 8B)
Nickel Chloride	-	Inhalation (mgNi/m3) Acute local 0.027-1.71* Acute long-term 0.027-1.71* Long-term systemic and local 0.009-0.57* Dermal Long-term local (mgNi/cm2/day) 0.000006 -0.000881* *PROC 0: Cleaning and maintenance of plant, solutions and premises **PROC 3, 4, 5, 8a, 8b, 9, 13 & 15: Surface finishing	-	-	Inhalation (mgNi/m3) Acute local 0.03-2.58* Acute long-term 0.03-2.58* Long-term systemic and local 0.01-0.086* Dermal Long-term local (mgNi/cm2/day) 0.00003 -0.001** *PROC 0: Cleaning and maintenance **PROC 8b: Raw material handling	-

Nickel Sulphide	-	-	-	Inhalation, mg/m³ systemic, long-term 0.02 systemic, acute 0.06 local, long-term 0.02 local, acute 0.06 Dermal, local, long-term 5E-4 mg/cm²	In situ: Inhalation, mg/m³ systemic, long-term 0.02 systemic, acute 0.06 local, long-term 0.02 local, acute 0.06 Dermal, local, long-term 5E-4 mg/cm² Ex-situ Inhalation, mg/m³ systemic, long-term 0.026 systemic, acute 0.078 local, long-term 0.026 local, acute 0.078 Dermal, local, long-term 5E-4 mg/cm²	-
Trinickel disulphide	-	-	-	Inhalation, mg/m³ systemic, long-term 0.02 systemic, acute 0.06 local, long-term 0.02 local, acute 0.06 Dermal, local, long-term 5E-4 mg/cm²	In situ: Inhalation, mg/m³ systemic, long-term 0.02 systemic, acute 0.06 local, long-term 0.02 local, acute 0.06 Dermal, local, long-term 5E-4 mg/cm² Ex-situ Inhalation, mg/m³ systemic, long-term 0.026 systemic, acute 0.078 local, long-term 0.026 local, acute 0.078 Dermal, local, long-term 5E-4 mg/cm²	-
Nickel hydroxycarbonate	-	Inhalation, mg/m³ systemic, long-term 0.003-0.034* systemic, acute 0.01-0.203* local, long-term 0.003-0.034* local, acute 0.01-0.203* Dermal, local, long-term 0.076-0.76* µg/cm²	-	-	Inhalation, mg/m³ systemic, long-term 0.036 systemic, acute 0.11 local, long-term 0.036 local, acute 0.11 Dermal, local, long-term 1E-5 mg/cm²	Inhalation, mg/m³ systemic, long-term 0.003-0.034* systemic, acute 0.01-0.203* local, long-term 0.003-0.034* local, acute 0.01-0.203*

		*CLEANING/REMOVAL OF DUST (PROC 28)				Dermal, local, long-term 0.076-0.76 µg/cm² *CLEANING/REMOVAL OF DUST (PROC 28)

Welding

Welding is the method typically used to join two or more metal parts using heat. The heat causes the metals (or some other material) to melt and, after cooling, to create a strong connection between the metal parts. Welding generates fumes that are essentially a mixture of metallic oxides (including nickel), fluorides, and silicates. Therefore welding has the potential to expose workers to welding fumes containing nickel (estimated at 800,000 full time welders worldwide (NIOSH 2002).

There are many types of welding and all the conventional welding processes can be used to weld nickel and its alloys, and matching welding consumables are available. The one to be used depends upon the metal substrates, the application, and a variety of other variables. Some of the most commonly used welding methods are described below, and related to potential nickel exposure (by Kendzia et al 2017 in the exposure section, Table 11) as extracted from the German exposure database MEGA:

- Gas Metal Arc Welding (GMAW) is an automatic welding process. The application utilises a welding gun that automatically feeds the weld metal through the gun for use. The gun also distributes a shield gas for protection from the natural elements. Used widely in automobile repair and manufacturing, the process is suitable for fusing mild and stainless steel. Another name for it is MIG (Metal Inert Gas) Welding.
- Flux-Cored Arc Welding (FCAW) is a process where a special tubular wire filled with flux is used and shielding gas is not always needed, depending on the filler. This type of welding is well-known for being extremely inexpensive and easy to learn. Flux-cored is often used in automatic, fast-speed applications, and applied most often in construction environments.
- Tungsten Inert Gas Welding (TIG) is very similar to MIG Welding (see GMAW). The main difference is that TIG uses a tungsten current form while MIG uses a metal electrode. TIG, therefore, requires a filler since the tungsten does not melt. It is used predominantly on stainless steel.
- Shielded metal arc welding (SMAW), also known as “stick welding” is popular due to low costs. It is a process that uses a consumable electrode covered with a flux to lay the weld. An electric current, in the form of either alternating current or direct current from a welding power supply, is used to form an electric arc between the electrode and the metals to be joined, creating an “arc”.
- Autogenous welding is a process that coalesces two or more metals without the addition of filler metal. Autogenous welding can be performed on many different joint types. A wide variety of materials and welding processes can be used for autogenous welding.
- Laser welding is a technique whereby two or more pieces of material (usually metal) are joined by together through use of a laser beam. It is a non-contact process that requires access to the weld zone from one side of the parts being welded. The weld is formed as the intense laser light rapidly heats the material.
- Submerged arc welding (SAW) is a process requiring a continuously fed consumable solid or tubular (metal cored) electrode. The molten weld and the arc zone are protected from atmospheric contamination by being "submerged" under a blanket of granular fusible flux consisting of lime, silica, manganese oxide, calcium fluoride, and other compounds. When molten, the flux becomes conductive, and provides a current path between the electrode and the work. This thick layer of flux completely covers the molten metal thus preventing spatter and sparks as well as suppressing the intense ultraviolet radiation and fumes that are a part of the shielded metal arc welding (SMAW) process.
- Plasma arc welding (PAW) is an arc welding process where an electric arc is formed between an electrode (which is usually but not always made of sintered tungsten) and

the workpiece. The electrode is positioned within the body of the torch and the plasma arc can be separated from the shielding gas envelope. The plasma is then forced through a fine-bore copper nozzle which constricts the arc and the plasma exits the orifice at high velocities (approaching the speed of sound) and a temperature approaching 28,000°C or higher.

- Resistance welding is a welding technology widely used in manufacturing industry for joining metal sheets and components. The weld is made by conducting a strong current through the metal combination to heat up and finally melt the metals at localised point(s) predetermined by the design of the electrodes and/or the workpieces to be welded. A force is always applied before, during and after the application of current to confine the contact area at the weld interfaces and, in some applications, to forge the workpieces.

There are also other techniques or variations on the already described processes.

5.3 Occupational exposure

5.3.1 Occupational exposure across all the main uses and production of nickel and nickel compounds

Exposure concentrations obtained from six industrial site studies (entries 2, 5, 6, 7, and 8), two professional worker studies (entries 3 and 4) and one simulation (entry 1) study are presented in Table 11.

Table 11: Inhalation and dermal exposure concentrations and biomonitoring data obtained from the literature

No.	Reference	Test substance	Industry	Exposure concentration	Exposure route	Comment
1	Bertram et al 2014	Nickel metal	Welding (study, not actual activity monitoring) Reported data/information ambiguous	1) Real-time challenge welding fume particle mass conc. 2.5 mg m^{-3}, measured via direct reading instrument {Tapered Element Oscillating Microbalance (TEOM Series 1400a)} Laboratory study where airborne challenge conc. designed to be <3 mg m^{-3}, the German OEL for respirable fumes. 2) Possible 36 static samples (or less) taken, Size fraction not reported, Mean airborne conc. 0.029 mg(Ni) m^{-3}, Range 0.025-0.035 mg(Ni) m^{-3}, Exposure duration ~6 hour	Inhalation (12 healthy males exposed to welding fumes for 6 h)	Mean Ni levels in urine after exposure = 1.65 (SD=1.28), not significant difference
2	Day et al 2009	Nickel metal (dust)	Cemented tungsten carbide production (3 facilities in US)	GM Ni levels measured by skin wipe samples for half a shift:- 1)Forming/machining- 30 neck wipe samples, GM 0.7µg(Ni, neck); 30 hand wipe samples GM 0.7µg(Ni, hands) 2)Powder handling- 15 neck wipe samples, GM 6 µg(Ni, neck) ; 15 hand wipe samples, GM 24 µg(Ni), hands)	Dermal	GM Ni levels measured by surface wipe samples:- 1)Forming/machining-36 samples, 11 µg(Ni)/100 cm^2 2)Powder handling- 48 samples, 51 µg(Ni)/100 cm^2 3)Metal separation- 73 samples 20 µg(Ni)/100 cm^2

				3)Metal separation- 12 neck wipe samples, GM 4 µg(Ni, neck); 12 hand wipe samples, GM 20 µg(Ni, hands) 4) Range 0.2-49 µg(Ni, neck) & 0.3-80 µg(Ni, hands)		4) Range 1.1-185 µg(Ni)/100 cm^2
3	Hughson et al 2009	Nickel (various insoluble and soluble species)	Various (3 nickel refineries, a stainless steel plant and a powder metallurgy plant) (Europe)	1)1547 (soluble & total Ni) dermal skin wipe samples taken (205 <LOD);- GM Stainless Steel Pl 0.11 (total Ni, hands&foreams) ug/cm^2, GSD 2.7; 0.02 (sol Ni, hands&foreams) ug/cm^2, GSD 1.8. GM Recovery (EW/El) 0.56 (total Ni, hands&foreams) ug/cm^2, GSD 2.5; 0.34 (sol Ni, hands&foreams)ug/cm^2, GSD 2.2. GM Ni comp powder packers 1.17 (total Ni, hands&foreams) ug/cm^2, GSD 4.0; 0.61 (sol Ni, hands&foreams)ug/cm^2, GSD 3.0 GM powder metallurgy 1.69 (total Ni, hands&foreams) ug/cm^2, GSD 5.2; 0.08 (sol Ni, hands&foreams) ug/cm^2), GSD 3.4. GM Ni powder packers 8.73 (total Ni, hands&foreams) ug/cm^2, GSD 1.8; 2.59 (sol Ni, hands&foreams)ug/cm^2), GSD 1.6.	Inhalation, dermal	Overall, dermal exposures were relatively low, but variation due to inconsistent use of personal protective equipment, varying working practices, and different standards of automation and engineering controls within each exposure category. Dermal exposure measurements to neck, face and chest also reported

				2) 62 (67) personal inhalable samples taken with IOM inhalable head & 25 mm quarts fibre filter GM Stainless Steel Pl 3.9 (inhal dust) mg m^{-3}, GSD 2.1; 0.03 (Ni) mg m^{-3}, GSD 2.3. GM Recovery (EW/El) 0.9 (total inhal dust) mg m^{-3}, GSD 1.5; 0.04 (Ni) mg m^{-3}, GSD 3.0. GM Ni comp powder packers 0.5 (total inhal dust) mg m^{-3}, GSD 2.8; 0.02 (Ni) mg m^{-3}, GSD 2.6. GM powder metallurgy 1.0 (l inhal dust) mg m^{-3}, GSD 1.8; 0.05 (Ni) mg m^{-3}, GSD 3.9. GM Ni powder packers 1.7 (inhal dust) mg m^{-3}, GSD 2.3; 0.77 (Ni) mg m^{-3}, GSD 3.0.		
4	Jeyamala et al 2012	Nickel metal	Electroplating (India) Reported data/information ambiguous and some data does not appear in tables as referenced in text.	23 blood samples analysed Max Ni for ‘exposed group’ 89.13 (Ni, whole blood) ppm Highest Ni level for ‘workers’ 24.6 (Ni, perhaps blood serum?) ppm Highest/average? level Ni in hair 274.95 (Ni) ppm. Bioaccumulation of Ni (ppm) show highest Ni conc. in hair (258.5 ppm)	inhalation, ingestion, or skin contact	Levels of other blood parameters were recorded for comparison between the controls and the ‘workers’.

				and blood (18.9 ppm) for oldest workers (45-50 years)		
5	Sivulka & Seilkop 2009	Nickel-various	Nickel alloy industry (US) Retrospective study looking at exposures of occupation cohorts used in epidemiological studies to assess cancer risk	Carcinogenicity-based OEL for ‘‘total” insoluble nickel in the nickel alloy industry of 0.5 mg Ni m^{-3} (or possibly higher), as roughly equivalent to 1 mg Ni m^{-3} inhalable insoluble nickel. One estimated value of a value of 0.67 mg Ni/m^3 as average cohort wide exposure for 20 years around 1970s	Inhalation	Reconstruction of historical doses in the US nickel alloy industry using impinger and gravimetric exposure measurements and derived conversion factors.
6	Yokota et al 2007	Nickel hydroxide	Battery plant (Japan)	1) 32 personal inhalation samples; Mean personal inhalation TWA exposure concentration 0.481 mg (Ni) m^{-3}. Range 0.018-2.376 mg (Ni) m^{-3}. Aerosol fraction not specified, probably inhalable fraction (13mm Swinnex filter holder, Teflon binder filter medium, flow rate 200 ml min^{-1}) Sampling duration ~ 9hr (shift 12 hrs)	Inhalation & urine	No statistical difference between pre- and post- shift urine samples AM 1st day pre-shift 17.5 µg L^{-1}, range 5.0-39.0 µg L^{-1} AM 1st day post-shift 21.5 µgL^{-1} SD=17.4, range 5.0-67.5 µg L^{-1} AM 2nd day pre-shift 20.1 µg L^{-1} range 6.3-39.4 µg L^{-1} AM 2nd day post-shift 20.9 µgL^{-1} SD=16.7, range 4.7-52.9 µg L^{-1}

7	Kendzia et al 2017	Nickel metal	Various industries (Germany)	Median of all Ni concentrations was 9 µg/m^3 and the 95th percentile was 460 µg/m^3.	Inhalation	

Five papers reported on occupational Ni exposure during industrial production and use (2009-2012) and one paper reported on a welding simulation study (2015).

One study (Yokota et al 2007) monitored (Ni and Co) inhalation exposures and urinary (Ni and Co) levels during $Ni(OH)_2$, cobalt oxyhydroxide (CoO(OH) and Co metal use in electrode manufacture in a Japanese battery plant. The workers were making anode plates and undertook mixing, filling, drying, rolling and board processing tasks. The study aimed to establish if there was a correlation between airborne Ni concentration levels and those in urine. Thirty valid inhalation samples were collected from sixteen workers, sampled for at least 9 hours (two samples were void). The study aimed to establish if there was a correlation between airborne Ni concentration levels and those in urine. Thirty valid personal inhalation samples were collected from sixteen workers, sampled for at least 9 hours (two samples were void). The sampling seems to have been conducted over the two shifts per day, for half a week (assumed 3-4 days). Sixty-four urine samples were collected. The personal Ni inhalation exposures ranged from 0.018 to 2.376 mg (Ni) m^{-3} and the mean time weighted average (TWA) personal Ni exposure concentration was 0.481 mg (Ni) m^{-3}. Pre and post shift Ni in urine concentrations were 17.5 µg L^{-1} (range 5.0-39.0 µg L^{-1}) and 21.5 µg L^{-1} (range 5.0-67.5 µg L^{-1}) for the first day of sampling and 20.1 µg L^{-1} (range 6.3-39.4 µg L^{-1}) and 20.9 µg L^{-1} (range 4.7-52.9 µg L^{-1}) for the second day of sampling. There was no statistically significant difference in the pre- and post-shift Ni levels in urine and no correlation was observed between external (inhalation) and internal (urine) Ni exposures.

A retrospective study (Sivulka et al 2009) re-examined considerable historical and some more recent data from the Ni alloy industry in the USA to reconstructed historical exposures. A mean of 0.67 mg (Ni) m^{-3} was considered the conservative ‘‘best estimate” of the average across 6 production processing and 2 non-production processing work areas from back extrapolation.

In Europe, dermal (as 1547 individual and 67 sets of hands and forearms) and inhalation (62 individual) samples were collected at 5 industrial sites (Hughson et al 2010). The air sample concentrations were expressed as total inhalable dust, then through detailed chemical analyses were speciated as soluble, sulfidic, metallic and oxidic nickel personal exposure concentrations. The Ni exposures, expressed as the geometric mean, of nickel refinery workers involved with electrolytic Ni recovery processes had the highest soluble dermal Ni exposure (expressed as the geometric mean) of 0.34 µg cm^{-2}. Refinery workers involved in packing nickel metal powders (and end-user powder operatives in magnet production) had the highest soluble Ni dermal exposure of 2.59 mg cm^{-2}. The hands, forearms, face, and neck of these workers all received greater dermal nickel exposure compared with the other jobs included in this study. The highest inhalation soluble Ni exposure (geometric mean of 0.04 mg (total Ni) m^{-3} and containing 82% soluble nickel) was also recorded for this operation. The soluble Ni dermal exposures for stainless steel production workers were at or slightly above the limit of detection (0.02 mg cm^{-2}). The highest inhalable Ni concentrations, expressed as the geometric mean, were observed for the workers involved in Ni powder packing (0.77 mg m^{-3} containing 2% soluble Ni). The geometric mean of the soluble dermal Ni exposure for workers involved in packing nickel salts (nickel chloride hexahydrate, $NiCl_2 6H_2O$, $NiSO_4 6H_2O$, and NiHydCarb) was 0.61 mg cm^{-2}, although the soluble component comprised only 2% of the total nickel content. The stainless steel workers were exposed to low concentrations of relatively insoluble airborne nickel species (geometric mean concentration of 0.03 mg (total Ni) m^{-3}, containing 1% soluble nickel). Dermal exposures to nickel, nickel compounds, and nickel alloys were relatively low. A statistically significant correlation was observed between dermal exposures for all anatomical areas across all tasks and for the dermal and inhalable (total) nickel exposures. Inconsistent use of personal protective equipment, varying working practices, and different levels of automation and control contributed to variable exposures. The summary inhalation results for inhalable dust, total nickel, soluble, sulphidic, metallic and oxidic species are presented in Tables 11 and 12.

Table 12: Summary of inhalable dust and nickel exposure for primary nickel production and primary user sites (Hughson et al 2010)

Industry/task	N	Inhalable dust (mg m^{-3})				Total nickel (mg m^{-3})			
		Median	GM	GSD	Range	Median	GM	GSD	Range
Front-end refinery	6	1.2	1.4	1.9	0.8-3.5	0.16	0.13	2.3	0.05-0.40
Electro-winning/electrolysis	12	0.8	0.9	1.5	0.4-1.7	0.04	0.04	3.0	0.01-0.18
Packing nickel metal products	7	0.8	0.8	1.2	0.6-1.2	0.10	0.08	3.3	0.01-0.34
Packing nickel compounds	12	0.4	0.5	2.8	0.1-5.9	0.02	0.02	2.6	0.01-0.10
Packing nickel powders	7	1.6	1.7	2.3	0.5-5.0	0.81	0.77	3.0	0.13-2.81
Powder metallurgy (magnet production)	8	1.0	1.0	1.8	0.4-2.6	0.03	0.05	3.9	0.01-0.36
Stainless steel production	10	4.7	3.9	2.1	1.2-11.6	0.04	0.03	2.3	0.01-0.12

Table 13: Airborne nickel species by process area (Hughson et al 2010)

Process/task	N	Airborne nickel species (percentage of total nickel content) GM (and GSD) values			
		Soluble	Sulfidic	Metallic	Oxidic
Front-end refinery process	6	25 (1.6)	44 (1.5)	3 (6.8)	13 (3.1)
Electro-winning/electrolysis	12	82 (1.5)	1 (8.7)	<1 (6.3)	1 (9.5)
Packing nickel products	7	21 (1.5)	1 (7.0)	30 (1.2)	31 (1.4)
Packing nickel compounds	12	76 (1.3)	2 (12)	<1 (1.0)	3 (12)
Packing nickel powders	7	2 (2.3)	1 (2.1)	33 (1.5)	60 (1.3)
Powder metallurgy (magnet production)	8	1 (10)	3 (6.3)	42 (2.1)	35 (1.4)
Stainless steel production	10	1 (10)	1 (8.8)	<1 (7.2)	89 (1.1)

Another study (Day et al 2009) reported on dermal and surface sampling during the production of Ni- and Cr-containing Co/tungsten carbide alloys known as cemented tungsten carbides (CTC). Monitoring of Co, Cr and Ni was carried out for 2 days at 3 separate production plants (metal separation, powder handling and forming/machining). Two hundred and twenty-eight dermal wipe samples were collected from 57 workers' necks (114 samples) and hands (114 samples). Each worker was sampled 4 times during the shift. A summary of the dermal monitoring results are presented in Table 14 as the geometric mean (and geometric standard deviation) of the measurements results. The highest level of Ni on the hands was measured for powder handling workers (24 µg). This results were significantly greater than the highest level measured recorded for forming/machining workers (7 µg), but not significantly different from that for metal separation workers' hands (20 µg). The assumed highest levels of nickel on workers' necks for forming/machining (0.7 µg) were significantly lower than that for powder handling (6 µg) and metal separation (4 µg).

Table 14: Ni masses on neck and hands by plant and work area (Day et al 2009)

Plant	Work area	N	Nickel mass (µg) on neck		Nickel mass (µg) on hands	
			GM	GSD	GM	GSD
Metal separation	Metal separation	2	137	3.5	98	4.6
	Reclamation A	2	7.4	1.2	14	2.3
	Reclamation B	2	2.6	1.7	11	4.2
	Carbide	2	0.4	4.1	5.2	4.9
	Maintenance	2	37	2.7	488	4.4
	Administration	2	0.2	1.0	1.7	1.3
Powder handling	Inventory control	2	1.4	1.5	13	1.2
	Powder mixing	3	7.2	3.7	21	3.9
	Milling	2	6.3	1.1	64	3.4
	Spray drying	2	16	4.7	29	1.5
	Screening	2	4.4	7.2	29	4.6
	Shipping (powder)	2	8.4	1.5	17	1.3
	Maintenance (powder)	2	3.7	3.6	17	4.6
Forming/ machining	Production control	2	1.1	1.5	141	1.4
	Pressing	4	0.4	2.8	2.4	1.4
	Extrusion	2	0.3	2.3	2.2	1.3
	Shaping	4	0.6	3.6	6.6	9.8
	Breakdown	2	1.3	1.9	5.6	1.1
	Grinding	6	0.5	1.8	7.6	1.8
	Sandblasting	2	0.4	1.2	1.6	1.4
	Shipping (product)	2	0.6	1.3	31	1.1
	Maintenance	2	2.7	1.9	11	3.0
	Tray preparation	2	0.9	1.9	4.9	1.0
	Administration	2	1.2	2.8	6.0	1.4

Jeyamala et al report (2012) on the Ni content of blood, blood glucose, serum creatinine, haemoglobin and hair for 23 electroplating workers and 7 controls in India. Personal (height, age, weight and health status) and work history data was collected. The authors reported a maximum blood Ni of 89.13 ppm for electroplaters and below the limit of detection levels for the control group. Most workers were reported as having Ni in blood levels higher than that of the background (0.027 ppm). It is also reported that 30% of the workers had background levels greater than 50 ppm. The tabulated Ni bioaccumulation data (by 7 worker age groups) reports 18.9 ppm as the highest blood Ni level for the oldest (45-50 years of age) workers.

In a simulation study (Bertram et al 2014), urine samples were collected from 12 non-welders who were exposed to an airborne concentration of 2.5 mg m^{-3} welding fumes during 6 hours of manual metal arc welding of low alloyed steel (< 0.1% Ni); manual metal arc welding of high alloyed steel (10% Ni) and 'filtered' air (zero emission) in a threefold crossover study. These samples (before and after exposure) were analysed for Ni and Cr content. Of the 72 urine samples, 11 had a Ni content below LOD. Mean Ni in urine concentrations (expressed as the difference between pre and post exposure) for filtered air; low alloyed steel and high alloyed steel were obtained as 0.20 µg L^{-1}, 0.03 µg L^{-1} µg L^{-1} and 0.35 µg L^{-1} respectively. Ni levels were not observed to increase above background levels or have any dependence on the three situations (manual metal arc welding or filtered air atmospheres).

Occupational exposure across a number of nickel uses in Germany

Kendzia et al (2017) aimed to estimate average occupational exposure to inhalable nickel (Ni) with an emphasis on welding, using the German exposure database MEGA. This database contains 8052 personal measurements of nickel collected between 1990 and 2009 in conjunction with information on the measurement and workplace conditions. It was found that exposure to nickel in welders is strongly influenced by the welding process applied and the nickel content of the used welding materials. Welding with consumable electrodes of high Ni content (>30%) was associated with 10-fold higher concentrations compared with those with a low content (<5%). Nearly every other concentration of inhalable nickel was above the proposed OEL of 10 µg/m^3 of SCOEL, and welding techniques such as GMAW can hardly comply with it (compliance was only observed when the nickel content of welding material was <5%).

The highest exposure levels (geometric mean ≥ 20µg/m^3) were observed in gas metal and shielded metal arc welders using welding materials with high nickel content, in metal sprayers (33 µg/m^3), grinders (24 µg/m^3) and forging-press operators (25 µg/m^3), and in the manufacture of batteries (27 µg/m^3) and accumulators (23 µg/m^3).

Table 15: Model-based estimates of the geometric means of occupational exposure to inhalable nickel predicted for the year 1999 with adjustment for sampling time (MEGA database, 1990–2009) (Kendzia et al 2017)

Welder Occupation	Ni content of welded material %	Number of measurements	Geometric Mean (µg/m³) (adjusted for 2h sampling time)
GMAW		1159	13
	<5	156	5
	5-30	405	25
	>30	56	48
FCAW		93	7
	<5	11	3
	5-30	16	12
	>30	0	-
TIG		799	3
	<5	18	1
	5-30	430	5
	>30	21	10
SMAW		479	10
	<5	34	4
	5-30	140	19
	>30	22	37
Autogenous welding		20	6
Lase welding		35	2
Submerged arc welding		26	2
Plasma arc welding		64	9
Resistance welding		12	1
Others/not specified		368	14

NiPERA review of nickel exposure in various industries

The Nickel Institute has identified a wide range of occupations with direct exposure to nickel and they can be summarised within 13 different industrial sectors (NiPERA 2008):

- refining, main part of the refining processes;
- last stage refining, handling of primary nickel;
- alloy production, melting and foundry techniques;
- alloy production, powder metallurgy;
- batteries, nickel metal as feedstock;
- batteries, unknown type of nickel species as feedstock;
- nickel catalysts, nickel metal as feedstock;
- nickel catalyst, unknown type of nickel species as feedstock;
- nickel in the production of chemicals;
- contact with coins;
- contact with tools and other nickel releasing surfaces;
- use of batteries; and
- use of catalysts.

The first two sectors correspond to the nickel- producing industry, while the rest belong to the nickel-using industry. The table below reports exposures in these sectors. Unfortunately there are no literature references to indicate where the exposure

concentrations have come from but the information in the table would benefit from closer examination.

Table 16: Table extracted from NI's Safe Use of Nickel in the Workplace showing exposures by industrial sector (NiPERA 2008[10])

Table 3-1:	Estimated Inhalation and Dermal Exposure to Nickel Species in Nickel-Producing and -Using Industries													
Industry Sector	Time scale of exposure		Estimated exposure to inhalable nickel (mg/m³)									Dermal exposure (mg/day)			
	Duration (hr/day)	Frequency (day/year)	Full shift (8 hour time weighted average)						Short-term			Typical		Worst-case	
			Typical level		Method	Worst-case level		Method	Level		Method				
Refining, main part of the refining processes	6-8	200	0.004 0.0064 0.003 0.065	M[1] SO SU O	Meas.[3]	1.1 0.33 0.55 9	M SO SU O	Meas.	2.2 0.65 1.1 18	M SO SU O	Exp.[4]	0.4[3] 0.6[3]	U SO	2.0[3] 1.8[3]	U SO
Last stage Refining, handling of primary nickel	6-8	200	0.06 0.006	M SO	Meas.	6.0	M	Meas.	12	M	Exp.	13[3] 5.1[3]	U SO	22[3] 8.7[3]	U SO
Alloy production, melting and foundry techniques	6-8	200	0.012 0.0012 ~0 0.045	M SO SU O	Meas.	7 0.28 ~0 7	M SO SU O	Meas.	14 0.6 ~0 14	M SO SU O	Exp.	1.8[6] 0.4[6]	U SO	16[6] 1.8[6]	U SO
Alloy production, powder metallurgy; the powder was considered to be all metallic nickel	6-8	200	0.5	M	Meas.	2.1	M	Meas.	4.2	M	Exp.	13[7] 5.1[7]	U SO	22[7] 8.7[7]	U SO
Batteries, nickel metal as feedstock	6-8	200	0.3	M	Meas.	2.7	M	Meas.	5.4	M	Exp.	13[7] 5.1[7]	U SO	22[7] 8.7[7]	U SO
Batteries, unknown type of nickel species as feedstock	6-8	200	0.02	T	Meas.	0.3	T	Meas.	0.6	T	Exp.	13[7] 5.1[7]	U SO	22[7] 8.7[7]	U SO
Nickel catalysts, nickel metal as feedstock	6-8	200	0.06[5]	M	Meas.	5.0[5]	M	Meas.	10[5]	M	Exp.	13[7] 5.1[7]	U SO	22[7] 8.7[7]	U SO
Nickel catalyst, unknown type of nickel species as feedstock	6-8	200	0.09[5]	T2	Meas.	1.2[5]	T[2]	Meas.	2.4[5]	T[2]	Meas.	13[7] 5.1[7]	U SO	22[7] 8.7[7]	U SO
Nickel in the production of chemicals	6-8	200	0.006- 0.45[9]	T	Meas.	7.0[5]	T	Meas.	14[5]	T	Exp.	13[7] 5.1[7]	U SO	22[7] 8.7[7]	U SO
Contact with coins	6-8	200	0.001	M	Meas.	0.018	M	Meas.	0.036	M	Exp.	0.04[8]	M	0.12[8]	M
Contact with tools and other nickel releasing surfaces	6-8	200	~0	M	Exp.	~0	M	Exp.	~0	M	Exp.	0.04[8]	M	0.12[8]	M
Use of batteries	6-8	200	~0	M	Exp.	~0	M	Exp.	~0	M	Exp.	~0	M	~0	M
Use of catalysts	6-8	200	~0	M	Exp.	~0	M	Exp.	~0	M	Exp.	~0	M	~0	M

1: M = Metallic nickel; O = Oxidic nickel; SO = Soluble nickel; SU = Sulphidic nickel; T = The predominant nickel species include metallic nickel, oxidic nickel, and soluble nickel salts; U = Other nickel species than soluble nickel. 2: Exposure to sulphidic nickel cannot be excluded. 3: The estimate was derived from measured data. 4: "Expert judgement". 5: The values may be overestimates. 6: The mass of material deposited on the skin was estimated by analogy to dermal exposure measured for cathode cutting and briquette packing operators 7: Estimated by analogy to measured data for nickel powder packing operators. 8: The estimate is for both hands (surface area 840 cm2). 9: Range of estimated typical exposure levels.

The paper argues that it is clear from the table that the range of exposures in any given industry sector can vary widely. It is also clear that the data was acquired over a large time period and from a variety of sources. Workers employed in some jobs and activities in a sector with generally low exposures could well be exposed for days, weeks, or even

[10] Nipera (2008) provides the following clarification for the table, i.e that it is built on data– generally acquired over the past 10 to 20 years, but occasionally representing data recorded since the late 1970s–typically represent actual measurements derived from standard procedures of 'total' aerosol sampling (e.g. through methods developed by the UK's Health and Safety Executive or the US' National Institute of Occupational Safety and Health). The data for this table come from a variety of sources including: a) published, peer-reviewed literature, b) company or agency reports in general circulation, c) company or agency internal reports not in general circulation but accessible through those organizations, d) company or agency databases and log-books obtainable through direct personal contacts, and e) follow-up through direct personal contacts (where appropriate and feasible) to fill gaps in information relevant to the evaluation.

years to levels of nickel aerosols well above those of some workers employed in another sector which experiences generally high exposures.

While it is clear that certain forms of nickel tend to predominate in different industry sectors (e.g., soluble nickel in plating), it appears that in no industry sector are workers exposed purely to one form of nickel.

5.3.2 Considerations on particulate matter in order to establish size selective OEL values

Traditionally when measuring airborne particles, the 37 mm sampler was used to measure the “total dust” in the US and some European countries.

However, in 1993 the International/ European Standard 481 was published. The standard provides definitions of the inhalable, thoracic and respirable size fractions, and target specifications (conventions) for sampling instruments to measure these fractions.

After the publication of the standard, the 37 mm sampler (and other samplers available in the market) were tested to determine their performance (both in laboratory or field conditions) and those indicated that the 37 mm undersampled the bigger particles. This means that a “correction factor” is needed to fit the inhalable fraction. Many studies compared the results of the 37 mm sampler with those from a sampler fitting the inhalable convention. The factor is different for different type of dust as it depends on the particle size distribution the aerosol (in practice depends the chemical sampled and the process). This is a correction that has been taken into account in other cases like the wood dust in SCOEL.

A number of publications compare the results of concentration of airborne nickel in different processes measured with the IOM sampler and the 37 mm. The results seems to justify a correction factor of 2 for epidemiological studies where the 37 mm sampler was used (see Chpter 7.7.1). This need of correction is compatible with the measurements of particle size distribution in nickel workplaces showing a significant amount of particles being in the coarser fraction.

5.4 Routes of exposure and uptake

5.4.1 Worker exposure

The primary route of exposure for the worker population is by dermal contact or by inhalation of aerosols, dusts, fumes, or mists containing nickel. Dermal contact may also occur with nickel solutions, such as those used in electroplating, nickel salts, and nickel metal or alloys. Nickel-containing dust may be ingested where poor work practices exist or where poor personal hygiene is practiced.

5.4.2 General population

The main routes of exposure to nickel for humans are inhalation, ingestion and absorption dermal.

It has been reported (ATSDR 2005) that the general population is exposed to low levels of nickel in ambient air, water, and food. Exposure also occurs from smoking. However, the general population takes in most nickel through food. The average daily dietary nickel intake for U.S. diets is 69–162 µg (NAS 2002; O’Rourke et al. 1999; Pennington and Jones 1987; Thomas et al. 1999). These values agree with those from European studies. Typical average daily intakes of nickel from drinking water and inhalation of air are approximately 8 and 0.04 µg, respectively.

The CONTAM Panel (EFSA 2015) concluded that the exposure via the diet is likely to represent the most important contribution to the overall exposure to nickel in the general population. Both for smokers and non-smokers not occupationally exposed to nickel, exposure by inhalation may be expected in general to represent a negligible or minor addition to the daily exposure via the diet.

It has also been reported (ATSDR 2005) that the highest general population exposures to nickel are typically observed in communities surrounding nickel refineries. This is reflected, for example, in the intakes of nickel from water and air reported in Sudbury, Ontario, Canada, of 140 and 15 µg/day, respectively. Other potential sources of nickel exposure are from contaminated intravenous fluids, dialysis, and leaching and corrosion of nickel from prostheses.

6. Monitoring Exposure

6.1 External exposure

The principle of most of the methods is trapping the sample on a suitable filter by using a particle sampler (for inhalable or respirable fraction). The nickel compounds are then extracted with different solutions depending on what are the compound(s) of interest and further analysed using a suitable technique (e.g. atomic absorption). Only exception is the method based on X-ray fluorescence where there is no extraction step before the analysis. The LOQ is given as mass of nickel. The scope of the methods explains what type of nickel compounds (organic, inorganic, all compounds etc) are targeted by the method, but normally modification in the sample preparation (extraction step(s)) will allow determination of the nickel compounds of interest.

The table states whether the method includes sampling of inhalable, respirable fraction or both as reflected in the sample and analysis methods. When a specific particulate sampler (and its associated flow rate) has been recommended, the calculations of the sampling time have used the maximum flowrate recommended by the method. However, the latter does not exclude that the methods have the potential to use other sampler at different flowrates that may allow to achieve lower LOQ or to collect a different aerosol fraction. The methods appearing under “similar methods” have a similar methods principle and analytical technique and may differ in the sample preparation or in details such as the filter, or the sampler used.

The methods included in this table have validation data that show compliance with the requirements of the standard EN 482 “Workplace exposure. General requirements for the performance of procedures for the measurement of chemical agents” or potential to met these requirements for the proposed OEL Validation data can be consulted in the “methods sheets” provided by the Gestis – Analytical methods database available at: (http://www.dguv.de/ifa/gestis/gestis-analysenverfahren-fuer-chemische-stoffe/index-2.jsp) and or in the actual analytical method.

Table 17: Methods for nickel and nickel compounds in air

METHOD / Fraction	Analytical technique	LOQ and sampling volume ad time	Similar methods / comments
ISO 15202 (Parts 1, 2 and 3) [1,2,3] (Inhalable or respirable fraction)	ICP-AES (Inductively coupled plasma atomic emission spectroscopy)	0.00045 mg/m^3 for a 1200 l sample (2 hours)[1]	NIOSH 7300, NIOSH 7301, NIOSH 7303, OSHA ID-125G, OSHA ID-206
MDHS 42/2[2] (Inhalable fraction)	ETAAS (Electrothermal Atomic Absorption Spectrometry)	0.00006 mg/m3 for a 480 l sample (less than 3 hours) Flow rate: 2 l/min	A sampler for the respirable fraction could be used if required
	FAAS (Flame Atomic Absorption Spectroscopy)	0.001 mg/m3 for 480 l sample (less than 3 hours) Flow rate: 2 l/min	
MDHS 91 (Inhalable fraction)	X-ray fluorescence spectrometry	0.003 mg/m3 for a 60 l sample (30 min sample) 0.0004 mg/m3 for 480 l/ sample Flow rate: 2 l/min	A sampler for the respirable fraction could be used if required
DGUV-I 213-510 (Inhalable or respirable fraction)	GFAAS	0.00047 mg/m3 for a 1200 l sample (2 hours)[1]	
OSHA ID- 212 Inhalable fraction (sampler not completely fitting the standard)		0.0052 mg/m3 for a 480 l sample (4 hours) Flow rate: 2 l/min	The sampler is not an inhalable sampler. (A sampler fitting the EN 481 could be used instead) A sampler for the respirable fraction could be used if required

Notes:

(1) Sampling time calculated for the maximum flow of 10 l/min (maximum flow rate for common inhalable and respirable fraction samplers)

(2) Method not for nickel carbonyl

6.2 Biomonitoring of exposure (internal exposure)

Several biomarkers for exposure to nickel have been studied. These include concentration of nickel in urine and blood (whole blood, plasma or serum). Normally the specimen chosen is urine, due to various reasons: less invasive or stressful for the person, the concentrations in urine being higher than those in blood (ratio 8:1) and the analytical methods for nickel in urine being more sensitive at the moment (DFG 1995, 2010a,

2010b). Furthermore, the databases containing values of nickel exposure and nickel levels in urine are very extensive (DFG 1995).

6.2.1 Background levels of nickel

People are exposed to nickel and nickel substances present in the environment mainly via food, drinking water, soil, dust, and air.

Typical ambient air concentrations of nickel range from 0.03 ng Ni/m3 (North Sea remote site) to 21 ng Ni/m3 (industrially influenced site) (Working Group on As, Cd and Ni Compounds 2000).

In aquatic systems, such as in ambient or drinking water, nickel is usually present as the nickel cation (Ni^{2+}), together with other anions such as hydroxyl (OH^-), sulphate (SO_4^{2-}), chloride (Cl^-), carbonate (CO_3^{2-}), or nitrate (NO_3^-). Sources of nickel in ambient waters include chemical and physical degradation of rocks and soils, deposition of atmospheric nickel-containing particulate matter, and discharges from industrial processes. Reported ambient dissolved nickel concentrations for typical European freshwater systems range from 1 to 6 µg Ni/L (EU Risk Assessment Report Nickel 2008). Higher and lower concentrations may be encountered in waters with specific geological influences, but nickel concentrations for most freshwater systems will fall within this general range.

Nickel levels in soil vary between 5 and 500 µg Ni/g depending on geological factors (EU Risk Assessment Report Nickel 2008). The primary man-made source of nickel to soils is disposal of sewage sludge or application of sludge as a fertilizer. Secondary sources include industrial nickel production and use, and emissions from electric power utilities and automobiles.

Dietary intake is the most important exposure pathway for metals in the general population followed by consumption of drinking water (De Brouwere 2012).

Assuming that in urban areas the nickel concentrations in air are on average 20 ng/m^3, then the daily uptake of this metal by inhalation is considerably less than the oral uptake (DFG 1995).

Background concentrations for nickel in urine of a reference population of working age are usually below 1 µg/l and may reach 3 µg/l (Hartwig and Drexler 2010). The DFG proposed in 2009 a BAR (“biologischer Arbeitsstoff-Referenzwert) value of 3 µg nickel/l urine. Canada has also proposed references values (RV_{95}) for nickel: 1.1 µg nickel/l blood and 4.4 µg nickel/l urine (Saravanabhavan et al 2017). Other reviews on background nickel concentrations in urine in the general population show higher levels of urinary nickel (with RV_{95} ranging between 3 and 7,5 µg nickel/l urine) depending on the country (INVS 2010, Hoet et al, 2013).

Table 18 summarizes background concentrations of nickel/l urine in different countries and populations. The table shows a high variability for background levels of nickel in urine.

The P95 aims to describe the background level of a substance that is present concurrently at a particular time in a reference population of working age that are not occupationally exposed and is based on the 95th percentile.

Due to the high variability between populations of the levels of nickel in urine, it is proposed not to set a biological guidance value.

Table 18: Urinary concentrations of nickel in urine in non-occupationally exposed individuals from diverse geographic samples in Europe

Authors	Country(population)	n	Mean ± SD (µg Ni/L)	Range, P90/P95
Kiilunen et al. (1987)	Finland	299	4.1*	10 P95
Darsow et al. (2012)	Germany (Munich) - adult females	164	-	0.2 – 10.1; 3.9 P95
Kasper-Sonnenberg et al. (2011)	Germany – adult females	579	2.1	8.1 P95
Merzenich et al. (2001)	Germany (Bremen) - men	429	0.85*	2.5 P90
	Germany (Bremen) - women	164	1.03*	3.4 P90
Heitland and Koster (2006)	Germany – adults	87	0.3*	2.5 P95
Schwegler et al. (2009)	Germany – females	163	-	3.9 P95
Andersen et al. (1978)	Norway	15	2.3 ± 0.58	1.4 – 3.4; 3.4 P95
Smith-Sivertsen et al. (1998)	Norway-Sor-Varanger	902	0.9	0.3 – 11
	Norway-Tromso (control)	302	1.4	0.3 – 6
Nisse et al. (2017)	France	1992	2.00*	5.99 P95
Fréry et al. (2010)	France	1949	1.36*	4.54 P95
Hoet et al. (2013)	Belgium	1022	1.73*	4.73 P95
Minoia et al. (1990)	Italy	878	0.9	0.1 – 3.9; 1.74 P95
Chellini et al. (2017)	Italy (Arezzo) – industrial	153	3.85*	0.53-15.33
	Italy (Arezzo) – urban	92	4.75*	0.54-18.32
	Italy (Arezzo) – rural	55	2.71*	0.48-9.74
Stojanović et al. (2004)	Serbia – smokers	69	1.20 P50	<0.01-8.20
	Serbia – non-smokers	78	0.50 P50	<0.01-4.60

* Geometric mean

6.2.2 Occupational exposure

The levels of nickel in plasma and urine are highly dependent on the nickel compounds in air. Less soluble compounds, such as oxidic and sulphidic nickel, give relatively lower plasma and urine values than a corresponding level of soluble chlorides or sulphates (EFSA 2015). These differences are due to the different rate of absorption of the different nickel compounds. Readily soluble nickel compounds, such as nickel(II) chloride, are quickly absorbed and over 90% is excreted via the kidneys. The half-time of nickel elimination from the plasma and urine is 1–1.5 days, as was ascertained in the investigation of workers who were exposed to nickel in an electroplating works (DFG 1995). At workplaces where sparingly soluble nickel compounds are predominant (e.g. stainless steel welders, smelting

works), two phases are observed in elimination, which are quoted as having values between 30 and 50 hours and between 30 and 120 days. Possibly, however, the rapid elimination phase can be attributed to the fact that readily soluble compounds occur at such workplaces, which are excreted far more rapidly than sparingly soluble nickel compounds. (DFG 2010a).

6.2.2.1 Relationship between external and internal nickel exposures

Nickel and sparingly soluble nickel compounds

Table 19 below shows a summary of studies with external and internal nickel exposure at different workplaces. In all workplaces the exposure was to sparingly soluble nickel compounds. (DFG 1995)

Table 19: Summary of studies with external and internal nickel exposure at different workplaces (DFG 1995)

	Occupational	Test persons	Exposure concentration Air (µg/m³)			Urine (µg/l)			Plasma/serum (µg/l)			Authors
			Mean (range)	S	m	Mean (range)	S	m	Mean (range)	S	m	
1	Polishers of aeroplane parts	6M 1F	26 (0.05-129.0)	41	-	4.1 (0.5-9.5)	3.2	-				Bernacki et al., 1978
	Grinders (nickel alloys)	7M 2F	1.6 (0.02 –9.5)	3.0	-	5.4 (2.1 – 8.8)	2.4	–				
	Welders (MMA)	7M 3F	6.0 (0.2 –46.0)	14.3		6.3 (1.6 -14.0)	4.1	–				
	Aviation mechanics	4M 4F	52.0 (0.01 –252.0)	94.0	–	12.2 (1.4 41.0)	13.6	–				
	Flame sprayers	4M 1F	2.4 (0.04- 6.5)	2.6		17.2 (1.4-26.0)	9.8					
2	**Nickel refining**											
	Roasting, melting,	24	860.0	1200.0		65	58		7.2	2.8		Høgetveit et al., 1980
	Other areas	13	420.0	490.0		45	27		6.4	1.9		
3	**Nickel refining**											
	Insoluble nickel compounds			240			31.7					Høgetveit et al., 1980
4	Welders (high alloyed stainless steel; up to 34 % Ni) (MMA)	10M	(30.0-1780.0)	150	-	(7.8 - 26.5)	11.5 *	-	(0.58-2.9) (B)	1.2 (B)	-	Rahkonen et al., 1983
5	Nickel catalyst production	73	(<200.0–5870.0)		-	(9.0-300.0)	64					Zwennis and Franssen, 1983
6	Stainless steel welders (TIG)	10 M	(0.7-0.9)	-	2.3	(1.4-9.5)	-	4-6				Zober et al., 1984
7	**Smelting ores containing nickel**											
	Drying of nickel oxides	67	(10.0-5000)	310	-	24	24	-				Morgan and Rouge, 1984
	Drying of nickel oxides	37							8.9	5.9	-	
	Production of nickel powder	48	(90.0-1530)	310	-							

	Occupational	Test persons	Exposure concentration Air (µg/m³)			Urine (µg/l)			Plasma/serum (µg/l)			Authors
			Mean (range)	S	m	Mean (range)	S	m	Mean (range)	S	m	
	Production of nickel powder	25							7.2	4.8	-	
	Contact with Sparingly soluble nickel compounds	15 7	(220-4180)	1540		39	28	-	7.4	5.1	-	
8	Welding of high alloyed steel (75 % Ni)	11M	(70.0-1100)	440	-	(9.7-38.0)	18					Åkesson and Skerfing, 1985
9	Welders (stainless steel) (MMA)	41M	(95% <500)			(2.5-144.0)	-	23.8				Zober and Weltle, 1985
10	**Hollow glass industry-mould manufacturing +maintenance**											
	Mechanics	406	(18- 3800)			(2.9-24.3)	7.4	-				Zober and Weltle, 1985
	Mechanics	140							0.9 (0.75–2.05)			
	Powder flame sprayers	114	(3 -600)			(8.5-81.5)	25.3	-				
	Powder flame sprayers	40							(0.75-3.25)	1.95		
	Combined jobs	394	(300-410)			(0.75-3.25)	17.5					
	Combined jobs	108							(0.75-4.10)	1.65		
11	Stainless steel welders (MAG, MMA)	103M	93 (<50- 320)	81.4	60	18.5 (0.1-209.4)	28.5	10.2	4.9 (<1.8-19.6)	4.0	3.9	Angerer and Lehnert, 1990
	Stainless steel welders											
12	MMA	61	(7.4-52.7)*		24	(3.4-20.1)*		10.1	(0.4-3.2)*			Emmerling et al., 1989
	MAG	46	(22.1-238.7)*		68.6	(4.4-34.3)*		14.0	(0.7-2.8)*			
	TIG	16	(2.1-20.3)*		8	(1.8-15.4)*		5.7	(0.2-2.7)*			

Notes (to Table 19):

S: standard deviation
M: median
-: no data
M: male
F: female
MAG: metal active gas welding
MMA: manual metal arc welding
TIG: tungsten inert gas welding
* 68 %-range

Some of the correlation developed by the studies above were taken into account by DGV to develop exposure equivalents for nickel sparingly soluble compounds (See Table 20).

Table 20: Correlation between the concentration of sparingly soluble nickel compounds in the air of the workplace and the metal concentration in the body fluids c_U; c_A: nickel concentration in the urine and air (from DFG 1995)

Linear regression	n	r	References
c_U (µmol/l) = 0.08 + 0.8 c_A(mg/l)	10	0.95	Rahkonen et al., 1983
c_U (µg/g creatinine) = 13.5 + 0.05 c_A(µg/m^3)	22	0.52	Raithel, 1987
c_U (µg/l) = 10.84 + 0.007 c_A(µg/m^3)	174	0.52	Emmerling et al., 1989
c_U (µg/l) = 8.49 + 56.88 c_A(mg/m^3)		0.86	Sunderman et al, 1986b*according to data by Morgan and Rouge, 1984

* Correlation on the basis of groups exposed to different extents

Taking into account the equations above DFG developed exposure equivalents for sparingly soluble nickel compounds (see Table 21).

Table 21: Correlation between external and internal nickel exposure for nickel and sparingly soluble nickel compounds (DFG 1995)

Air Nickel (mg/m3)	Urine Nickel (µg/l)
0.1	15
0.3	30
0.5	45

Notes:

Sampling time: end of shift after several consecutive shifts plasma samples can be considered to confirm questionable results from urinary nickel

A more recent study among welders (Weiss et al 2013) measured external and internal exposure to chromium and nickel among welders. The median exposure was 3 µg/m^3 for the respirable fraction and 6 µg/m^3 for the inhalable with the higher median being for flux cored arc welding that resulted in 88 µg/m^3 and 123 µg/m^3 of for respirable and inhalable nickel respectively. At these concentration levels only half of the welders had concentration above the German reference value for nickel in urine (3 µg/L).

The authors compared their results with the correlations for sparingly soluble nickel compounds develop by the DFG (Table 21). The association found for nickel was overall consistent with the relation derived for metallic nickel and nickel compounds of low solubility. In the low-dose range, the association was weaker, and the slope faded to a horizontal shape below 10µg/m^3. This airborne concentration of 10 µg/m^3 was associated with nickel in urine of about 3µg/L, which corresponds to the German reference value (BAR). Values below that level are predominantly represented by mild-steel welders and are within the range observed in the general population.

This results together with the equations in Table 20 and correlations in Table 21 indicate that the use of a biological limit value for nickel in urine may not be feasible when setting an OEL around 10 µg/m^3 or lower as the levels in urine from workers may not be significantly different from those of the general population.

Soluble nickel compounds

The table below summarizes studies were air concentration of soluble nickel compounds were compared to nickel concentrations in air and plasma.

Table 22: Relationship between concentration of readily soluble nickel species in workplace air and nickel concentration in blood and urine of exposed persons (DFG 2010

Workplace	Exposed persons	Exposure in air (µg/m3)	Plasma/serum (µg/L)	Urine (µg/L)	References
		MV ± SD (Range)	MV ± SD (Range)	MV ± SD (Range)	
Electroplating	21M	not specified	not specified	27.5 ± 21.2 (3.6–65)	Bernacki et al. 1978
Electroplating	90M	0.23 ± 0.42	11.9 ± 8.0	129.2 ± 105.6	Høgetveit et al. 1978
Electroplating (NiSO4)	4M, 1F	(30–160)	1.2 (< DL-1.7)	6.6 (3–10)	Tola et al. 1979
Electroplating	66M (personal air sampling), 68M (measurement in the urine)	0.5 ± 2.47 (0.01–20)	not specified	65 ± 42 (10–200)	Morgan and Rouge 1979
Electroplating	5M (personal air sampling), 8F (measurement in the urine)	9.3 ± 4.4 (4.7–16.4) (measured over 3 days)	not specified	34 ± 32 (7–142) (before shift) 64 ± 63 (9–262) (during shift) 46 ± 32 (5–139) (after shift)	Bernacki et al. 1980
Electroplating	3 M	(0.02–0.14) (during a working day)	(2.5–18.5) (during a working day)	(25–255) (during a working day)	Høgetveit et al. 1980
Electroplating	15M, 4F	not specified	not specified	27.1 ± 21.2 (3.1–82)	Sunderman et al. 1986a
Battery factory (Ni-H2)	4M, 3F	not specified	not specified	32.2 ± 40.4 (2.8–103)	Sunderman et al. 1986a
Electroplating (NiSO4, NiCl2)	11M	not specified	3.8 ± 0.5	28 ± 4	Sunderman et al. 1988a
Electroplating (NiSO4)	10 M	(2.8–116.7)	not specified	10.5 ± 7.5 (before shift) 20.6 ± 18.1 (after shift)	Oliveira et al. 2000

Some of the correlation developed by the studies above were taken into account by DGV to develop and exposure equivalents for nickel compounds (See Table 23).

Table 23: Correlations between the concentration of readily soluble nickel compounds in the work place air (A) and the concentration of the metal in urine samples (from DFG 2004)

Linear regression	n	r	References
Ni (U) [µg/l] = 26.8 + 522.8 Ni (A) [mg/m^3]	19	0.82	Tola et al. 1979
Ni (U) [µg/l] = 2.0 + 700 Ni (A) [mg/m^3]			Nieboer et al. 1999
Ni (U) [µg/g creatinine] = 6.0 + 430 Ni (A) [mg/m^3]	13	0.96	Oliveira et al. 2000

Taking into account the equations above DFG developed exposure equivalents for nickel readily soluble compounds (see Table 24).

Table 24: Correlation between external and internal nickel exposure for readily soluble nickel compounds (DFG 2004)

Air Nickel (mg/m3)	Urine Nickel (µg/l)
0.025	25
0.050	40
0.100	70

Notes:

Sampling time: end of shift after several consecutive shifts

6.2.3 Biomonitoring analytical methods

There are analytical methods able to reach these low concentration of nickel in urine, even in the range of the general population background concentrations. For instance the method proposed by Angerer, J. and Heinrich-Ramm (2012) allows the determination of nickel in urine with a detection limit of 1 µg nickel/l urine and the NIOSH method 8310 (NIOSH 1994) with a detection limit of 0.1 µg/sample (2µg/L)

It is important to avoid contamination of the biological material during and after sampling. In this respect it is recommended to take the samples in atmosphere free of contamination and that the test person changes into street clothes before sampling. High single values of nickel in urine should be cross-checked and determination of nickel in plasma may be considered to confirm high unexpected results.

7. Health Effects

7.1 Toxicokinetics (Absorption, distribution, metabolism and excretion - ADME)

Toxicokinetics of nickel and nickel compounds have been extensively studied and are reported in several reviews including ATSDR (2005), the Danish EPA (2008) and EFSA (2015). The following summary is adapted from these reports.

7.1.1 Human data

Absorption

Exposure to nickel compounds by inhalation may be in the form of aerosols (dusts) or attached to particles. Inhaled nickel particles are deposited in the upper and lower respiratory tract and are subsequently absorbed by several mechanisms. Whether particles are inhaled depends on the particle size (aerodynamic diameter) and particles with

aerodynamic diameters below 100 µm have the potential to be inhaled (inhalable fraction) and deposited in the respiratory tract (Danish EPA 2008, ATSDR 2005).

The deposition pattern in the respiratory tract is related primarily to particle size, but also to the shape, density, hygroscopicity, and electric charge as well as the respiratory dynamics of the individual (breathing pattern and thus, the respiratory minute volume). These factors determine the degree to which particles are affected by inertial impaction, sedimentation, and diffusion. Large particles (5–30 µm) deposit in the upper airways, the nasopharyngeal area where higher airstream velocities and airway geometry promote inertial impaction (Gordon and Amdur 1991). Smaller particles (1 –5 µm) pass through the nasopharyngeal region and enter the trachea and bronchiolar region where they deposit principally by sedimentation. The smallest particles (<1 µm) enter the alveolar region of the lungs where diffusion and electrostatic precipitation of the particles occurs (ATSDR 2005).

Following inhalation exposure, about 20–35% of nickel deposited in the lungs of humans is absorbed into the bloodstream. The remainder is either swallowed, expectorated, or remains in the respiratory tract. Absorption from the respiratory tract is dependent on the solubility of the nickel compound, with higher concentrations of urinary nickel were found in workers exposed to soluble nickel compounds (nickel chloride, nickel sulphate) than in those exposed to less-soluble nickel compounds (nickel oxide, nickel subsulfide), indicating that the soluble compounds were more readily absorbed from the respiratory tract (ATSDR, 2005).

Absorption of nickel from the gastrointestinal tract occurs after ingestion of various nickel compounds in food, beverages, or drinking water. In the occupational environment, an appreciable amount of nickel dust may be swallowed via the mucociliary clearance mechanisms, (i.e. particles deposited in the tracheobronchial region), as well as larger particles deposited in the extrathoracic region (which contain higher nickel mass) can also be swallowed and absorbed through the gastrointestinal tract. The rate of nickel absorption from the gastrointestinal tract is dependent on the chemical form and thus the solubility. The rate of oral absorption of nickel salts in humans can be quite high especially in the fasting state, but is reduced significantly in the presence of some food such as milk and coffee. The bioavailability of ingested nickel ranges from 1 % up to 40 % (EFSA 2015). Nickel binds to albumin, histidine and α2-macroglobulin and is widely distributed in the organism. Although absorbed nickel is mainly excreted in the urine, it is also excreted to a minor extent in bile and sweat (EFSA 2005, EFSA 2015).

Studies in humans and experimental animals indicate that nickel can penetrate the skin following dermal contact to various nickel compounds but to a limited extent with a large part of the applied dose remaining on the skin surface or in the stratum corneum. Recent human *in vivo* studies of nickel sulphate and nickel metal (Hostýnek et al. 2001a) has shown that a large part of the administered dose remained on the surface of the skin after 24 hours or had penetrated into the stratum corneum.

Distribution

Nickel tends to deposit in the lungs of workers occupationally exposed to nickel following inhalation of nickel compounds. Nickel has been shown to cross the human placenta.

Limited information exists on tissue distribution in humans however, in analyses from autopsies of individuals non-occupationally exposed to nickel (Tipton and Cook 1963), nickel was found with high frequency in all tissues with the highest concentrations measured in the adrenal glands, colon, and skin. In another autopsy study, the highest concentrations of nickel were found in the lung and in the thyroid and adrenal glands (Reuke et al., 1987).

Nickel concentrations were reported in serum and urine from healthy persons without occupational exposure to nickel (Templeton et al. 1994, Sunderman 1993). The body

burden of nickel in adult humans averages about 0.5 mg per 70 kg with the highest concentrations in the lung and in the thyroid and adrenal glands (WHO 2000).

Workers occupationally exposed to nickel have higher lung burdens of nickel than the general population. Nickel levels in the nasal mucosa are higher in workers exposed to less-soluble nickel compounds relative to soluble nickel compounds (Torjussen and Andersen 1979). These results indicate that, following inhalation exposure, less-soluble nickel compounds remain deposited in the nasal mucosa.

Systemic availability 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 (EURAR 2008). The bioavailability of ingested nickel in human volunteers, ranged from levels as low as 1 % up to 40 %. In particular a lower absorption was observed when exposure occurred in the presence of food or under non-fasted state, than when nickel was dosed in drinking water in the absence of food, or under a fasted state.

Metabolism

Upon entry into the bloodstream, the nickel ion is bound to specific serum components and rapidly distributed throughout the body. In serum, nickel is present in three forms: 1) as a complex associated with albumin; 2) as a complex associated with a nickel-metalloprotein (nickeloplasmin); and 3) as ultrafiltrable material. In human serum, 40% of the nickel is present as ultrafiltrable material, 34% is associated with albumin, and 26% is associated with nickeloplasmin. Limited information exists on tissue distribution in humans (Danish EPA 2008).

Nickel is bound to proteins including albumin, and α2- macroglobulin or to L-histidine (Sarkar, 1984; Sunderman et al. 1986c). The principal binding site is the histidine residue at the third amino acid position from the amino terminus in albumin from humans as well as that from rats and bovines (Hendel and Sunderman, 1972). Sakar (Sarkar 1984) proposed a transport model that involves the removal of nickel from albumin to histidine via a ternary complex composed of albumin, nickel, and L-histidine. The low molecular weight L-histidine nickel complex can then cross biological membranes. In the serum, there is also a non-exchangeable pool of nickel tightly bound to nickeloplasm, which is α-macroglobulin (Sunderman 1986d).

Excretion

Nickel that is absorbed via any route, is excreted in the urine whereas nickel that is not absorbed (such as from the gastrointestinal tract) is excreted via faeces. Absorbed nickel can to a lower extent be excreted in breast milk. An estimated elimination half-life of 28 ± 9 hours was calculated in human volunteers. (EFSA 2015, ATSDR 2005).

In a human volunteers study (Sunderman et al. 1989), it was reported that excretion via the faeces was 102 % ± 8 % and via urine 2 %, reflecting the lower bioavailability of nickel when dosed in food than when dosed via drinking water.

In nickel workers, an increase in urinary excretion was found from the beginning to the end of the shift and also as the workweek progressed. Nickel is also excreted in the faeces of nickel workers, but this is most likely resulting from mucociliary clearance of nickel from the respiratory system to the gastrointestinal tract. Higher nickel levels were found in the urine of workers exposed to soluble nickel compounds as compared to workers exposed to insoluble nickel compounds. In humans, most ingested nickel is excreted in the faeces; however, the nickel that is absorbed from the gastrointestinal tract is excreted in the urine (ATSDR 2005).

7.1.2 Animal data

Absorption

Studies in rats and dogs indicate that nickel compounds are systemically bioavailable after inhalation, but the amount of nickel absorption via the lungs depends to large extend on the solubility of the compound. Studies in rats and dogs indicate that 1–10% of nickel, given as nickel, nickel sulphate, or nickel chloride in the diet or by gavage, is rapidly absorbed by the gastrointestinal tract (Ambrose et al. 1976; Ho and Furst 1973; Tedeschi and Sunderman 1957). .

The lung retention times are substantially longer for the poorly soluble nickel oxide and nickel subsulphide than for the readily soluble nickel sulphate. Lung half-life in rodents is reported with 1 to 3 days for nickel sulphate, 5 days for nickel subsulfide and greater that 100 days for nickel oxide (NTP a,b,c 1996). The retention time for metallic nickel in an inhalation study with Wistar rats (Oller et al 2008) was found to be similar to poorly soluble nickel compounds. Following exposure to green nickel oxide, nickel was only excreted in the faeces indicating that the dominant mechanism for removing nickel oxide from the lungs is macrophage-mediated rather than dissolution-absorption. In contrast, following exposure to nickel subsulfide, nickel was excreted in both the urine and the faeces, with greater amounts in the urine on day 6–14 post-exposure (Benson et al. 1994).

Nickel can enter animal cells by three different mechanisms: uptake via metal ion transport systems, diffusion of lipophilic nickel complexes through the membrane, and phagocytosis. Differences in cellular uptake of soluble and insoluble forms of nickel compounds play an essential role in the observed differences in the toxicity among these compounds. The cellular uptake of soluble and insoluble nickel compounds are different as insoluble nickel compounds enter the cell via phagocytosis, while soluble nickel compounds are not phagocytised, but enter the cell via metal ion transport systems (particularly the magnesium transport system or through membrane diffusion.

In laboratory animals nickel is rapidly but poorly absorbed following ingestion. The gastrointestinal absorption of nickel correlates with the water solubility. Poorly water soluble nickel compounds have a lower bioavailability than water soluble nickel compounds (EFSA 2015).

Studies in experimental animals indicate that nickel can penetrate the skin following dermal contact to various nickel compounds. One study in guinea pigs (Lloyd 1980 - quoted from IPCS 1991) indicate that nickel chloride can be absorbed following dermal contact, but only to a very limited extent (indicated by low levels in blood plasma and in urine up to 24 hours of exposure). Other studies in rabbits and guinea pigsalso indicate that nickel can penetrate the skin (Lloyd 1980; Norgaard 1957; Mathur and Gupta 1994). The data indicate that experimental animals absorb nickel to a greater extent following dermal contact than humans do, which is in accordance with the general understanding that the permeability of human skin is often lower than that of animal skin. However, overall the the available data indicate that absorption of nickel following dermal contact to various nickel compounds can take place, but to a limited extent with a large part of the applied dose remaining on the skin surface or in the stratum corneum.

Distribution

Nickel was found primarily in the kidneys of animals following both short- and long-term oral exposure to various soluble nickel compounds. Substantial levels of nickel were also found in the liver, heart, lung, and fat as well as in the peripheral nerve tissues and in the brain (EFSA 2015, ATSDR 2005).

The tissue distribution of nickel in experimental animals does not appear to depend significantly on the route of exposure (inhalation/intratracheal instillation or oral administration) although some differences have been observed.

Metabolism

In rats, similar to humans (see above), the third amino acid position from the amino terminus in albumin is a preferred binding site for nickeli (Hendel and Sunderman, 1972). Dog albumin does not have a specific nickel-binding site. In dogs most of the nickel (> 85 %) is not bound to proteins and as a result the relevance of studies in dogs for human risk assessment is unclear (ATSDR, 2005).

Excretion

The elimination routes for nickel in humans and animals depend, in part, on the chemical form of the nickel compound and on the exposure route. Following oral exposure, the elimination of nickel is primarily in the faeces due to the relatively low gastrointestinal absorption. It was reported in rats (Ho and Furst 1973) that 94–97 % of the nickel administered orally was excreted via faeces and 3–6 % via urine, within a day.

Once absorbed, nickel is excreted in the urine regardless of the route of exposure. Other routes of elimination, which are of minor importance, include hair, saliva, sweat, tears, and milk. (IPCS 1991).

Following intratracheal administration, the route of excretion of nickel depends on the solubility of the nickel compound. The more soluble compounds (nickel chloride or nickel sulphate) were excreted in the urine, but the less-soluble compounds (nickel oxide, nickel subsulfide), a greater fraction of the dose was excreted in the faeces as a result of mucociliary clearance.

7.1.3 *In vitro* data

An *in vitro* study with cultured A549 cells is reported in which cell uptake and distribution of water soluble nickel chloride and particulate nickel oxide is compared. In both exposed cell cultures the nickel content in the cytoplasm and the nucleus was increased with a higher fraction of nickel reaching the nucleus in case of nickel oxide. (Schwerdtle and Hartwig, 2006).

Abbracchio et al (1982) compared the intracellular fate of particulate crystalline alpha NiS, an inducer of neoplastic transformation which is readily phagocytized by cultured cells with that of particulate amorphous NiS, which does not have these properties. A 20-30% increase in intracellular acid phosphatase activity was observed after treatment with crystalline, but not amorphous, NiS, suggesting enhanced lysosomal activity.

7.1.4 Further *in invitro* studies are reported in section 7.6.3. Toxicokinetic modelling

A physiologically-based kinetic model (PBK model) for humans (Sunderman et al. 1989) is described by EFSA (EFSA 2015). The PBK model was developed for oral exposure to nickel and based on two studies in eight human volunteers, in which levels of nickel in serum and faecal excretion were determined for 2 days before and 4 days after administration of nickel sulphate at dose levels of 12, 18 or 50 µg Ni/kg b.w. in water or in food to same subjects.

The model was adapted from a preliminary multi-compartmental model developed for rabbits and rats, and was limited to the prediction of the serum levels and urinary excretion levels following oral exposure to nickel and did not include the prediction of nickel levels in other compartments.

Hsieh et al. (1999a) described a dosimetric model of nickel deposition and clearance from the lung in rats, which he modified (Hsieh et al. 1999b) to develop a model of deposition and clearance of nickel in humans. The rat model was shown to have good agreement between the predicted lung burdens and measured burdens, but the modified human model was not verified. However, Yu et al. (2001) modified the human model and to predict lung burdens in nickel refinery workers; the predicted burdens were compared to

measured lung burdens in deceased nickel refinery workers (Andersen and Svenes 1989). Good agreement between predicted and measured body burdens was found. The modifications of the Hsieh et al (1999a) model allow for estimation of human lung burdens.

7.1.5 Biological monitoring

Plasma and urine concentrations of nickel are influenced by the chemical and physical properties of the nickel compound studied, and by the time of sampling (usually at the end of a working shift) and the analytical methods used. Elevated levels of nickel in biological fluids and tissue samples only indicate uptake of nickel anddo not identify the route of absorption. Relationship between nickel levels in body fluids and a specific health risk could not be established Sunderman (1993).

Subjects exposed to the same species of nickel from the same absorption route, serum nickel (S-Ni) and especially urine nickel (U-Ni) are useful biomarkers of exposure and can be used for bio-monitoring purposes, as occurs in the case of occupational setting. Further information on this topic, including relationships found between airborne and blood urine concentrations, is available in section 6.2.

7.1.6 Summary

Nickel and its inorganic compounds can be absorbed in humans and in animals via the gastrointestinal tract as well as the respiratory passages. Percutaneous absorption is negligible quantitatively. The relative amounts of nickel absorbed are determined, not only by the quantities administered, but also by the physical and chemical characteristics of the nickel compound. Solubility is an important factor in all routes of absorption. Nickel that is absorbed via any route, is excreted in the urine whereas nickel that is not absorbed (such as from the gastrointestinal tract) is excreted via faeces.

Nickel exists in different forms, some of which are more bioavailable than others and the bioavailability depends on various characteristics of the individual nickel compounds of which solubility is considered as being particularly important for the release of nickel ion and thus the systemic bioavailability of the nickel ion (see section 7.9). It is assumed that the nickel cation is the determining factor for systemic toxicity.

7.2 Acute toxicity

Acute toxicity has been reported in several reviews including ATSDR (2005), EU RAR (2008), Danish EPA (2008) and EFSA (2015). The following section includes information from these reviews and where relevant, includes more recent published literature from searches conducted for this report.

7.2.1 Human data

Acute oral toxicity

As reported (EFSA 2015) in humans, non-carcinogenic health effects of oral exposure to nickel include effects on the gastrointestinal, haematological, neurological and immune system. Gastrointestinal and neurological symptoms were the most reported effects after acute exposure. Exposure through skin or by inhalation may lead to nickel sensitization. Whereas oral exposure to nickel is not known to lead to sensitization, oral absorption of nickel is able to elicit eczematous flare-up reactions in the skin in nickel-sensitized individuals.

The acute lethality of nickel following oral exposure is dependent upon the chemical form of nickel. It has been reported (ATSDR 2005) that a fatal case of nickel poisoning was reported for a 2 year-old girl who had ingested 15g of nickel sulphate (Daldrup et al. 1983); the cause of death was cardiac arrest. Death due to nickel-induced Adult Respiratory Distress Syndrome (ARDS) was reported for a worker spraying nickel using a thermal arc process (Rendall et al. 1994). Death occurred 13 days following 90-minute

exposure to an estimated nickel concentration of 382.1mg/m^3; total nickel intake was estimated at nearly 1g.

Nausea, vomiting, abdominal pain, diarrhoea, headache, cough, shortness of breath, and giddiness were reported for workers of an electroplating plant who drank water contaminated with nickel chloride and nickel sulphate (1.63 g/L) (Sunderman et al. 1988a). Signs and symptoms of toxicity lasted for up to 2 days with uneventful recoveries for all 32 workers. The nickel doses were estimated to be 0.5 to 2.5 g, serum nickel concentrations were 13 to 1340 µg/L, and urinary nickel concentrations were 0.15 to 12 mg/g creatinine.

It has been reported (EU-RAR 2008) that nausea, vomiting, weakness, headache, and palpitations were observed after iatrogenic exposure (injection, orthopaedic, prosthesis, implants etc) of 23 patients to high levels of nickel during haemodialysis due to leaching from a nickel-plated, stainless steel, water heating tank. The symptoms were observed at plasma nickel concentrations of approximately 3 mg Ni/l and disappeared upon cessation of dialysis. (Webster et al. 1980).

Some studies have provided information indicating the aggravation of nickel-induced dermatitis in women following exposure to dietary nickel (ATSDR 1988).

7.2.2 Animal data

Acute oral toxicity

The acute oral toxicity of nickel metal shows that it has low toxicity via the oral route with an acute oral LD50 of greater than 9000 mg/kg bw (EU-RAR 2008).

Generally, soluble nickel compounds are more toxic than insoluble compounds: single-dose oral lethality studies indicated that soluble nickel compounds are acutely toxic to rats whereas less soluble compounds or insoluble nickel compounds are not acutely toxic to rats; the Ni(II) ion bioavailability being important in determining toxicity (ATSDR 2005). Oral LD_{50} values for rats range from 39 mg nickel/kg b w for nickel sulphate to >9000mg nickel/kg b.w for nickel oxide black/green (ATSDR, 1988; EFSA 2015; Danish EPA 2008). A summary is given in the table below.

Table 25: oral LD50 values

Nickel compound(s)	**Oral LD_{50} (mg Ni /kg bw)**	**References** (cited in ATSDR, 1988; EFSA 2015; Danish EPA 2008a)
Nickel (metallic)	>1472	Haro et al., 1968; Itskova et al., 1969; Smyth et al., 1969; Kosova, 1979; FDRL, 1983a-h; Mastromatteo, 1986; ATSDR, 1985; Henderson et al., 2012
Ni sulphate	39–190	
Ni chloride	43–130	
Ni nitrate	>303	
Ni acetate	116–325	
Ni carbonate	402-625	
Ni hydroxide	>1000	
Ni oxide, dihydroxide, trioxide, sulphide, subsulphide	>2 000	
Ni oxide black or Ni oxide green	8 796 to >11 000	

Some specific observations following oral administration to rats:

- Single oral administration to Wistar male rats of nickel sulphate through drinking water led to an increase of hepatic lipid peroxidation and to a decrease of antioxidant enzyme activities (Das and Dasgupta, 2002).
- Non-specific effects such as hypoactivity and piloerection were observed in rats treated with nickel acetate tetrahydrate, nickel chloride hexahydrate or nickel sulphate hexahydrate. At high doses red intestines were reported.
- A 2-week exposure of rats to 1000 ppm nickel chloride in the drinking water resulted in excessive mortality (RTI 1987).

Acute dermal toxicity

A more recent study conducted according to OECD test guidelines reported acute dermal LD_{50} values ranging from 600-835 mg/kg: the study is summarised in the table below.

Table 26: Summary table of an animal study on acute dermal toxicity

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels duration of exposure	Results LD_{50}	Reference
The OECD guidelines for testing of Chemicals, Acute Oral Toxicity- method of adjusting doses; 2006.	Animal (Mice of NMRI strain (18–22 g) of both sexes)	Ni(SMX)2(Cl)2]·H2O, Ni(MIZ)2(Cl)2(H2O)2]·H2O, Ni(MPBO)2(OH)2]·2H2O	0, 250, 750, 1250, 1500, 1750 mg/kg body weight by oral gavage Single dose, then observed for 14 days	The LD50 value for [Ni(SMX)2(Cl)2]·H2O complex is 835 mg/kg ± 2.66 body wt. The LD50 value for [Ni(MIZ)2(Cl)2(H2O)2]·H2O complex is 700 mg/kg ± 5.69 body wt. The LD50 value for [[Ni(MPBO)2(OH)2]·2H2O complex is 600 mg/kg ± 15.65 body wt.	Bouchoucha et al 2013

Acute inhalation toxicity

There is limited available data on acute inhalation effects and in the absence of such data, data from repeated dose inhalation studies can be used. There is evidence (EU-RAR 2008) for acute oral toxicity for the soluble as well as the less soluble compounds (but not insoluble or metallic nickel). It should be noted that the use of results from repeated dose studies is considered to be a conservative approach, since greater toxicity is expected from repeated exposure compared to a single 4h exposure.

Acute toxic effects will be dependent upon the chemical form, exposure concentration, and exposure duration.

Acute inhalation toxicity studies in animals have provided LC_{Lo} values ranging from 0.97 mg/m^3 for 6-hour exposure of rats to nickel subsulphate to 15 mg/m^3 (time not specified) for guinea pigs exposed to nickel dust (USAF 1990) and no mortality seen at concentrations up to 24mg Ni/m^3 for metallic nickel (WIL Research Laboratories, 2002) and up to 23.6 mg Ni/m^3 for nickel oxide (NTP 1996b). A range of studies are summarised in the table below.

Inhalation studies in mice (ATSDR 1988) indicated that 2-hour exposure to nickel chloride at concentrations of 0.25 to 0.50 mg nickel/m^3 caused a suppression of immune responses. A 16-day repeated dose toxicity study of nickel sulphate (NTP 1996a) reported

a NOAEC/LOAEC (lethality) of 0.7 mg Ni/m3 and observed reduced body weight and adverse effects in the respiratory tract (atrophy and inflammation).

More recent studies reported that nickel oxide as nano particles showed an increase in indicators of inflammation in the lungs. These studies are summarised in the table below.

Table 27: Summary table of animal studies on inhalation toxicity

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Results LC_{50}	Reference
6h/day, 5d/week for 4 weeks	rats	metallic nickel	concs up to 24 mg Ni/m^3	No mortality	WIL Research Laboratories, 2002
(Not specified)	Guinea pigs	nickel dust	(Not specified)	LC_{Lo} 15 mg/m^3	USAF 1990
2h exposure	mice	nickel chloride	0.25 to 0.50 mg nickel/m^3	suppression of immune responses	ATSDR 1988
6h exposure	rats	nickel subsulphate	(Not specified)	LC_{Lo} 0.97 mg/m^3	USAF 1990
16d repeat dose (12 exposures during 16 days)	mice and rats	nickel subsulphide	(Not specified)	LOAEC of 7.33 mg Ni/m3	NTP 1996b
16d repeat dose (12 exposures during 16 days)	mice and rats	nickel oxide	concs up to 23.6 mg Ni/m^3	No mortality	NTP 1996b
6h/day, 5d/week for 12 days	mice and rats	Green nickel oxide	0.9-23.6 mg/m^3	No deaths	Sax et al 1989
6h/day, 5d/week for 12 days	mice and rats	nickel sulphate	0.8;1.7;3.3;6.7;13 mg/m^3	Rats: death ≥3.3 mg/m^3 Mice: death ≥1.7 mg/m^3	Sax et al 1989
16d repeat dose (12 exposures during 16 days)	rats	nickel sulphate	(Not specified)	NOAEC/LOAEC (lethality) of 0.7 mg Ni/m^3; observed reduced body weight and adverse effects in the respiratory tract (atrophy and inflammation)	NTP 1996a
Intratracheal instillation	Wistar rats (female)	NiO (among a panel of nano-particle	500 cm2/mL (relates to SA of particles) (0.5ml	NiO caused significant recruitment of	Lu et al 2009

Method, guideline, deviations if any	Species, strain, sex, no / group	Test substance,	Dose levels duration of exposure	Results LC_{50}	Reference
		metal oxides)	instilled into lungs) 24 hrs	PMNs into lungs. Response to nickel oxide NPS far greater than to other metal oxides	
Pharyngeal aspiration	Mice (male, C57BL/6J, 7-weeks-old)	NiO (nano) in 4 dispersion media	0–80 mg/mouse At 1 and 7 d post-exposure	NiO NPs induce cell death and neutrophil recruitment at concentrations and time points used. Increased dispersion correlates with increased biological effect	Sager et al 2016
Oropharyngeal aspiration (OPA)	Wild-type (WT) and T-bet−/− mice	Nickel nanoparticles	4 mg/kg Necropsy was performed at 1 and 21 days	Ni exposure ↑ mucous cell metaplasia, chronic alveolitis at 21 days ($p<0.001$)	Glista-Baker et al 2014

7.2.3 *In vitro* data

There are no *in vitro* data on acute toxicity.

7.2.4 Summary

Generally, soluble nickel compounds are more toxic than insoluble compounds. Non-carcinogenic health effects of oral exposure to nickel include contact dermatitis and systemic effects on the gastrointestinal, haematological, neurological and immune system.

In large doses (>0.5 g), some forms of nickel may be acutely toxic to humans when taken orally. Gastrointestinal (vomiting, cramps, and diarrhoea) and neurological symptoms (giddiness, headache, and weariness) were the most reported effects after acute exposure (EFSA 2015). Acute inhalation exposure of humans to nickel may produce headache, nausea, respiratory disorders, and death. Asthmatic conditions have also been documented for inhalation exposure to nickel.

Oral toxicity in animals varies from acutely toxic to not acutely toxic to rats. Inhalation exposure to some nickel compounds can cause toxic effects in the respiratory tract and immune system. Inhalation LC_{50} values for animals range from 0.97 mg nickel/m^3 for rats (6-hour exposure) to 15 mg nickel/m3 for guinea pigs (time not specified).

7.3 Specific target organ toxicity / Repeated dose toxicity

Repeat dose toxicity has been reported in several reviews including ATSDR (2005), US EPA (1996), NiPERA (1996); TERA (1999), EU RAR (2008), Danish EPA (2008) and EFSA (2015). The following section includes information from these reviews and where relevant, includes more recent published literature from searches conducted for this report.

7.3.1 Human data

A number of human studies have examined the potential of nickel and nickel compounds to induce respiratory effects, although studies on non-malignant respiratory diseases in nickel-exposed workers are limited. Most of these studies were cohort mortality studies in nickel-exposed workers. Generally, chronic inhalation exposure to nickel dusts and aerosols contribute to respiratory disorders such as asthma, bronchitis, rhinitis, sinusitis, and pneumoconiosis (USAF 1990). Chronic exposure to nickel and nickel compounds have been implicated in carcinogenic responses which are described later in section 7.7.

Muir et al (1993) studied 745 workers from the Ontario Copper Cliff sinter plant exposed to high concentrations of airborne dusts containing nickel up to 100 mg/m^3. Chest X-rays were scored according to the ILO classification. There was no comparison group in the study and no information on smoking or exposure to asbestos or crystalline silica was available to adjust for their effects. The prevalence of small irregular lung opacities varied between the five radiologist reading the X-rays. The authors concluded the prevalence was within the range identified in cigarette smokers or in workers exposed to dusts of low fibrogenicity.

Berge and Skyberg (2003) analysed radiographs of 1046 workers in a nickel refinery in Norway, according to the ILO standards. Pulmonary fibrosis (PF) was defined as a reading of ILO score ≥1/0 and following this criterion, 47 cases (4.5%) were identified. In logistic regression models, controlling for age and smoking, there was evidence of increased risk of PF with cumulative exposure to soluble nickel or sulfidic nickel (p = 0.04 for both). The relative risk of an ILO score of $\geq$ 1/0 for the highest cumulative exposure category of soluble nickel (> 1.8 mg/m^3 x years) was increased, but not statistically significantly: 2.24 (95% CI 0.82 – 6.16) when adjusted for age, smoking, asbestos exposure and exposure to sulfidic nickel. The relative risk of an ILO score of $\geq$ 1/0 for the highest cumulative exposure category of sulfidic nickel (> 0.6 mg/m^3 x years) was increased, but not statistically significantly: 2.04 (95% CI 0.54 – 7.70) when adjusted for age, smoking, asbestos exposure and exposure to sulfidic nickel. However the overall incidence ILO category $\geq$ 1/0 in chest X-rays taken at a nickel refinery (4.5%) was not significantly different from the incidence among “normal” X-rays from a hospital (4.2%), and was lower than for X-rays from quarry workers (13.6%). Logistic regression models with cumulative exposure to one nickel species at time, age and smoking (pack-years) predicted a 10% (soluble Ni) or 15% (sulfidic Ni) increase in the prevalence of ILO score $\geq$ 1/0 per 1 mg/m^3 –year to the prevalence predicted by age and smoking alone. The above exposure estimates were not corrected for the sampler correction factor. With the standard correction factor of 2 and the reported average exposure time of 21.8 years, the 75th percentile cumulative exposure levels corresponded to average exposure levels of 0.17 and 0.6 mg/m^3 for soluble and sulfidic Ni, respectively. It is to be noted that an ILO profusion score of $\geq$ 1/0 does not necessarily correlate with clinical (or histopathological) diagnosis of lung fibrosis.

The latest follow-up of the non-sinter workers of the Ontario nickel refineries found a significantly increased mortality frompneumoconiosis as well as from silicosis/anthracosilicosis among workers with at least 15 years of employment, but no deaths among those employed for less than 15 years (Lightfoot et al 2016). However about 80% of both pneumoconiosis and silicosis/anthracosilicosis deaths occurred among underground miners presumably exposed to crystalline silica. The mortality update of a cohort of nickel refinery workers at Clydach (Sorahan and Williams, 2005) did not find an increased risk of mortality from non-malignant respiratory disease (SMR = 0.97; 95% CI 0.57 – 1.5).

A mortality study of workers with predominant exposure to metallic nickel in alloy production did not find an increased mortality due to non-malignant respiratory disease (Arena et al., 1998). No study-specific exposure data were recorded, but only approximate data from experience for the specific work area, which were scattered over a very wide concentration range. The average airborne nickel concentrations were highest in the area

of powder metallurgy with 1.5 mg/m^3, followed by the grinding operation with 0.3 mg/m^3 and the hot working areas with 0.1 mg/m^3, whereas the means in the other areas were lower. No adjustment for any confounding factor was included in this mortality study or the ones reported below. A mortality study of workers involved in the production of stainless steel and alloyed steel showed similar results (Moulin et al., 1990). A mortality study update of hydrometallurgical workers demonstrated a lack of excess mortality due to respiratory (non-cancer) effects associated with relatively high inhalable exposures metallic nickel (mean levels 2 and 4 mg/m^3 in the two departments) during refining (Egedahl et al., 2001). A more recent study of 2,000 workers employed for a minimum of five years in a U.K. plant manufacturing nickel alloys reported a standardized mortality ratio (SMR) of 69 for non-malignant diseases of the respiratory system (Sorahan, 2004). Mean exposure to metallic nickel in the two departments were 2 and 4 mg Ni/m^3 (or 4 – 8 mg Ni/m^3 as inhalable nickel, Sivulka 2005).

7.3.2 Animal data

It has been reported (ATSDR 2005; EU RAR Background Document 2008) that studies in rats and mice demonstrate that chronic active inflammation in the lungs is the most prominent effect following inhalation exposure to the insoluble, nickel subsulfide and nickel oxide and also for the soluble nickel sulphate. Less severe effects were seen for nickel chloride. Thus, it appears that the effects following inhalation exposure to nickel compounds do not depend on the solubility characteristics.

The US National Toxicology Program (NTP) carried out a series of inhalation studies in rats and mice with three nickel compounds (NTP 1996a, 1996b, 1996c): soluble nickel sulphate hexahydrate, and the insoluble compounds nickel subsulphide and nickel oxide. Male and female rats and mice were exposed by inhalation for 16 days, 13 weeks, or 2 years. The studies are summarised in Table 28 below. In the 13 weeks studies in rats exposed to nickel sulphate and nickel subsulphide (NTP 1996b, 1996c) the incidence and severity of chronic lung inflammation were similar at the dose level of 0.11 mg Ni/m^3. The slopes of the dose-response for inflammation between 0.11 and 0.22 mg Ni/m^3 were similar for nickel subsulfide and sulfate. Although these studies had only 10 animals per group, 5 exposure groups were included and demonstrated that nickel subsulfide is not more toxic than nickel sulfate in rats (and in mice).

The incidence and severity of chronic lung inflammation (chronic active inflammation, alveolar proteinosis, and fibrosis) also after 2-years (NTP 1996b, 1996c) of inhalation exposure to 0.11 mg Ni/m^3 nickel subsulfide were similar to those observed with 0.11 mg Ni/m^3 of nickel sulfate in rats based on 100 animals per group. In the chronic nickel sulfate study rats were exposed to the lower exposure level 0.06 to 0.03 mg Ni/m^3, resulting in a significant decrease in incidence and severity of lesions to background inflammation levels. A similar steep dose-response for inflammation is expected for nickel subsulfide, based on results from 13-week studies.

For the soluble nickel sulphate hexahydrate a LOAEC for chronic lung inflammation and fibrosis could be determined at 0.06 mg Ni/m^3, and a definitive NOAEC for these effects could be be set at 0.03 mg Ni/m^3 in the 2-years study. However, for the less soluble nickel compounds a NOAEC could not be defined in the chronic studies. It should be noted that LOAEL and NOAEL values have been reported in other studies (e.g. see Table 30). These NTP studies are summarised in the table below.

Table 28: Summary table of NTP Repeat dose inhalation studies

Method, GI, deviations if any, species, strain, sex, no/group	Test substance, dose levels, duration of exposure	Results	Reference
16d study, inhalation, F344/N rats, Main group: 5m/5f Satellite group: 5m/5f Satellite group for tissue burden study	**Nickel oxide**, Main group: 0, 1.2, 2.5, 5, 10, 30 mg NiO/m^3 (0, 0.9, 2.0, 3.9, 7.9, 23.6 mg Ni/m^3) Satelite group:0, 1.2, 5, 10 mg NiO/m^3 6 h/day, 5 days/week	Dose dependent increased severity in effects **10 and 30 mg/m^3 :** Lung: incr abs/rel organ weight, min to moderate bronchial LN hyperplasia, inflammatory interstitial cell infiltrates, foci of acute inflammation (neutroph infiltr), incr in alveolare MΦ, black pigment in MΦ and lung Nose: min olfactory epithelium atrophy (30 mg/m^3) **Lower dose groups:** black pigment in lungs, accumulation in alveolar MΦ	NTP 1996a
16d study, Inhalation B6C3F mice, Main group: 5m/5f Satelite group: 5m/5f Satelite group for tissue burden study	**Nickel oxide**, Main group: 0, 1.2, 2.5, 5, 10, 30 mg NiO/m^3 (0, 0.9, 2.0, 3.9, 7.9, 23.6 mg Ni/m^3) Satelite group: 0, 1.2, 2.5, 5 mg NiO/m^3 6 h/day, 5 days/week	**30 mg/m3:** Slight bw loss (m), Lung: min enlargement of broncial LN, lymphoid hyperplasia, inflammatory cell infiltrate in pulmonary interstitium, incr in alveolare MΦ, black particles in alveolare MΦ and Lung **Lower doses:** Lung: accumulation of alveolare MΦ and pigment particles No effects in 1.2 mg/m^3 group	NTP 1996a
13w study, inhalation, F344/N rats, Main group: 10m/10f Satelite group: 18m/18f Satelite group for tissue burden study	**Nickel oxide**, Main group: 0, 0.6, 1.2, 2.5, 5, 10 mg NiO/m^3 (0, 0.4, 0.9, 2.0, 3.9, 7.9 mg Ni/m^3) Satelite group: 0, 0.6, 2.5, 10 mg NiO/m^3 6 h/day, 5 days/week	Dose dependent increased severity in effects, Ni conc in lungs incr at 0.6 mg/m^3 and higher **5 and 10 mg/m^3:** red sperm count (10 mg/m^3), incr in HK, Hb, lymphocytes (f), erythrocyte in m/f Lung: abs/rel incr weight and red lungs collapse (10 mg/m^3), pigment in lungs and LN, mild to moderate alveolare MΦ and LN hyperplasia, moderate chronic active and granulomatous inflammation, mild interstitial infiltrate **1.2 and 2.5 mg/m^3:** incr in HK, Hb and erythrocyte in f, min mean cell volumes reduction and min increase in Hb conc (f), incr in total nucleated erythrocytes (f) Lung: min pigment in lungs und LN, min alveolare MΦ and LN (2.5 mg/m^3) hyperplasia, min chronic active inflammation (2.5 mg/m^3), min interstitial infiltrate **0.6 mg/ m^3:** incr in neutrophils and nucleated erythrocytes (f) Lung: Pigment in lungs (m), alveolare MΦ hyperplasia	NTP 1996a

Method, GI, deviations if any, species, strain, sex, no/group	Test substance, dose levels, duration of exposure	Results	Reference
13w study, inhalation, B6C3F mice, Main group: 10m/10f Satelite group: 6m/6f Satelite group for tissue burden study	**Nickel oxide**, Main group: 0, 0.6, 1.2, 2.5, 5, 10 mg NiO/m^3 Satelite group: 0, 0.6, 2.5, 10 mg NiO/m^3 6 h/day, 5 days/week	Dose dependent increased severity in effects **10 mg/m^3:** min lymphocytosis (m), incr in HK and erythrocyte (f), liver weight decr (m), Lung: incr rel/abs lung weight, min alveolare MΦ hyperplasia, chronic active and granulomatous inflammation, pigment in lungs, min perivascular lymphocytic infiltration, min broncial LN hyperplasia (3m/3f), pigment in LN **5 mg/m^3:** Incr HK, Hb conc and erythrocyte (f), decr liver weight (m) Lung: incr rel/abs lung weight (f), min alveolare MΦ hyperplasia, min pigment in lungs and LN, min perivascular lymphocytic infiltration, min broncial LN hyperplasia **0.6 to 2.5 mg/m^3:** Lung: min alveolare MΦ hyperplasia, min pigment in lungs, min broncial LN hyperplasia and pigment in LN (2.5 mg/m^3)	NTP 1996a
16d study, inhalation F344/N rats, Main group: 5m/5f Satellite group: 3m/3f Satellite group for tissue burden study	**Nickel subsulfide**, Main group: 0, 0.6, 1.2, 2.5, 5, 10 mg Ni_3S_2/m^3 (0, 0.44, 0.88, 1.83, 3.65, 7.33 mg Ni/m^3) Satelite group: 0, 0.6, 2.5, 10 mg Ni_3S_2/m^3 6 h/day, 5 days/week	Dose dependent increased severity in effects **10 mg/m^3:** severe bw red, laboured respiration (m/f), dehydration (f), incr Ni concentr in lung/kidney Lung: incr abs/rel lung weight (m/f), red rel thymus weight (m), red lungs collapse, moderate diffuse lung inflammation (necrosis, mucus in bronchioles lumen, neutrophils, incr of MΦ, alveolare MΦ with pigment), Nose: min olfactory epithelium athrophy, **5 mg/m^3:** bw gain red, laboured respiration (f), incr Ni concentr in lung/kidney, dehydration (f), Lung: incr abs/rel lung weight (m/f), mild diffuse lung inflammation (necrosis, mucus in bronchioles lumen, neutrophils, incr of MΦ, alveolare MΦ with pigment), Nose: min olfactory epithelium athrophy **2.5 mg/m^3:** bw gain red (f), incr Ni conc in lung/kidney Lung: incr abs/rel lung weight (m/f), moderate lung inflammation (lymphocytes, focal incr of MΦ), Nose: min olfactory epithelium athrophy, **0.6 and 1.2 mg/m^3:** incr Ni concentr in lung/kidney Lung: incr abs(m)/rel lung weight (f), min lung inflammation, min focal incr MΦ Nose: min olfactory epithelium athrophy.	NTP 1996b

Method, GI, deviations if any, species, strain, sex, no/group	Test substance, dose levels, duration of exposure	Results	Reference
16d study, inhalation B6C3F mice, Main group: 5m/5f Satelite group: 3m/3f Satelite group for tissue burden studies	**Nickel subsulfide** , Main group: 0, 0.6, 1.2, 2.5, 5, 10 mg Ni_3S_2/m^3 (0, 0.9, 2.0, 3.9, 7.9, 23.6 mg Ni/m^3) Satelite group: 0, 0.6, 2.5, 10 mg Ni_3S_2/m^3 6 h/day, 5 days/week	**10 mg/m³:** day5 laboured respiration (m/f), all animals died before study termination, moderate lung inflammation, Nose: moderate olfactory epithelium athrophy **1.2, 2.5, 5 mg/m³:** Slight BW loss (m), abs/rel lung weight incr (5 mg/m³), mild lung inflammation and fibrosis (5 mg/m³), mild to moderate bronchial LN hyperplasia, Nose: marked olfactory epithelium athrophy **0.6 mg/m³:** no effects	NTP 1996b
13w study, inhalation, F344/N rats, Main group: 10m/10f Satelite group: 18m/18f Satelite group for tissue burden studies	**Nickel subsulfide** , Main group: 0, 0.15, 0.3, 0.6, 1.2, 2.5 mg Ni_3S_2/m^3 (0, 0.11, 0.22, 0.44, 0.88, 1.83 mg Ni/m^3) Satelite group: 0, 0.15, 0.6, 2.5 mg Ni_3S_2/m^3 6 h/day, 5 days/week	Dose dependent increased severity in effects and Ni conc in lungs/kidney **1,2 and 2.5 mg/m³:** bw and bw gain red (m), laboured respiration (m/f), slight incr HK, Hb and erythrocyte, nucleated erys, lymphocytes, Lung: incr abs/rel lung weight (m/f), mod to marked alveolar MΦ hyperplasia, min to moderate interstitial infiltrate, moderate to marked chronic active inflammation, mild to moderate bronchial and mediastinal LN hyperplasia, Nose: min to mild olfactory epithelium atrophy **0.6 mg/m³:** Lung: incr abs/rel lung weight (m/f), min alveolar MΦ hyperplasia (10/10), mild interstitial infiltrate, min chronic active inflammation, min bronchial and mediastinal LN hyperplasia, Nose: min olfactory epithelium atrophy **0.15 and 0.3 mg/m³:** Lung: incr abs/rel lung weight (m/f), min alveolar MΦ hyperplasia (10/10), min interstitial infiltrate, min chronic active inflammation (0.3 mg/m³)	NTP 1996b
13w study, inhalation, B6C3F mice, Main group: 10m/10f Satelite group: 6m/6f Satelite group for tissue burden studies	**Nickel subsulfide** , Main group: 0, 0.15, 0.3, 0.6, 1.2, 2.5 mg Ni_3S_2/m^3 Satelite group: 0.15, 0.6, 2.5 mg Ni_3S_2/m^3 6 h/day, 5 days/week	Dose dependent increased severity in effects **1.2 and 2.5 mg/m³:** Lung: incr abs/rel lung weight (m/f), mild to moderate alveolar MΦ hyperplasia, min to mild interstitial (perivascular) infiltrate, min chronic active inflammation in lungs with fibrosis, min LN hyperplasia, Nose: mild to moderate olfactory epithelium atrophy **0.3 and 0.6 mg/m³:** Lung: min alveolar MΦ hyperplasia, min interstitial (perivascular) infiltrate, min Nose: olfactory epithelium atrophy (0.6 mg/m³) **0.15 mg/m³:** min interstitial infiltrate (3/20)	NTP 1996b

Method, GI, deviations if any, species, strain, sex, no/group	Test substance, dose levels, duration of exposure	Results	Reference
16d study, inhalation, F344/N rats, Main group: 5m/5f Satellite group: 4m/5f Satellite group for tissue burden studies	**Nickel sulphate hexahydrate**, Main group: 0, 3.5, 7, 15, 30, 60 mg $NiSO_4$ $6H_2O/m^3$ (0, 0.7, 1.4, 3.1, 6.1, 12.2 mg Ni/m^3) Satelite group: 0, 3.5, 15, 30 mg $NiSO_4$ $6H_2O/m^3$ 6 h/day, 5 days/week	2m and 5f died at 60 mg/m^3, 1f died at 30 mg/m^3 **All dose groups:** bw loss, bw gain red (m), incr and laboured respiration, red activity, abs/rel thymus weight red, red lungs collapse (60 and 30 mg/m^3), Lung: abs/rel lung weight incr (60 mg/m^3 m/all f), mild lung inflammation, mild bronchiolar epithelium degeneration or necrosis (60 mg/m^3), mild bronchial and mediastinal LN hyperplasia (not 30 mg/m^3) Nose: mild to moderate olfactory epithelium atrophy, min respiratory epithelium degeneration	NTP 1996c
16d study, inhalation, B6C3F mice, Main group: 5m/5f Satelite group: 5m/5f Satelite group for tissue burden studies	**Nickel sulphate hexahydrate**, Main group: 0, 3.5, 7, 15, 30, 60 mg $NiSO_4$ $6H_2O/m^3$ (0, 0.7, 1.4, 3.1, 6.1, 12.2 mg Ni/m^3) Satelite group: 0, 3.5 mg $NiSO_4$ $6H_2O/m^3$ 6 h/day, 5 days/week	**7 mg/m^3 and greater:** lethality in 5/5 m and 5/5 f of all doses, emaciation, lethargy, rapid respiration, red abs/rel thymus weight, Lung: abs/rel lung weight incr, diffus reddened lungs **3.5 mg/m^3:** Lung: abs/rel lung weight incr, mild inflammation, moderate lymphoid hyperplasia (1/5 f), Ni concentration in lung increased Nose: mild olfactory epithelium atrophy	NTP 1996c
13w study, inhalation, F344/N rats, Main group: 10m/10f Satellite group: 6m/6f Satellite group for tissue burden studies	**Nickel sulphate hexahydrate**, Main group: 0, 0.12, 0.25, 0.5, 1, 2 mg $NiSO_4$ $6H_2O/m^3$ (0, 0.03, 0.06, 0.11, 0.22, 0.44 mg Ni/m^3) Satelite group: 0, 0.12, 0.5, 2 mg $NiSO_4$ $6H_2O/m^3$ 6 h/day, 5 days/week	Dose dependent increased severity in effects and Ni conc in lungs **1 and 2 mg/m^3:** incr in neutr granulocytes (m/f) and lymphocytes, HK, Hb and erythrocytes (f), Lung: incr abs/rel lung weight (m/f), mild to moderate alveolar MΦ hyperplasia, min interstitial infiltrate, min chronic active inflammation, min to mild bronchial and mediastinal LN hyperplasia, Nose: min olfactory epithelium atrophy (high dose) **0.25 and 0.5 mg/m^3:** incr in neutr granulocytes (f), Lung: incr abs/rel lung weight (m/f), min alveolar MΦ hyperplasia, interstitial infiltrate and min chronic active inflammation (0.5 mg/m^3), Nose: min olfactory epithelium atrophy **0.12 mg/m^3:** Lung: min alveolar MΦ hyperplasia.	NTP 1996c

Method, GI, deviations if any, species, strain, sex, no/group	Test substance, dose levels, duration of exposure	Results	Reference
13w study, inhalation, B6C3F mice, Main group: 10m/10f Satelite group: 5-6m/5-6f Satelite group for tissue burden studies	**Nickel sulphate hexahydrate**, Main group: 0, 0.12, 0.25, 0.5, 1, 2 mg $NiSO_4$ $6H_2O/m^3$ (0, 0.7, 1.4, 3.1, 6.1, 12.2 mg Ni/m^3) Satelite group: 0, 0.12, 0.5, 2 mg $NiSO_4$ $6H_2O/m^3$ 6 h/day, 5 days/week	Effects showed dose dependent increase **2 mg/m³:** Incr segmented neutophil count in blood (f), min Hb incr (f) Lung: incr abs/rel lung weight (m/f), min alveolar MΦ hyperplasia, min interstitial infiltrate (16/20), min to mild chronic active inflammation, min to mild fibrosis, min bronchial LN hyperplasia Nose: olfactory epthelium atrophy **1 mg/m³:** Incr segmented neutophil and lymphocyte count in blood (f), min Hb incr (f) Lung: incr abs/rel lung weight (m/f), min alveolar MΦ hyperplasia, min interstitial infiltrate (3/20), min chronic active inflammation, min fibrosis **0.5 mg/m³:** Incr segmented neutophil and lymphocyte count in blood (f) Lung: min alveolar MΦ hyperplasia No significant effects in lower doses	NTP 1996c

Method, GI, deviations if any, species, strain, sex, no/group	Test substance, dose levels, duration of exposure	Results	Reference
2y study inhalation, F344/N rats, 65m/65f per group Interim evaluation after 7m and 15m	**Nickel oxide,** 0, 0.62, 1.25, 2.5 mg NiO/m^3 (0, 0.5, 1.0, 2.0 mg Ni/m^3) 6 h/day, 5 days/week	**2.5 mg NiO/m^3:** mean bw slightly reduced (m/f). Lung: incr abs/rel lung weight alveolar epithelial hyperplasia, alveolar and LN pigments, moderate chronic inflammation, proteinosis, incr of alveolare MΦ with hyperplasia, LN hyperplasia Alveolar/bronchiolar adenoma (2m/4f), alveolar/bronchiolar carcinoma incl squamous differentiation (2m/1f); (overall rate 8%m/9%f) Adrenal glands: incr in benign and malignen pheochromocytoma in m/f (benign 62%m/34f; malignant 12%m) **1.25 mg NiO/m^3:** mean bw slightly reduced (f). Lung: incr abs/rel lung weight atypical alveolar epithelial hyperplasia Min alveolar pigments, mild chronic inflammation in lung, eosinophilic material in lungs (proteinosis), mild pigment in LN, mild bronchial LN hyperplasia, incr of alveolare MΦ, MΦ hyperplasia incr benign pheochromocytoma (2%m/11%f) alveolar/bronchiolar adenoma (3m/1f), alveolar/bronchiolar carcinoma incl squamous differentiation (3m/2f); (overall rate 11%m/11%f) **0.62 mg/m^3:** Lung: abs lung weight increased Squamous metaplasia (1m) atypical alveolar epithelial hyperplasia Min alveolar pigments, min chronic inflammation, eosinophilic material in lungs (proteinosis), incr of alveolare MΦ, MΦ hyperplasia, min pigment in LN, min to mild bronchial LN hyperplasia alveolar/bronchiolar adenoma (1m; 2%m)	NTP 1996a

Method, GI, deviations if any, species, strain, sex, no/group	Test substance, dose levels, duration of exposure	Results	Reference
2y study, inhalation, B6C3F mice, 76-79m/74-76f Interim evaluation after 7m and 15m	**Nickel oxide**, 0, 1.25, 2.5, 5 mg NiO/m^3 6 h/day, 5 days/week	**5 mg/m³:** Lung: abs/rel lung weight incr, mild broncial LN hyperplasia (cortical/paracortical lymphocytes), mild pigment in LN, min to mild chronic inflammation, min bronchialization, mild alveolus pigmentation, min to mild proteinosis, Alveolar/bronciolar adenoma and carcinoma **2.5 mg/m³:** Lung: abs lung weight increased mild broncial LN hyperplasia, mild pigment in LN, min to mild chronic inflammation, min bronchialization, min to mild alveolus pigmentation, min proteinosis, alveolar/bronciolar adenoma and carcinoma **1.25 mg/m³:** Lung: abs lung weight increased mild broncial LN hyperplasia, mild pigment in LN, min to mild chronic inflammation in lung, proteinosis and alveolus pigmentation, min bronchialization alveolar/bronciolar adenoma and carcinoma	NTP 1996a
2y study, inhalation, F344/N rats, 63m/63f per group Interim evaluation after 7m and 15m	**Nickel subsulfide**, 0, 0.15, 1.0 mg Ni_3S_2/m^3 (0, 0.11, 0.73 mg Ni/m^3) 6h/day 5 days/week	**1.0 mg/m³:** rapid/shallow breathing, lower mean bw, mild incr in HK, Hb and erythrocytes, Ni in kidneys Lungs: incr in abs/rel lung weight, Ni burden, mild to moderate fibrosis and chronic active inflammation, mild focal hyperplasia of alveolar epithelium (11m/11f), moderate alveolar MΦ hyperplasia, moderate alveolar proteinosis, mild lymphoid bronchial hyperplasia and interstitial cellular infiltratation, squamous metaplasia (3m), mild bronchial LN hyperplasia, min MΦ hyperplasia in LN Bronchiolar/alveolar adenoma Nose: mild chronic active inflammation, min olfactory epithelium atrophy Adrenal glands: Benign pheochromocytoma **0.15 mg/m³:** Ni in kidneys Lungs: incr in abs/rel lung weight, Ni burden, mild to moderate fibrosis and chronic active inflammation, mild focal hyperplasia in alveolar epithelium (6m/10f), alveolar MΦ hyperplasia and alveolar proteinosis, min lymphoid bronchial hyperplasia, min interstitial cellular infiltration, mild bronchial LN hyperplasia, min MΦ hyperplasia in LN squamous metaplasia (2f) Bronchiolar/alveolar adenoma and carcinoma, squamous cell carcinoma (1f) (overall rate carcinoma/adenoma Adrenal glands: Benign pheochromocytoma	NTP 1996b

Method, GI, deviations if any, species, strain, sex, no/group	Test substance, dose levels, duration of exposure	Results	Reference
2y study, inhalation, B6C3F mice, 80m/80f per group Interim evaluation after 7m and 15m	**Nickel subsulfide**, 0, 0.6, 1.2, mg Ni_3S_2/m^3 (0, 0.44, 0.88 mg Ni/m^3) 6 h/day, 5 days/week	**1.2 mg/m³:** red bw, laboured respiration, incr HK, neutrophils and lymphocytes (f), incr abs/rel lung weight (m/f), incr Ni concentration in lungs Lung: min fibrosis, min chronic active inflammation, mild bronchialization, mild alveolar MΦ hyperplasia, moderate alveolar proteinosis, mild interstitial cellular infiltrate, bronchial LN mild lymphoid and min MΦ hyperplasia, Nose: min olfactory epithelium atrophy **0.6 mg/m³:** red bw, laboured respiration, incr abs/rel lung weight (m/f), incr Ni concentration in lungs Lung: min fibrosis and chronic active inflammation, min bronchialization, mild alveolar MΦ hyperplasia, mild alveolar proteinosis, mild interstitial cellular infiltrate, bronchial LN mild lymphoid and min MΦ hyperplasia, Nose: min olfactory epithelium atrophy	NTP 1996b
2y study, inhalation, F344/N rats, Main group: 63-65m/63-64f per group Interim evaluation after 7m and 15m	**Nickel sulfate hexahydrate**, 0, 0.12, 0.25, 0.5 mg $NiSO_4$ $6H_2O/m^3$ (0, 0.03, 0.06, 0.11 mg Ni/m^3) 6 h/day, 5 days/week	Dose dependent incr in Ni lung burden **0.5 mg/m³:** Lung: incr abs/rel lung weight (m/f), mild chronic active inflammation and alveolar proteinosis, mild alveolar MΦ hyperplasia and bronchial LN hyperplasia, min to mild fibrosis, Nose: incr in olfactory epithelium atrophy **0.25 mg/m³:** Lung: min to mild chronic active inflammation, min alveolar MΦ hyperplasia, alveolar proteinosis and fibrosis	NTP 1996c
2y study, inhalation, B6C3F mice, 80m/80f per group Interim evaluation after 7m and 15m	**Nickel sulfate hexahydrate,** Main group: 0, 0.25, 0.5, 1 mg $NiSO_4$ $6H_2O/m^3$ (0, 0.6, 1.1, 2.2 mg Ni/m^3) 6 h/day, 5 days/week	**1 mg/m³:** Red bw gain (m/f) Lung: min chronic active inflammation, bronchialisation, interstitial infiltration and mild alveolar proteinosis, mild MΦ hyperplasia in lung and bronchial LN (lymphoid) Nose: olfactory epthelium atrophy **0.5 mg/m³:** Red bw gain (f) Lung: min chronic active inflammation, bronchialisation, interstitial infiltration and alveolar proteinosis (f), MΦ hyperplasia in lung and bronchial LN Nose: olfactory epthelium atrophy **0.25 mg/m³:** Red bw gain (f) Lung: min chronic active inflammation, bronchialisation and MΦ hyperplasia	NTP 1996c

Table 29: Summary table of Repeat Dose inhalation studies

Method, GI, deviations if any, species, strain, sex, no/group	Test substance, dose levels, duration of exposure	Results	Reference
2y study, plus up to 11m recovery Inhalation Wistar rat Core study: 50m/50f Satellite group for Ni lung burden /hematology / BALF: 22m/22f	**Nickel metal powder** 0, 0.1, 0.4, 1 mg Ni/m^3 6 h/day, 5 days/week	Dose dependent incr in Ni lung burden **1 mg/m^3:** Early termination after 1y exposure due to increased mortality **0.4 mg/m^3:** High mortality in f, incr respiratory rate, cyanosis of extremities, red BW/bw gain, incr in HK, Hb, erythrocyte count (m/f), incr abs/rel adrenal gland weight benign/malign pheochromocytomas in adrenal medulla (m), adenoma/carcinoma of adrenal cortex (f) Lung: incr abs/rel weight, alveolar proteinosis and intra alveolar MΦ, neutrophil count incr, chronic active inflammation, bronchio-alveolar hyperplasia, neutrophil count, LDH, benign/malign pheochromocytomas in adrenal medulla (m) **0.1 mg/m^3:** incr respiratory rate, red BW/bw gain (m), incr in HK, Hb, erythrocyte count (m) Lung: incr abs/rel weight non-significant incr, alveolar proteinosis, neutrophil count incr LOAEL 0.1 mg Ni/m^3	Oller et al 2008

Repeated dose toxicity studies in rats or mice by the oral route (gavage, drinking water or dietary) have shown that soluble nickel compounds like acetate, chloride or sulphate induce mainly non-specific indications of toxicity such as decreases in body weight, feed or water consumption (ATSDR 2005; Danish EPA (2008). In addition reduced survival was also often observed. Nickel sulphate ingestion via feed or drinking water was associated with weight loss, and increased urinary albumin. In a 2 year gavage study with rats, decreased survival and reduced body weight gain was found. Reduced survival was also found with gavage administration of nickel chloride. In a 180-day study in mice, the primary toxic effects were observed in the myeloid system. There are no data on effects following repeated oral exposure with insoluble nickel compounds.

EFSA (2015) reported that the lowest NOAEL for long-term exposure to nickel is 2.2 mg Ni/kg b.w. per day from a 2-year oral rat study (Heim et al. (2007). This study is summarised in the table below.

Table 30: Summary table of Repeat Dose oral study

Method, GI, deviations if any, species, strain, sex, no/group	Test substance, dose levels, duration of exposure	Results	Reference
2y study, Oral gavage F344 rats, 60m/60f per group	**Nickel sulfate hexahydrate,** 0, 10, 30, 50 mg $NiSO_4$ $6H_2O$/kg bw daily	**50 mg/kg bw:** Red bw gain (m/f), **30 mg/kg bw:** Red bw gain (m), **10 mg/kg bw:** No adverse effects NOAEL 10 mg/kg bw/d (2.2 mg Ni/kg bw/d) LOAEL 30 mg/kg bw/d (6.7 mg Ni/kg bw/d)	Heim et al 2007

Dermal repeated dose toxicity data are lacking for soluble as well as insoluble nickel compounds. Dermal absorption is expected to be limited.

7.3.3 *In vitro* data

There are no *in vitro* data related to repeated dose toxicity available.

7.3.4 Summary

Generally, chronic inhalation exposure to nickel dusts and aerosols contribute to respiratory disorders such as asthma, bronchitis, rhinitis, sinusitis, and pneumoconiosis (USAF 1990). A number of human studies have examined the potential of nickel and nickel compounds to induce respiratory effects, although studies on non-malignant respiratory diseases in nickel-exposed workers are limited. Most of these studies were cohort mortality studies in nickel-exposed workers.

Whereas oral exposure to nickel is not known to lead to sensitization, oral absorption of nickel is able to elicit eczematous flare-up reactions in the skin in nickel-sensitized individuals.

Studies in rats and mice demonstrate that chronic active inflammation in the lungs is the most prominent effect following inhalation exposure and the major effects observed following oral exposure were decreases in body weight, effects on organ weights (liver and kidneys), hepatotoxicity, nephrotoxicity, and irritation of gastrointestinal tract at high doses.

7.4 Irritancy and corrosivity

There is very little published human or animal data on the irritation/corrosion of the skin or the eye irritation by nickel or its compounds. The available data are included in reviews such as ATSDR (2005), the EU RAR (2008), the Danish EPA (2008) and more recently in the EFSA Scientific Opinion (EFSA 2015) and refer to studies done more than 20 years ago. There are two nickel compounds with corrosive classifications, namely nickel octanoate and nickel diperchlorate.

7.4.1 Human data

Although there is very little reported human studies, the impairment of the skin barrier by skin irritants for the development and induction of allergic reactions is well known. Human data shows that solutions of nickel sulphate at concentrations > 20% are irritating and a

similar effect is also seen with nickel dichloride (Environment Canada and Health Canada, 1994).

Kalimo & Lammintausta (1984) tested nickel chloride and nickel sulphate in patch tests with 24 and 48 h exposures. A 5% nickel chloride solution also caused irritation under occlusion, whilst a 2.5% solution could be used for patch testing. The standard patch test material for nickel sulphate (assumed to be 5%) was also irritant after occlusion.

Frosch & Kligman, (1976) included nickel sulphate in a study performed to develop a new test for skin irritancy and reported “a marginal irritant” at 0.13% but “a ferocious one at 1%: on scarified skin nickel sulphate gave a dose-dependent response in the test, ranging from a score of 1 at a concentration of 0.13% to 4 at 1%.

The respiratory tract is also a target organ for allergic manifestations of nickel exposure and mucosal irritation and asthma (in workers) have been reported following exposure to inorganic nickel compounds (WHO 2000) (see also section 7.5)

Mechanical irritation of the eye may be caused by exposure to nickel metallic particles based on physical properties and it is therefore recommended that metallic nickel powders should be labelled as an eye irritant.

7.4.2 Animal data

Adverse effects were observed in rats treated dermally with ≥40 mg Ni/kg/day as nickel sulphate for 15 or 30 days (Mathur et al. 1977). The effects included distortion of the epidermis and dermis after 15 days and hyperkeratinization, vacuolization, hydropic degeneration of the basal layer, and atrophy of the epidermis at 30 days.

Biochemical changes in the skin (enzymatic changes, increased lipid peroxidation, and an increase in the content of sulfhydryl groups and amino nitrogen) were observed in guinea pigs dermally exposed to nickel sulphate for up to 14 days (Mathur et al. 1988, 1992). Additive effects were observed when nickel sulphate was given in combination with sodium lauryl sulphate.

The Danish EPA (Danish EPA 2008) reported that there is a marked difference in the results of animal studies on eye irritation with nickel sulphate and nickel dinitrate. Whilst there is little sign of irritation with nickel sulphate, animal data shows severe eye irritation with nickel nitrate. It has been suggested that this is related to the oxidising potential of the compound.

7.4.3 *In vitro* data

There are limited *in vitro* data related to irritancy/corrosivity. The following study by Suh et al (2014) includes *in vitro* data on Reconstructed human epidermal (RHE) tissue.

Table 31: Summary table of *in vitro* data on skin corrosion/irritation

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
In vitro dermal toxicity assays were conducted based on the OECD guidelines	Electric arc furnace (EAF) steel slag (w 0.004% Ni)	Reconstructed human epidermal (RHE) tissue 25mg, 1 & 3h OECD 431 and 439: dermal corrosion and irritation testing	Not corrosive and no irritation.	Suh et al 2014

7.4.4 Summary

Metallic nickel is not a skin or an eye irritant, although mechanical irritation of the eye may be caused by metallic powders. The available data for skin irritation produced by the soluble nickel salts indicates that they are skin irritants, although the data are not entirely consistent. As most nickel compounds are skin sensitisers and the impairment of the skin barrier by skin irritants for the development and induction of allergic reactions is well known, it can be concluded that many nickel compounds will exhibit some degree of skin irritation, although skin irritation is not required for skin sensitisation.

7.5 Sensitisation

7.5.1 Human data

Respiratory sensitization

Nickel sulphate has been established to cause occupational asthma (Baur and Bakehe 2014). However, the occurrence of nickel-induced asthma among exposed workers is rare compared to contact dermatitis (Fernández-Nieto et al. 2006a).

In the literature, there have been several case reports of nickel-induced asthma associated with exposure to nickel sulphate; some have been confirmed by inhalation challenge test. Specific IgE antibodies to nickel-human serum albumin conjugate have been reported in some cases (Malo et al. 1982, Block and Yeung 1982, Novey et al. 1983, Dolovich et al. 1984; Nieboer et al. 1984, Malo et al. 1985, Estlander et al 1993; Fernández-Nieto et al. 2006b). Nevertheless, there are actually only few case reports suggesting evidence for specific IgE, positive skin tests and positive provocation tests with nickel sulphate in exposed persons, and pointing to a workplace related asthmatic diseases (Cirla et al. 1982, Bright et al. 1997).

Asthmatic disease resulting from inhalation exposure to nickel and nickel compounds has been reported for nickel-plating workers and stainless steel welders (ATSDR 1988). Nicklin and Nielsen (1994) categorized these responses as (1) a rapid onset attack (antibody-mediated Type I hypersensitivity) associated with acute bronchospasm, (2) a late response reaction at 6-12 hours after exposure (antigen-antibody immune complex-mediated inflammatory reaction), and 3) a mixed or combined response.

Occupational asthma is also caused by stainless steel welding fumes which contain both chromium and nickel compounds. Hannu et al. (2007) reported a series of 34 cases in 1993-2004 with diagnosis confirmed with an inhalation challenge test using stainless steel welding fumes in a special welding chamber. Skin prick tests were performed with nickel, chromium and cobalt salts in 70% and none showed positive allergic reactions. No serum measurements for specific IgE to nickel, chromium or cobalt salts were performed. The underlying mechanism of stainless steel induced occupational asthma is unsettled, but based on the results Hannu et al. (2007) estimated an occupational asthma incidence of 0.9 – 2.0 per 1000 per year in Finland.

Recently, lymphocyte transformation was demonstrated in patients with nickel-induced asthma, suggesting that cell-mediated hypersensitivity may play a part in nickel induced asthma (Cruz et al. 2006). However, in most occupational activities, salts of – mostly transition – metals and nickel are usually manipulated in combination (Fernández-Nieto et al. 2006a). In some cases, cell-mediated immunity to nickel as well as cobalt is implicated with asthma induced by hard metal dust comprised principally of tungsten and cobalt, but sometimes containing also nickel (Shirakawa et al. 1990, Kusaka et al. 1991).

As reported (Danish EPA 2008) the Ni^{2+} ion is considered exclusively responsible for the immunological effects of nickel. As nickel sulphate is considered to induce respiratory sensitisation it must be assumed that nickel chloride, nickel dinitrate, nickel carbonate and nickel hydroxide also may have the potential to induce respiratory sensitisation and thus, should be regarded as respiratory sensitisers. However, it may be noted that nickel

carbonate and nickel hydroxide are not as water soluble and so the potential for sensitisation may not be the same.

Skin sensitization

Nickel is a well-known skin sensitiser and allergic contact dermatitis is a commonly reported effect in humans exposed to nickel.

Skin sensitisation appears to occur across a very wide range of nickel compounds with the soluble salts showing considerable potency as initiators of this effect, although the insoluble nickel oxides are also considered to meet the criteria for classification as skin sensitisers.

Allergic skin reactions to nickel (dermatitis) have been documented both in nickel workers and in the general population. Allergic contact dermatitis, (i.e. type IV hypersensitivity), is the most prevalent effect of nickel in the general population (Hostynek, 2006). However, in contrast, to the reported decrease of nickel as a cause of occupationally-induced skin reaction (WHO 2000), there is evidence that nickel is increasingly a major allergen in the general population. It has been reported (EFSA 2015) that in the USA, nickel allergic contact dermatitis has an incidence of 14.3 %, and is on the rise from 10 years ago when the incidence was 10 %. Similar figures have been reported by Schnuch et al. (2002), who reviewed information from EU, Asia and USA, and by Mortz et al (2013) (see table below) reporting on a cohort study of school children, and in which nickel sensitization was observed in 11.8 % of the study group. A rise in nickel sensitization has been presumed to represent an increased exposure to nickel in the environment-especially in costume jewellery and belt buckles (Silverberg et al., 2002). There have been a number of recent reports supporting this trend and its presence in working environments, which may have some relevance for monitoring purposes. The table below summarises relevant recent studies. It is also noted that there are a number of studies investigating prevalence of nickel allergy in the EU in which downward trends have been observed (Thyssen et al. (2009), Carøe et al. (2011), Schnuch et al. (2011), Schnuch and Schwitulla (2013), Vongyer and Green (2015), Smith et al. (2016), Fall et al. (2015), however the studies did not allow a conclusion to be drawn regarding this trend in nickel sensitised people. This report does not further discuss this.

Table 32: Summary table of human studies on skin sensitisation

Type of data / report	**Test substance** (exposure substance)	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
Cross-sectional	Nickel metal	Human (cohort of eighth grade students in Denmark, 15 year follow-up) n=442 (with patch tests) 66, 33 and 11 µg/cm2 Patches were removed after 48 hr, and test readings were performed at D3/4.	Point prevalence of nickel allergy was 11.8% (clinical relevance 80.8%). The 15-year incidence rate was 6.7%. In women, childhood atopic dermatitis associated with nickel allergy in adulthood, only ear piercing before the Danish nickel regulation was associated with adult nickel allergy	Mortz et al 2013
Cross sectional	Nickel metal	Human (adolescents in Poland)	Positive patch tests in nickel (12.3% of	Krecisz et al 2012a

Type of data / report	Test substance (exposure substance)	Relevant information about the study (as applicable)	Observations	Reference
		n=528 5.0% nickel sulfate in petrolatum Readings after 2 and 4 days after test application.	females; 1.4% of males); tested items for nickel content: 10.0% of earrings, 11.4% of snaps, and 56.2% of belt buckles	
Cross-sectional	Nickel-unspecified	Human (representing various occupations) n=21 0.05-45 µg/cm2 48 hours. Finger-immersion technique - using the International Contact Dermatitis Research Group classification.	Nickel levels on the fingers of nickel platers, cashiers, sales assistants, caterers, and office staff were at or above 0.035 µg/cm2. A single application of 5 µg/cm2 when read at 2 days induced a dermatitis reaction in six of 21 nickel-allergic subjects.	Gawkrodger et al 2011
Cross-sectional study	Nickel-unspecified	Human (adults in Copenhagen aged 18-69 years) n=3203 Readings after day 2	Contact sensitization to at least one allergen, but not nickel and thimerosal' was significantly associated with atopic dermatitis (odds ratio 2.53 (1.59-4.04). In a subanalysis in nonpierced women, a positive association was also found for nickel sensitization.	Thyssen et al 2012
Cross-sectional study	Nickel-unspecified	Human (patients in Italy) n=12492 (n=4334; 34.7% with positive patch results) nickel sulfate 5.0% in petrolatum 48 h exposure, examined after 24 hrs post removal	Nickel sensitisation significantly higher in females OR=6.1(5.2-7.1); and in those with cosensitization with cobalt, with chromium, or with both metals, also ↑ in metal and mechanical workers and cleaners	Rui et al 2012b
Cross-sectional study	Nickel-unspecified	Human (patients with suspected allergic dermatitis in Italy) n=19 088 (67.2% women, 32.8% men). Nickel sulphate 5.0% in petrolatum. Patches were removed after 48 hr, and test readings were performed at D3	The prevalence of nickel sensitization decreased significantly among younger women (≤26 years), from 38.3% (1996–1998) to 29.0% (2008–2010), whereas an increase was observed in the 36–45-year and 46–58-year age groups.	Rui et al 2012a

Type of data / report	Test substance (exposure substance)	Relevant information about the study (as applicable)	Observations	Reference
			Study showed decreasing trend of nickel sensitization only among younger women.	
Cross-sectional study	Nickel-unspecified	Human n=529 in 12 factories in China 0.2mg/cm2 in patch-test	In workers with OCD, patch-tests identified nickel sulfate as the most frequent allergic response. 1-year prevalence for clothing employees = 10.8% for workers vs 3.2% for managers	Chen et al 2017
Review + Case report	v	Human n=3	Contact allergic dermatitis developed through occupation-related exposure (chemical laboratory assistant, flight attendant, or cashier). In general prevention measures reduced effects.	Tanko et al 2008
Cross-sectional	Nickel-unspecified	Human (adult patients in Lithuania) n=297 5% concentration Examined patches after 3, 4, and 7 days	30.6% showed nickel allergy; 16.4% increase in sensitization in 2006-2008 and 30.6% increase in 2014-2015 ($p<0.0001$)	Linauskien et al 2016

Systemic Nickel Allergy Syndrome (EFSA 2015)

Whereas contact allergy is the most frequent clinical pattern in nickel-sensitized individuals and resistance to infections may be influenced, many other clinical elements may demonstrate that the systemic absorption of nickel, e.g. by the oral route, is able to elicit gastrointestinal (e.g. abdominal pain, diarrhoea and/or constipation, nausea and/or vomiting), atypical systemic manifestations (e.g. Nickel in food and drinking water EFSA Journal 2015;13(2):4002 90 headache, chronic fatigue) and chronic dermatological symptoms (e.g. urticaria-angioedema), that are called Systemic Nickel Allergy Syndrome (SNAS). Whereas the relationship between acute contact dermatitis (ACD) and contact with nickel is undisputed and widely confirmed in literature, the situation is different for SNAS, where further evidence is needed to confirm the effects. The current information that is available about SNAS and its relationship with oral nickel exposure does not allow

to draw final conclusions and further and broader studies, more rigorously conducted, are needed.

7.5.2 Animal data

Respiratory sensitization

There are no available data on respiratory sensitisation in animals.

Skin sensitization

There is limited available data on nickel sensitivity in animals, with some old studies where nickel sensitisation has been induced in guinea pigs following skin painting or intradermal injection with nickel sulphate (Turk and Parker 1977; Wahlberg 1976; Zissu et al. 1987; Rohold et al 1991; Nielsen et al 1992) and dermal sensitisation has been seen in mice (Siller and Seymour 1994). However very little sensitisation was seen in similar studies with nickel chloride (Goodwin et al 1981; Hicks et al 1979).

However the mouse local lymph node assay (LLNA) has failed to show a positive response for nickel sulphate, even with different vehicles and exposure regimens (Kimber et al., 1990; Ikarashi et al., 1992; Ryan et al., 2002) and only a modest response for nickel chloride (Basketter et al., 1994). Nickel has been regarded as a "false negative" in the LLNA, and in other animal tests for measurement of skin sensitization potential (Kimber et al 2011).

More recent studies show similar results nickel chloride andnickel sulphate as reported in earlier studies; these studies are summarised in the table below.

Table 33: Summary table of animal studies on skin sensitisation

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Results	Reference
Dermal exposure	Female mice (C57BL/6, C3H/HeN, C3H/HeJ)	$NiCl_2$ (10%)	~100 mg/ear of 10% NiCl2 in white pet., applied to ears for sensitisation, then challenged twice on consecutive days, after 3 weeks Sacrificed 2 days after first challenge	Sensitised mice displayed larger degrees of swelling compared to naive mice and untreated mice, and sensitised mice had significant increases in CD4+ and CD8+ T lymphocytes	Vennegaard et al 2014
Intradermal application	Female C57BL/6 mice	Ni(II) or Ni(III) chloride (for sensitization)	Sensitisation: 10mM Ni by (A) intradermal injection, (B) epicutaneous application, (C) topical administration, or (D) gavage. Challenge: (A) injection into ear, (B) epicutaneous application, (C) and (D) intradermal. Challenge	Ni exposure classified as irritant, not allergic response: No significant differences in skin reactions in sensitized and non-sensitized mice	Johansen et al 2010

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Results	Reference
			performed 10 days after sensitisation. Observations made 2 days after challenge.		
Tests for local effects after implantation. ISO 10993-6:1994. Also OECD 406	Guinea Pigs	Ni (metal) implants, (patch test for sensitisation with 5% Ni sulfate in petrolatum)	Ni implants inserted in muscle 9 months	Both treatment groups: displayed sensitisation - determined by patch test (allergic contact dermatitis), and ↑ peripheral blood eosinophils	Kręcisz et al 2012b
OECD 404 and 406: dermal (A) toxicity and delayed (B) contact sensitization testing	Rabbits, guinea pigs	Electric arc furnace steel slag w/nickel	Slag contains 44.2 mg/kg Nickel. (A) 0.5 g of slag was mixed with 0.25 ml of distilled water, (B) 3 induction doses of 0.5g slag plus 1 challenge dose of 0.5g slag (A) applied for 4 hours monitored up to 7 days, (B) applied for 2h/week for 3 weeks, then challenged 14 days after last induction dose	No toxicity or sensitisation	Suh et al 2014

7.5.3 *In vitro* data

There are no *in vitro* data on sensitisation in animals.

7.5.4 Summary

Nickel is a well-known skin sensitiser and allergic contact dermatitis is a commonly reported effect in humans exposed to nickel. In contrast to this extensive documentation for skin sensitisation, the data for respiratory sensitisation is very limited and only for nickel sulphate based on a limited number of cases, although it would be prudent to assume that other “water soluble” nickel compounds such as nickel chloride, nickel dinitrate, nickel carbonate and nickel hydroxide may also have the potential to induce respiratory sensitisation, although it may be noted that nickel carbonate and nickel hydroxide are not as water soluble and so the potential for sensitisation may not be the same.

Exposure through skin or airways may lead to the respective nickel sensitization (i.e. the type of sensitisation is associated to the route). A combination of nickel with circulating or tissue protein gives rise to new antigens and acts as a contact allergen and causes sensitization. Whereas oral exposure to nickel has not been demonstrated to lead to

sensitization, oral absorption of nickel is able to elicit eczematous flare-up reactions in the skin in nickel-sensitized individuals

There is limited available data on nickel sensitivity in animals, with clear evidence for skin sensitisation with nickel sulphate but less evidence for nickel chloride.

7.6 Genotoxicity

The genotoxicity of nickel compounds has been reviewed by several organizations including IARC (1990, 2012), US EPA (1996), NiPERA (1996); TERA (1999), ATSDR (2005), and EU RAR (2008) and EFSA (2015). The following section includes information from these reviews and where relevant, includes more recent published literature from searches conducted for this report.

7.6.1 Human data

DNA damage and chromosomal alterations have been analysed in cells from nickel exposed workers with inconsistent findings (EFSA 2015). The table below summarises the studies reported by EFSA giving both positive and negative examples.

Table 34: Summary table of studies in workers exposed to nickel

Type of data / report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
Analysis of genotoxic effects	nickel	Urinary concentrations of Ni in workers were 0.1–2 micromol/L measuring micronuclei frequency in smears from the buccal mucosa	No relationship was observed between micronucleus frequencies and levels of Ni in air, urine or blood.	Kiilunen et al. 1997
DNA damage /strand breaks	chromium and Ni	Measured DNA SSB and SCE frequencies in lymphocytes of welders exposed to chromium and nickel	elevated DNA SSB and SCE frequencies but not possible to assign the effects solely to Ni.	Werfel et al. 1998
A cross-sectional study to investigate the association between metal exposure and oxidative DNA damage	Chromium, cadmium, and Ni	824 participants was conducted from 1993 to 1994 (Germany)	A positive association between Ni levels and the rate of oxidative DNA lesions (Fpg-sensitive sites) was observed (odds ratio, 2.15; tertiles 1 versus 3, $P < 0.05$).	Merzenich et al., 2001.
A population study to monitor DNA damage	Cr and Ni	Welders and an equal number of control subjects; (i) monitor DNA damage in blood leucocytes; Comet Assay (ii) Micronucleus test on buccal epithelial cells	Welders + higher Cr + Ni content cf controls; Ni = 132.39 versus 16.91 µg/L; $P < 0.001$; Welders = significant increase in micronucleated cells cf controls; Significant effect on DNA mean tail Length from	Danadevi et al. 2004

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
			occupational exposure but not possible to say if due to chromium and/or Ni exposure.	

A review of the genotoxicty studies of patients exposed to nickel ions released from nickel containing orthodontic appliances shows equivocal results and that the DNA damage induced by the metal ions could not be exclusively due to the nickel because it is alloyed with metals that are known genotoxins.

A number of studies have been reported where an increase in DNA damage of buccal mucosa cells has been observed and also studies showing an increase in the frequency of micronuclei, however there are also a number of studies where there has been no significant difference in the micronuclei frequency and both *in vivo* and *in vitro* studies have demonstrated that nickel-titanium alloys have low or no cytotoxicity or genotoxicity (Wever et al., 1997; Es-Souni et al., 2005). Morán-Martinez et al (2013) reported that the DNA damage induced by metal ions could not be exclusively due to the nickel as it is alloyed with steel (Fe) and chromiumand both metals have known genotoxic effects. The table below summarises the studies.

Table 35: Summary table of studies in patients with Ni alloy orthodontic appliances

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
To determine genotoxicity	Ni alloy	AISI type 304 bands, AISI type 316 brackets (containing Fe, Cr, Ni, Mo), and Ni-Ti alloy arch wires (50.8% Ni, 49.2% Ti) for 2-4 years. nickel-titanium alloy; (nickel, 50.8%; titanium, 49.2%), stainless steel; nickel, 8.6%; iron, 72.6%; chromium, 20%), or chromium-cobalt-nickel alloy; nickel, 15%; iron, 16%; chromium, 20%; cobalt, 42%; molybdenum, 7%	observed an increase in the DNA damage of mucosa cells	Faccioni et al. (2003)
To determine genotoxicity	Ni alloy	treatment with standard stainless steel bracket of 50-80% Fe, 3-15% Ni, 13-23% Cr and stainless steel arch wire of 69.5% Fe, 9% Ni, 18% Cr, 2%	significant increase in DNA damage of buccal mucosa cells reported at 3 months but not at 6 months after treatment. Ti and Mn concentrations were greatest in the mucosa cells in contact with the stainless steel alloy whilst Cr and Fe	Hafez et al., 2011

Type of data / report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
			were highest in the cells in contact with the nickel-free alloy	
To determine genotoxicity	Ni alloy	stainless steel and nickel-free orthodontic brackets	induced increased DNA damage in the oral mucosa cells of patients 30 days after treatment	Fernández-Miñano et al., 2011
To determine genotoxicity	Ni alloy	The metal crowns were made of alloy containing 70.85% Fe, 19.28% Ni and 9.62% Cr To determine genotoxicity: (i) Ni in buccal epithelial cells; (ii) urinary excretion of Ni, in children (n = 37) with metal crowns; Micronuclei assays were performed using buccal cells from 37 patients: Ni levels were determined from urine samples using inductively coupled plasma mass spectrometry at 1 (basal value), 15, and 45 days following the placement of crowns in each patient.	Ni urinary excretion levels and the frequency of exposed micronuclei showed no significant increase in days 1-15 but a small increase (in males only) at day 45. post-crown placement.	Morán-Martínez et al., 2013
To determine genotoxicity	Ni alloy	AISI type 304 bands, AISI type 316 brackets and NiTi alloy archwires	significant increase in MN frequency at debonding in mucosal smears; reported "*no correlation could be established between micronuclei frequency and metal ion content*"	Natarajan et al., 2011
To determine genotoxicity	Ni alloy	orthodontic appliances of fixed stainless steel alloy (15.5-17.5% Cr, 3-5% Ni, 3-5% Cu, 1% Mn, 1% Si, 0.07% C, 0.15-0.45% niobium+tantalum)	a significant increase in MN frequency in buccal cells 30 days after treatment; observed no increase in Comet Assays 10 days after treatment	Westphalen et al., 2008
To determine genotoxicity	Ni alloy	AISI 302 stainless steel orthodontic brackets, bands, and NiTi or AISI 302 stainless steel arch wires.	no significant difference in the MN frequency before and 9 months after placement of orthodontic appliance	Heravi et al. (2013)

Type of data / report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
To determine genotoxicity	Ni alloy	stainless steel orthodontic brackets of 71% Fe, 8% Ni, 19% Cr, NiTi arch wires of 50.8% Ni, 49.2% Ti or stainless steel of 72.6% Fe, 8.6% Ni and 20% Cr	no significant difference in MN mucosa cells in patients before and at least 6 months after placement of stainless steel orthodontic appliance	Angelieri et al., 2011
cytotoxicity test, a guinea-pig sensitization test + 2 genotoxicity tests	NiTi alloy	an end-point dilution minimal essential medium (MEM) extract cytotoxicity test, a guinea-pig sensitization test and two genotoxicity tests: the Salmonella reverse mutation test and the chromosomal aberration test.	no cytotoxic, allergic or genotoxic activity observed	Wever et al., 1997
in vitro cytotoxicity, in vitro genotoxicity tests	NiTi Alloy	biocompatibility of NiTi shape memory alloys; Chemical induction of chromosome aberration; Bacteria reverse mutation assay; Mouse micronucleus test; Detection of DNA-single strand breaks via EM-ISEL	these alloys have low cytotoxicity (both in vitro and in vivo) as well as low genotoxicity	Es-Souni et al., 2005

7.6.2 Animal data (in vivo)

DNA damage

There is evidence that both soluble and insoluble nickel compounds give rise to both DNA breaks and DNA-protein crosslinks *in vivo* as reported by EFSA and the Danish EPA (EFSA 2015, Danish EPA (2008). Recent studies by Benson et al. (2002) have shown DNA-strand breaks (Comet assay) in the lung after repeated 3 or 13 week exposure to nickel sulphate (NOAEL 0.04 mg/m^3; LOAEL 0.11 mg/m^3) and nickel subsulphide (NOAEL 0.04 mg/m^3; LOAEL 0.11 mg/m^3). The levels associated with increased DNA strand breaks were also levels showing inflammation. Danadevi et al. (2004) have shown that nickel chloride induced single and double stranded DNA breaks as measured by the Comet assay in leucocytes in mice after oral administration.

The formation of DNA SSBs has been reported in rat lung and kidney (Saplakoglu et al 1997) and the induction of oxidative DNA damage has been reported by a variety of nickel compounds in rats (Kawanishi et al. 2002). Kawanishi et al (2002) investigated the participation of ROS in nickel-induced DNA damage and the authors have proposed that *in vivo*, nickel compounds mostly induce indirect oxidative damage via inflammation with the exception of Ni_3S_2 that also showed direct induction of oxidative damage via H_2O_2 formation. This double mechanism might account for its relatively high carcinogenic potential. A significant increase in mean comet tail length indicating induction of single/double-strand breaks was observed with $NiCl_2$ (Danadevi et al. 2004). A gradual decrease was reported at 72 hours indicating the occurrence of repair. These data clearly indicate that $NiCl_2$ is able to induce DNA damage *in vivo*.

Doreswamy et al, (2004) observed in testicular cells of adult albino mice following repeated i.p. administration of nickel chloride, a moderate increase in lipid peroxidation associated with a significant increase in DNA SSBs as measured by a DNA unwinding assay and increased apoptosis at higher doses. An increase in abnormal sperm were also recorded during the first three weeks.

Gene mutations

In vivo mutation studies with nickel compounds were mostly conducted in *Drosophila melanogaster* and showed weakly positive effects (EFSA 2015, Danish EPA 2008). This is consistent with the data seen *in vitro*.

Mayer et al. (1998) reported increased mutation frequency by nickel subsulphide in a lacI transgenic embryonic fibrblast cell line and significant increase of induced DNA strand breaks in nasal mucosa cells of mice but *in vivo* mutagenicity data did not show an increase of mutation frequencies in lacZ and lacI transgenic mice and rats compared to negative controls. DNA SSBs (single strand breaks) were detected in a dose-dependent manner in both cell types. These results support a non-genotoxic model of nickel carcinogenesis, which acts through gene silencing via DNA methylation and chromatin condensation.

Chromosomal effects

The induction of chromosomal aberrations and micronuclei in rodents treated with different nickel compounds is not consistent across studies, although overall, there are *in vivo* data confirming the *in vitro* clastogenicity of nickel compounds.

Chromosomal aberrations have been seen *in vivo* in a number of studies (Chorvatiovicova, 1983; Mohanty, 1987: Sharma et al., 1987; Dhir et al., 1991). This effect has been seen with nickel sulphate, chloride and nitrate. The authors of a much older study in bone marrow and spermatogonial cells (Mathur et al, 1978) claim a negative effect, but without reporting any data in support of this conclusion. The review of the mutagenicity data carried out by NiPERA (2003a) concludes that the Dhir et al. (1991) and the Chorvatovicova (1983) studies are positive. There is also evidence, sometimes with mixed exposure, to show that this effect is also seen in humans, although NiPERA (2003a) does not consider that these studies can be used as evidence.

The data from micronucleus tests are conflicting: negative results have been reported for nickel oxide (NTP 1996a), nickel subsulfide (NTP 1996b) and both nickel sulphate and nickel chloride (Morita et al., (1997). A micronucleus study of nickel sulphate in rats after oral administration (OECD 474) was also negative (Covance 2003) and Deknudt & Léonard (1982) found no effect on micronucleus induction. However, a number of largely Indian studies (Dhir et al., 1991, Sharma et al. 1987, Sobti & Gill, 1989,) have all shown positive results and NiPERA (2003a) agrees that the Dhir et al. (1991) intraperitoneal study is positive, but considers the oral studies (Sharma et al. 1987, Sobti & Gill, 1989) equivocal.

The data from dominant lethal tests (Deknudt & Léonard, 1982, Saichenko, 1985) suggests that there is no significant dominant lethal effect, although the soluble nickel compounds tested may reduce fertilisation rate after intraperitoneal administration. However, Doreswamy et al, (2004) observed that mating of nickel treated males (2.5 micromol/100 g b.w. per day for five days for five weeks) with untreated females resulted in a significant increase in male- mediated dominant lethal-type mutations (frequency of dead implantations) during the first three weeks and an increase in abnormal sperm.A study by Sobti & Gill (1989) also showed a significant increase in sperm head anomalies.

More recently (El-Habit and Abdel Moneim 2014) it has been reported that a dose-related significant increase of polychromatic erythrocytes with micronuclei was observed in bone marrow cells following animal exposure to nickel as compared to the control. Increased frequency of bone marrow cells with aneuploidy and chromosomal aberrations were also induced by nickel and the incidence of micronucleated PCEs decreased in bone marrow cells. Nickel was found to induce also significant DNA damage in mouse bone marrow cells as assessed by the comet assay. These genotoxic effects were associated with a dose-

dependent increase of oxidative stress markers (i.e. lipid peroxidation and nitric oxide) with a significant decrease of the antioxidant GSH content. According to the results obtained, genotoxicity and cytotoxicity effects of nickel *in vivo* are dose-dependent and are associated with oxidative stress. This study is summarised in the table below.

The table below summarises results from a literature search of published papers over the last 10 years.

Table 36: Summary table of mutagenicity/genotoxicity tests in mammalian somatic or germ cells *in vivo*

Method, guideline, deviations	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Bone marrow cells Subcutaneous dose, Comet assay	Ni Cl_2	Male mice bone marrow cells sc dose 1 x/day for 3 days. 40, 80, and 120 µmol/kg b.w./injection	dose-related significant increase of polychromatic erythrocytes with micronuclei increased frequency of bone marrow cells with aneuploidy and chromosomal aberrations significant DNA damage dose-dependent increase of oxidative stress markers + significant decrease of the antioxidant GSH content	El-Habit and Abdel Moneim 2014
Dose by gavage, OECD Guideline 474,	Nickel sulfate hexahydrate	Animals (Young adult male rats of the Sprague–Dawley strain) n=6 per group 125, 250, and 500 mg/kg/day. 3 d	No increase in micronuclie at any dose.	Oller & Erexson 2007
Intraperitoneally injected	NiCl2	Human (Human leukemia HL-60 cells) + animal (C57 mice) n=40 2 or 20 mg NiCl2/kg body weight Daily for 2 weeks	↑ conc of Ni^{2+} e.g.10 mM caused DNA fragmentation + cell death in HL-60 cells ↑ reactive oxygen species generation + DNA fragmentation in mice cells w/low conc of Ni^{2+}	Jia & Chen 2008
Metal mixture added to drinking water	NiCl2	Animals (male Wistar rats) n=50 0.0, 0.810, 8.10, 81.0 ppm or 1x, 10x, 100x	10x and 100x mode dose resulted in time- and dose-dependent in ↑ in lipid peroxidation	Jadhav et al 2007

Method, guideline, deviations	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
		mode dose in Ni concentrations found in groundwater samples in India 90 days	and ↓ in antioxidative defense systems.	
Oral and subcutaneous routes	NiCl2	Animal (Brown Norway rats) n=20 test, n=6 control 4.5 mg in 0.2 ml normal saline 14 weeks	↑ in select serum antibodies in oral and subcutaneous-treated Ni groups.	Al-Mogairen et al 2010
Inhalation	Nickel subsulfide	Animal (Fischer 344 rats) n=13 animals per each time point-exposure level combination. 0.0, 0.04, 0.08, 0.15, and 0.60 mg/m^3 one and four weeks (6 h/day, 5 days/week).	↑ inflammation only at the two highest concentrations activation of genes related to genotoxicity only seen at two highest dose levels BMDL10 for inflammatory pathways was 0.06 and for oxidative stress pathways 0.11	Efremenko et al 2014

7.6.3 *In vitro* data

DNA damage

Water-soluble as well as water insoluble nickel compounds have been shown to induce DNA single strand breaks (SSBs), DNA protein crosslinks (DPCL) and oxidative base damage in mammalian test systems (EFSA 2015, Danish EPA 2008).

Whilst there is very little data other than that on nickel chloride and nickel sulphate, the NiPERA (1996) review indicates that similar effects are seen with both soluble nickel compounds such as the sulphate and chloride and with other, less soluble compounds. The S-phase inhibition seen in CHO cells with metal dust is consistent with this.

Several studies have reported on DNA damage (EFSA 2015, Danish EPA 2008). There are some studies in bacteria showing differential toxicity between repair deficient and normal strains. There are positive studies of gene conversion in yeast, and a series of studies showing induction of DNA single strand breaks in mammalian cells. There is also evidence of DNA synthesis inhibition, disturbance of DNA damage recognition and inhibition of DNA repair. Human cells appear to be more resistant to nickel induced strand breakage than hamster cells (NiPERA, 1996).

Although nickel has a relatively weak affinity for DNA, it has a high affinity for chromatin proteins, particularly histones and protamines (Costa et al. 1994; Kasprzak et al. 2003b; Oller et al. 1997). Nickel's preferential and stronger interaction with proteins than DNA, is noted by the relatively low Ni(II) binding constants of 6.7 X 10^{-1} M^{-1} for adenosine and 7.3 X 10^2 M^{-1} for DNA. In contrast, binding constants of 4.37 X 10^9 M-1 for cysteine, 1.9 X 109 M-1 for histidine or 1-5 X 105 M-1 for other amino acids have been reported (Biggart and Costa, 1986).

Patierno and Costa (1987) reported the first evidence of the enhancement of DNA protein binding by Ni(II) in intact mammalian cells and Chakrabarti et al. (2001) showed that the formation of DPCLs by nickel subsulfide is caused by the formation of ROS. Two mechanisms for nickel induced oxidative DNA damage have been proposed (Inoue and Kawanishi, 1989; Kawanishi et al,1989): i) induction of indirect damage via inflammation, and ii) induction of direct oxidative damage via H_2O_2 formation as in the case of Ni_3S_2.

Pre-treatment of human blood lymphocytes with ROS scavengers or GSH precursors significantly reduced DNA SSBs induced by NiCH in both chromosomal and nuclear chromatin, suggesting the involvement of oxidative stress in SSB induction (M'Bemba-Meka et al. 2005).

Schwerdtle and Hartwig (2006) proposed that the higher carcinogenic potential of particulate nickel compounds may be due to much longer retention times *in vivo* (and therefore persistent DNA repair inhibition) more than to different mechanisms of action at cellular level.

Gene mutations

It is reported that nickel compounds gave negative results in bacterial assays with *S. typhimurium* and *E. coli*. and are inactive in almost all bacterial mutagenicity tests (EFSA 2015, Danish EPA 2008). Equivocal results were reported from an Ames test for nickel subsulfide (NTP 1996b) although overall evidence indicates that nickel compounds are not mutagenic in bacteria.

However, nickel compounds have been shown to be weakly mutagenic in cultured mammalian cells (EFSA 2015, Danish EPA 2008). Many of these studies showed positive results as reported in a mouse lymphoma test for nickel sulphate hexahydrate (NTP 1996c), although many were weakly positive. In some cases, only certain loci were affected (e.g. a positive result at the tk_{slow} locus, but not at the tk_{normal} or hprt loci, Skopek, 1995). Whilst these results may indicate gene mutation, the positive results in at least some of these studies could possibly be due to other genetic events, such as chromosomal aberrations and DNA methylation, rather than point mutations. It has been shown that the increases in mutant frequency seen at the *gpt* gene of v79 cells (Christie et al., 1992) were due to changes in DNA methylation (Klein et al, 1994, Lee et al 1995). DNA methylation seems to be related to the inhibition of tumour suppression genes (Costa & Klein, 1999).

Chromosomal aberrations / effects

The ability of nickel compounds to induce chromosome aberrations was first reported by Nishimura and Umeda (1979). Since then many studies have reported the induction of chromosome aberrations (CA), sister chromatid exchange (SCE), micronuclei, aneuploidy as well as spindle-inhibiting effect (EFSA 2015, Danish EPA 2008). One study showed a dose-dependent increase of chromosomal aberrations (Sen and Costa 1986).

Water-soluble and poorly water-soluble nickel compounds induce SCE, chromosomal aberrations and micronuclei at high (millimolar), cytotoxic levels in different mammalian cell systems. These effects are likely due to aneugenic as well as clastogenic actions. Both nickel chloride and nickel sulphate have been extensively studied.

Cell transformations

Most of the data on cell transformation comes from studies on nickel sulphate, although there are additional studies with nickel chloride and nickel metal. Many of these studies indicate an effect on cell transformation, anchorage independence and loss of cell communication (EFSA 2015, Danish EPA 2008).

EFSA reported four relevant studies with evidence of morphological transformation in different cell systems for soluble and poorly soluble nickel compounds; Costa and Mollenhauer (1980) and Costa et al (1982) suggested that the induction of DNA damage induced anchorage-independent growth, Conway and Costa (1989) identified deletions of

the long arm of the X chromosome. Miura et al. (1989) reported that soluble nickel sulphate and nickel chloride caused dose-dependent cytotoxicity after 48 hours treatments, but neither compound induced morphological transformation even at concentrations causing up to 94% cytotoxicity. Conversely, insoluble nickel subsulphide, nickel monosulphide, and nickel oxide caused dose-dependent cytotoxicity and a low, dose-dependent frequency of morphological transformation.

The table below summarises results from a literature search of published papers over the last 10 years.

Table 37: Summary table of mutagenicity / genotoxicity tests *in vitro*

Method, guideline, deviations	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
No formal guidelines acknowledged	human lymphoblastoid TK6 cell line; nickel chloride monohydrated (NiCl2·H2O) and potassium hexafluoronickelate (K2NiF6)	human lymphoblastoid TK6 cell line nickel chloride monohydrated (NiCl2·H2O) and potassium hexafluoronickelate (K2NiF6) NiCl2·H2O at 0.001-10mM, K2NiF6 at 1-150µM (difference based on solubility and toxicity): 3h DNA damage (comet)	Only NiCl2·H2O was found to be genotoxic.	Guillamet et al 2008
No formal guidelines acknowledged	human B lymphoblastoid cell line, HMy2.CIR nickel chloride (NiCl2)	human B lymphoblastoid cell line, HMy2.CIR nickel chloride (NiCl2) 0.08-0.64 mM; 24-48 h Viability, ROS production, lipid peroxidation (malondialdehyde), DNA damage	Ni only weakly cytotoxic and genotoxic; induced low levels of ROS; did induce lipid peroxidation	Lou et al 2013
No formal guidelines acknowledged	U2OS osteosarcoma cell lines (ATCC HTB-96) Nickel chloride	U2OS osteosarcoma cell lines (ATCC HTB-96) Nickel chloride Nickel chloride, 100 µM, 48hr double strand breaking	DNA repair mechanisms were altered dependent upon exposure dose; both low- and high-dose nickel exposures can effect these pathways, encouraging mutagenesis, inferring potential carcinogenicity.	Morales et al 2016
No formal guidelines acknowledged	Human CD4+ T cells (Th lymphoma Jurkat cell line); Ni++	Human CD4+ T cells (Th lymphoma Jurkat cell line) Ni++ (compared to other metal ions) 0.05-5 mM, 48 h DNA damage (comet), apoptosis, proliferation,	Ni ions caused cell death and reduced viability, and had greater genotoxicity than other metal ions	Caicedo et al 2007

Method, guideline, deviations	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
		viability (PI staining)		
No formal guidelines acknowledged	Structural changes in proteins essential for DNA repair, assessed in response to Ni ions Ni^{2+}	Structural changes in proteins essential for DNA repair, assessed in response to Ni ions Ni^{2+} Structural changes in xeroderma pigmentosum complementation group A protein (XPA) assessed.	Ni^{2+} induced conformational changes in XPA, weakening its effectiveness	Hu et al 2016
No formal guidelines acknowledged	In chemico, and human alveolar epithelial cell line (A549) Ni and NiO	In chemico, and human alveolar epithelial cell line (A549) Ni and NiO particles (nano and micro) 0.1-40 µg/cm2 of culture dish; 24-48 h In chemico assessment of Ni release and ROS production, viability, CFU, DNA damage (comet)	All particles were cytotoxic, nano-sized NiO and one micron-sized Ni induced DNA damage	Latvala et al 2016
In-vitro + In-vivo (intratracheal instillation) No formal guidelines acknowledged	Nickel oxide nanoparticles	Human (lung carcinoma A549 cells) + Animal (rat trachea) 0.2 mg per 0.4 ml (rats) 1, 4, 24, 72 hrs, 1 week	Nickel oxide nanoparticles induce oxidative stress related lung injury. In-vitro and in-vivo oxidative stress was induced resulting in activation of antioxidant systems.	Horie 2011
Inhalation. No formal guidelines acknowledged	Ultrafine NiO	Animals (male Wistar rats) n = 5 per group/time point (0.2mg/m3; 9.2×104 particles/cm3, 59 nm diameter) 6 h a day, for 4 weeks (5 days a week).	↑ gene expression associated with chemokines, oxidative stress, and matrix metalloproteinase 12 (Mmp12)	Fujita et al 2009
No formal guidelines acknowledged; mechanistic	Nickel - unspecified	T-REx 293 human embryonic kidney cells Cells were transfected with wt or truncated histone H2A, epigenetic impact assessed by microarray and PCR	Conclusion: epigenetic changes caused by nickel exposure may be due to Ni-induced truncation of histone H2A	Karaczyn et al 2009
No formal guidelines	Nickel- unspecified	human hepatoma cell line (HepG2)	Of the genes altered by Arsenic,	Kawata et al 2009

Method, guideline, deviations	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
acknowledged		Nickel (also cadmium, arsenic, N-dimethylnitrosoamine, 12-O-tetradecanoylphorbol13-acetate, and tetrachloroethylene) 150µM nickel, 48hr Gene expression	Cadmuim, and Nickel exposures, 31–55% were overlapped with those altered by three model carcinogenic chemical exposures.	

7.6.4 Summary

There is considerable evidence that both soluble and insoluble nickel compounds give rise to both DNA breaks and DNA-protein crosslinks *in vivo* and *in vitro.* Various types of DNA damage have been reported including DNA single strand breaks (SSBs), oxidative base damage and DNA protein crosslinks (DPCLs).

The overall evidence indicates that nickel compounds are not mutagenic in bacteria, however, they have been shown to be weakly mutagenic in cultured mammalian cells. Soluble nickel compounds can induce morphological transformation of mammalian cells *in vitro*.

The induction of chromosomal aberrations and micronuclei in rodents treated with different nickel compounds is not consistent across studies, although overall, there are *in vivo* data confirming the *in vitro* clastogenicity of nickel compounds. There have been many studies reporting ability of nickel compounds to induce chromosome aberrations (CA), sister chromatid exchange (SCE), micronuclei, aneuploidy as well as spindle-inhibiting effect. Chromosomal effects due to both aneugenic and clastogenic activity of soluble nickel compounds have been observed *in vitro*.

Considering the human data, the genotoxicity studies are limited and do not indicate clear positive effects directly linked to nickel exposures. However, altogether the *in vitro*, *in vivo* and human data support the consideration of a MOA-based threshold for nickel compounds (see section 7.9 for discussion on MoA).

There is evidence that genotoxicity and cytotoxicity effects of nickel *in vivo* are dose-dependent and are associated with oxidative stress. The formation of hydroxyl radicals by nickel is strongly suggested as the first step in the formation of all types of nickel induced DNA lesions and the inhibition of DNA repair (caused by nickel compounds) may account for their persistence.

In conclusion, the complexity of the genotoxic effects of nickel compounds reflect the multiple mechanisms that mediate nickel-induced carcinogenesis including ROS production, inhibition of DNA repair, hypoxia-mimicking effects and dysregulation of cell signalling (see section 7.9 on Mode of Action). On the basis of the current data, the genotoxicity of the nickel compounds is likely to be due to indirect effects.

7.7 Carcinogenicity

7.7.1 Human data

Carcinogenic effects of nickel compounds have long been recognised with first reports dating back to 1930s and 1950s as described in the comprehensive epidemiological report of the International Committee on Nickel Carcinogenesis in Man (ICNCM 1990). Several epidemiologic studies have identified an increased risk for lung cancer and cancer of nasal cavities among workers exposed in nickel sulfide ore smelting and nickel refining

processes. For example, workers employed in a nickel refinery in Clydach, South Wales, during the first two decades of operation (1902-1919) had about 6-fold risk of lung cancer mortality and 376-fold risk of nasal cancer mortality as compared to the general population. The refinery is still in operation, and, although procedures changed and exposure levels dropped, a 1.4-fold risk for lung cancer and about 10-fold risk for nasal cancer mortality was observed among workers hired after 1930 or 1953 (summarised by Grimsrud and Peto 2006, see Summary tables of cohort studies

Table 47, Table 48).

While the carcinogenic properties of nickel compounds have been widely accepted, several attempts have been undertaken to elucidate the relative contributions of diverse nickel species, i.e. metallic nickel, poorly water soluble nickel sulfide or nickel oxide and water-soluble nickel salts (Sivulka 2005, Goodman et al 2011, SCOEL 2011, Oller et al 2014).

Lung cancer

Increased risks for lung cancer have been reported in cohorts of nickel smelter and refinery workers in Canada (Ontario), Finland (Harjavalta), Norway (Kristiansand) and United Kingdom (Wales, Clydach) (see Summary tables of cohort studies

Table 47, Appendix 5). There have also been cohort studies among workers exposed to nickel compounds in stainless steel welding. As pointed out in the IARC assessment of the carcinogenic potential of nickel and its compounds such workers are, however, exposed also to chromium(VI) and other compounds and it is difficult to ascribe any excess risk in these cohorts to nickel compounds specifically (IARC 2012). The carcinogenic potential of stainless steel welding and other types welding were also recently re-assessed by IARC (Guha et al 2017). The human evidence concerning lung cancer was based on more than 20 case-control studies and nearly 30 occupational or population-based cohort studies. Welding fumes were classified as “carcinogenic to humans” (i.e. IARC Group 1). This IARC assessment did not, however, conclude on which components of welding fumes are responsible for the respiratory carcinogenic properties observed. As the studies in stainless steel or other welders do not contribute to the assessment of carcinogenic hazard properties of nickel or its compounds specifically, those studies are not further discussed. It is, however, evident that a revised OEL on nickel and its compounds would importantly improve also the occupational safety and health of stainless steel welders. An estimate on the number of stainless steel welders is the EU is not available, but worldwide, an estimated 11 million welders and around 110 million additional workers probably incur welding-related exposures (Guha et al. 2017).

<u>Metallic nickel and nickel alloys</u>

There is only one cohort study with exposure solely to the metallic form of nickel, the Oak Ridge Gaseous Diffusion Plant worker cohort (ICNCM 1990). High purity nickel powder was used to manufacture “barrier”, a special porous material used in the enrichment of uranium by gaseous diffusion. The mortality from lung cancer was not increased overall (SMR 0.54; 95% CI 0.25 – 1.0) and there was no evidence of an increase in risk by duration of employment. The median nickel concentration was 0.13 mg Ni/m^3 with a 90^{th} percentiles of 1.4 and 1.8 mg Ni/m^3 in the two working areas where 70% of the work force was assigned. However these measurements during 1948-63 were assumed to underestimate the historical values. Nevertheless, the average concentrations of airborne metallic nickel were estimated to have been below 1 mg Ni/m^3 (ICNCM 1990).

Egedahl et al (2001) followed a cohort of 1649 hydrometallurgical refinery workers exposed to nickel concentrates and metallic nickel. There was no increase in lung cancer mortality among the nickel exposed workers (SMR 0.67, 95% CI 0.24 – 1.5). Mean exposure to metallic nickel in the two departments were 2 (range 0.7 to 3) and 4 (range 0.3 to 49) mg Ni/m^3. There is, however, indication of a healthy worker effect that may have biased the results as the mortality was significantly below general population rates

overall (SMR 0.57; 95% CI 0.43 – 0.74) as well as for all cancer (SMR 0.47; 95% CI 0.25 – 0.81) as noted by IARC (2012).

Arena et al (1998) studied cancer mortality among 31165 employees from 13 US plants for the production of high nickel alloys. No study-specific exposure data were recorded, but only approximate data from experience for the specific work area, which were scattered over a very wide concentration range. The average airborne nickel concentrations were highest in the area of powder metallurgy with 1.5 mg/m^3, followed by the grinding operation with 0.3 mg/m^3 and the hot working areas with 0.1 mg/m^3, whereas the means in the other areas were lower. These exposure data were largely based upon measurements taken from one plant in the late-1970s. A recent reconstruction of historical exposures of these alloy workers (Sivulka and Seilkop, 2009) indicated that average exposures in process areas outside of powder metallurgy ranged between ≈0.3 and 1.8 mg Ni/m3, with an overall average of 0.65 mg Ni/m3 (1.5 mg/m3 as inhalable). When compared with the cancer mortality data of the total US population, a slight (SMR 1.13), but statistically significantly increased risk of lung cancer mortality was found among workers involved in the production of nickel alloys (see Summary tables of cohort studies

Table 47). The risk was, however, most predominant for employees in the allocated services, i.e. in work areas outside the actual production of alloys in which relatively low nickel concentrations were measured (average 0.07 mg/m^3). Analyses of lung cancer mortality in terms of length of employment and time since first employment did not provide a positive association for any work area or for any sub-cohort defined by sex or race. There was no adjustment for confounding by smoking in the study. When lung cancer mortality rates were compared to local reference rates instead of US national rates, no increase in risk of lung cancer mortality was observed (see Summary tables of cohort studies

Table 47) and the authors pointed out that the above-mentioned risk observed in comparison to US rates “is no larger than that which could be explained by some confounding factor, such as cigarette smoking”.

Sorahan (2004) reported the updated mortality rates among 1999 workers manufacturing nickel alloys in a UK plant. The study showed a statistically significant decrease in overall mortality (SMR 0.79, 95% CI 0.73 – 0.86) and total cancer mortality (SMR 0.81; 95% CI 0.69 – 0.94). This indicates a healthy worker effect. The mortality from lung cancer was decreased (SMR 0.87; 95% CI 0.87; 95% CI 0.67 – 1.1). There were no deaths from nasal cancer (expected number 0.33).

Grimsrud et al. (2002) analysed the role of different nickel species in the increased risk of lung cancer among Kristiansand nickel refinery workers. Although the risk was increased in the highest exposure category for metallic nickel, it was no longer increased after adjustment for the level of exposure to water soluble nickel (see Summary tables of cohort studies

Table 47).

In a study of the Clydach refinery workers Easton et al (1992) used a linear model to quantify the effects of different nickel species on lung cancer mortality. While the initial model suggested a possible role for metallic nickel in the cancers observed. A cross-validation test of the model was performed including only workers employed after 1930 and comparing cancer cases that the model predicted and cancer cases that were observed. This led the authors to conclude that they had likely “overestimated the risk for metallic (and possibly soluble) nickel and underestimated those for sulfide and/or oxides”. The authors also fitted the data to a model where exposure to metallic nickel was not included. This model with the three other nickel species included fitted the data only marginally worse than the original model.

Sivulka (2005) reviewed the human studies available and concluded that “exposure to metallic nickel does not appear to significantly increase the risk of respiratory cancer at concentrations that are as high or higher than those seen in current workplace environments”.

All in all, there seems not to be convincing epidemiological evidence of an increased risk of lung cancer related to metallic nickel.

Water soluble nickel

The human evidence for lung carcinogenicity of water-soluble nickel salts comes mainly from Kristiansand and Harjavalta cohorts and to some extent from the Clydach cohort.

Kristiansand

The Kristiansand workers were employed in electrolytic nickel refining. Until 1978 the exposure to water soluble nickel comprised predominantly of sulphates. After 1978 soluble nickel was found as sulphates in the roasting, smelting, and some other departments while the nickel electrolysis and closely associated departments were dominated by nickel chloride. An exposure matrix was built for epidemiologic analyses by exposure levels of different nickel species in the cohort (Grimsrud et al 2000, see chapter on temporal trends below). Soluble nickel (sulphate/chloride) accounted for more than 80-85% of nickel exposure (by weight) in the electrolysis department and electrolyte purification, while oxidic nickel was predominant in e.g. smelting and roasting. After 1978 the average concentration of nickel in the breathing zone was $\leq$ 0.7 mg/m^3. Before 1970 exposure levels for smelter and roaster workers were 2-6 mg/m^3 while those of workers in electrolysis department and electrolyte purification were 0.15 – 1.2 mg/m^3.

Andersen et al (1996) reported that among the Kristiansand workers the risk of lung cancer increased with increasing exposure to soluble nickel even when adjusted for exposure level of nickel oxide (see Summary tables of cohort studies

Table 47). The overall risk among the exposed was 3.2 fold compared to the national rates. Interestingly there was a 1.8-fold risk also among those refinery workers that were considered unexposed to nickel. There was also some indication suggesting that the interaction between nickel exposure and smoking produced a response greater than their individual responses.

In a later analysis with the above-mentioned refined exposure estimates and extended cancer follow-up Grimsrud et al (2002) analysed the role of water-soluble nickel, sulfidic nickel, oxidic nickel and metallic nickel in the risk of lung cancer. Water-soluble nickel was the only nickel species for which a statistically significant trend of risk was observed for increasing exposure quintiles when adjusted for smoking (see Summary tables of cohort studies

Table 47). The authors reported that a continuous log-linear variable representing exposure to sulphidic nickel produced a negative slope and a similar pattern was observed for oxidic nickel. For water soluble nickel a dose-response function was established that included a constant risk (odds ratio) of 1.5 regardless of exposure level (i.e. any exposure vs unexposed) and a unit increase of risk (odds ratio) of 1.7 per unit in the natural log-transformed exposure given oroginally in (mg/m^3) x years. The authors proposed that the dichotomous term (OR 1.5) would actually represent the risk from any nickel species as exposure to water soluble nickel occurred always when there was exposure to nickel. All in all the analyses by Grimsrud at al. (2002) indicate a peculiar supralinear dose-response for each nickel species, where the risk increases at relatively low cumulative doses (compared to other cohorts) and then increases only modestly (if at all) by increasing cumulative exposure (Summary tables of cohort studies

Table 47). All in all it can be concluded that in every department the exposure to total nickel was higher than the exposure to soluble nickel that was used as the quantitative exposure restimate in the above analysis. According to Grimsrud et al (2003) the fraction

of soluble nickel of total nickel was about 10% in crushing/grinding, old smelter building, calcining smelting department and roasting, about 50% in copper leaching and copper cementing and 80-90% in copper electrolysis, electrolyte purification and nickel electrolysis. As there is indication from animal and human data that the sulfidic and oxidic nickel species increase the risk of cancer, the effect from them should not be ignored. Unfortunately there is no risk estimate available combining the effect of all relevant nickel species in the Kristiansan cohort.

In the most recent cancer follow-up the risk of lung cancer showed a dose-response according to exposure level of water-soluble nickel when adjusted for age and smoking (Grimsrud et al 2003). However, due to collinearity of exposure of the different nickel species, it was not possible to include exposure levels of water-soluble and oxidic nickel in the model at the same time and there was indication of a dose-response also for oxidic nickel (see Summary tables of cohort studies

Table 47). In a later study Grimsrud et al (2005) found that the increased risk of lung cancer from exposure to water-soluble nickel persisted also after adjustment for exposure to other carcinogens in the refinery (arsenic, asbestos, sulfuric acid mist, cobalt) and estimated carcinogenic exposure in work outside the refinery.

More recently Goodman et al (2009) and Heller et al (2010) pointed out that the methodology developed by Grimsrud et al (2000) overestimates the role of water-soluble nickel species and underestimates that of insoluble nickel. In their reply Grimsrud and Andersen (2010) defended their approach that was based on the measurement methodology developed by the industry to differentiate between different nickel species. As summarised by Goodman et al (2011), regardless based either on the ICNCM (1990) or Grimsrud et al (2000) exposure estimate, lung cancer risks were strongly associated with working in electrolysis (with no roasting, smelting or calcining exposure and thus predominant exposure to soluble nickel) in Kristiansand (SMR 3.9; 95% CI 2.6 – 5.5 based on ICNCM 1990 and 5.1; 95% CI 3.2 – 7.7 based on Grimsrud et al 2000 exposure estimates.

Harjavalta

The Harjavalta cohort included workers exposed in the smelter and in the electrolytic refinery. The smelter workers were exposed mainly to nickel matte (mixture of nickel, nickel sulfides and subsulfides), nickel sulfides and nickel subsulfides (Anttila et al. 1998). The primary exposure in the electrolytic refinery was to soluble nickel sulphate although exposure to other nickel species may have occurred to a smaller extent. Until 1973 the leaching and grinding operations took place in the same building as the electrolytic operations resulting to a mixed exposure to soluble and insoluble nickel species. The cancer incidence was not analysed by exposure level but it was reported separately for workers of electrolytic, smelter and repair departments. Industrial hygiene measurements in the smelter in 1983 showed mean personal levels of nickel exposure between 0.02 and 0.2 mg/m^3 with the exception of a single value of 0.7 mg/m^3. The stationary measurements in the electrolysis hall in 1967-1988 remained stable at 0.2 – 0.8 mg/m^3 nickel. The range of nickel concentration in the breathing zone samples in 1979-81 was 0.1 to 0.4 mg/m^3 and the yearly personal mean levels of exposure of the electrolysis workers were estimated to be at most on the order of 0.25 mg Ni/m^3.

Anttila et al (1998) extended the follow-up of Karjalainen et al (1992) and found an increased incidence of lung cancer (SIR 2.6; 95% CI 1.0 – 5.7) in the electrolytic refinery workers. The risk was even higher when a latency time of 20 years from first employment was applied (See Summary tables of cohort studies

Table 47). Among the smelter workers the incidence was increased, but less (SIR 1.4; 95% CI 0.8 – 1.6). In the most recent follow-up a 2-fold risk was observed among the refinery workers and a 1.4 fold risk both among smelter workers and among maintenance workers (Pavela et al 2017, see Summary tables of cohort studies

Table 47). Smoking habits were not systematically collected for the cohort members and the effect of smoking could not be adjusted.

Clydach

The Clydach refinery uses the Mond nickel carbonyl process. The exposure to different nickel species varied between departments (ICNCM 1990). In the hydrometallurgy department water-soluble nickel had an important contribution to the overall nickel exposure, ranging from 30-40% in general to 100% in drying and bagging. The workers, however, had often worked in several departments. Men with more than 5 years of employment in the hydrometallurgy department and less than 1 year in (other) “high risk departments” nevertheless had a statistically significantly increased 3-fold lung cancer mortality as compared to national rates (ICNCM 1990). Easton et al (1992) carried out an updated analysis of the Clydach cohort members with 5 years of exposure before the end of 1969 and using exposures occurring before 1935. For lung cancer the best fitted model suggested risks for soluble and metallic nickel exposures and much less (if any) risk for nickel oxide or sulfide. However, as explained in the chapter for metallic nickel, authors concluded that their method had likely “overestimated the risk for metallic (and possibly soluble) nickel and underestimated those for sulphide and/or oxides”. Smoking habits were not systematically collected for the cohort members and the effect of smoking could not be adjusted.

Other cohorts

The risk of lung cancer was not increased among workers in those electrolysis department workers of the Port Colborne (Ontario, Canada) refinery who had not worked in leaching, calcining and sintering operations (see Summary tables of cohort studies

Table 47). The level of exposure to soluble nickel in the electrolysis department was estimated to be 0.25 mg/m^3 or less.

Grimsrud and Andersen (2012) have pointed out potential methodological problems in the cancer follow-ups of Port Colborne electrolysis workers and other Ontario cohort workers reported in ICNCM (1990). These include “exclusion” from follow-up 26% of the long-term refiners that had died from respiratory cancer in the earlier follow-ups or counting of the expected numbers of cancer for cohort members with unknown vital status at the end of the follow-up (up to 42% of electrolysis workers). A new follow-up study was published recently by Seilkop et al (2016) also clarifying these concerns. Notably no long-term refiners were excluded from follow-ups, while the discrepancy in the numbers of cancers between the studies seemed to be due to the cancer not having been the cause of death. The coverage of the vital status recording was also significantly improved in the latest follow-up, with only 10% of cases having some inaccuracy, and for them person years were calculated only until the date when they were for sure alive. In this latest follow-up Port Colborne electrolysis workers continued to show no clear evidence of increased lung cancer mortality or incidence (see Summary tables of cohort studies

Table 47).

When comparing exposure levels to soluble and insoluble nickel species and risk of respiratory cancer in Kristiansand, Clydach and Port Colborne cohorts ICNCM (1990) found some evidence that soluble nickel could accentuate the risk associated with other nickel compounds.

No increased lung cancer mortality (SMR 1.1; 95% CI 0.5 – 1.9) was found in a cohort of 284 nickel platers in England, who had been engaged in the electrolytic nickel plating of car components from 1945–1975 (Pang et al. 1996). The nickel salts handled by the workers were either chloride or sulphate. The validity of the study is limited because of the unusually short employment periods (median 0.86 years) and the absence of further exposure data.

Järup et al 1998 observed a statistically significant increase in lung cancer mortality (SMR 1.8; 95% CI 1.0 – 2.9) among Swedish battery workers exposed both to cadmium and nickel. There was, however, no dose-response according to cumulative nickel exposure. There was no adjustment for smoking. The exposure to nickel was reported to be to nickel hydroxide, which has a solubility lower than nickel sulphate or chloride but higher than that of nickel oxides and sulfides.

Altogether epidemiological evidence points towards a dose-related lung carcinogenic potential of water soluble nickel compounds. Especially when considering the Kristiansand cohort, where the lung cancer analyses allowed assessment of the roles of the different nickel species together with adjustment for smoking.

Sulfidic and oxidic nickel compounds

It is difficult to differentiate between sulfidic and oxidic compounds in epidemiology since sulfides are generally calcined to oxides in nickel-producing plants. Furthermore exposures to both oxidic and sulfidic compounds where often mixed with exposure to metallic and/or water-soluble nickel.

In the Kristiansand cohort Andersen et al. (1996) found that the risk of lung cancer showed a statistically significant increasing trend by increasing exposure to nickel oxide when adjusted for age, smoking and exposure to soluble nickel (see Summary tables of cohort studies

Table 47). In the later analysis with refined exposure estimates Grimsrud et al (2002), however, found that such a trend was not statistically significant when adjusted for smoking ($p = 0.201$) or when adjusted for smoking and exposure to soluble nickel ($p = 0.406$). In that study the results were similar for sulfidic nickel, p for trend = 0.119 when adjusted for smoking and $p = 0.344$ when adjusted for smoking and exposure to soluble nickel. There was, however, quite high correlation between the exposures to various nickel species, e.g the correlation coefficient between exposure to water soluble nickel was 0.48 for suplhidic nickel, 0.46 for oxidic nickel and 0.71 for metallic nickel. Consequently the results would probably be sensitive for any misclassification of exposure between the various nickel species. In the unadjusted analyses for every nickel species (including soluble nickel) the results indicated a supralinear pattern, where the risk increased at very low levels but then showed a less pronounced increase or no increase at all by increasing exposure (see Summary tables of cohort studies

Table 47).

In the multivariate model of Clydach cohort by Easton et al (1992) there was little if any indication of a lung cancer risk for oxidic or sulfidic nickel when analysing then in the same model with exposure to soluble and metallic nickel. However, as explained in the chapter for metallic nickel, authors concluded that their method had likely “overestimated the risk for metallic (and possibly soluble) nickel and underestimated those for sulphide and/or oxides”.

Doll et al (ICNCM 1990) reported that some of the highest lung cancer risks occurred in the Copper Cliff sinter plant and Port Colborne leaching, calcining and sintering department sub-cohorts of Ontario nickel workers (see Summary tables of cohort studies

Table 47) as well as the linear calcining sub-cohort of Clydach workers that had all been exposed to very high levels of sulfidic (and oxidic) nickel. Also comparisons of such sub-groups exposed to either high or low levels of sulfidic nickel but having similar (high or low) exposures to metallic or soluble nickel led the ICNCM (1990) to conclude that sulfidic and oxidic nickel species increased the risk of lung (and nasal) cancer. In the latest follow-up of the Ontario cohorts there continued to be a significantly increased risk of lung cancer mortality and incidence in each of the sub-cohorts with high exposure to suplhidic and oxidic nickel and low exposure to soluble nickel, i.e. Port Colborne leaching, calcining, sintering, Copper Cliff sinter plant, and Coniston sinter plant (Seilkop et al 2016, see Summary tables of cohort studies

Table 47).

The largest sub-cohorts in the Ontario cohort were those employed in mining and smelting (without any employment in sintering or electrolysis operations), both with more than 20 000 workers. These workers had lower exposure to nickel (any nickel species, including sulfidic and oxidic) than the sub-cohorts mentioned in the previous paragraph (see Table 49). The mortality or incidence of lung cancer, not adjusted for smoking, was only slightly increased among those workers both in the ICNCM 1990 and Seilkop et al 2016 analysis (SMR/SIR around 1.1 with narrow confidence intervals, see Summary tables of cohort studies

Table 47).

The ICNCM (1990) reported that no increased incidence of lung cancer was observed in the Hanna mining cohort (Oregon) and Societé le Nickel cohort (New Caledonia) that were exposed to lateritic nickel ore, for which there is low exposure to oxidic nickel (< 1 mg Ni/m^3) as compared to oxidic nickel exposures that occurred during sulfidic ore refining in Clydach (10-100 mg Ni/m^3) or Kirstiansand (8 mg Ni/m^3). Later follow-ups of the New Caledonia workers have also not observed an increase in risk (see Goodman et al 2011).

All in all there is epidemiological evidence of lung carcinogenic effects of insoluble oxidic and sulfidic nickel species, especially in the various sub-cohorts of the Ontario cohort exposed to high levels of these nickel species.

Sinonasal cancer

Increased risks for cancer of the nasal cavities have been reported in cohorts of nickel refinery workers in Ontario, Harjavalta, Kristiansand and Clydach (see Table 48, Appendix 5). Nasal cancer is a quite rare tumour, even in the nickel exposed populations. Consequently the studies usually did not have high enough cases for detailed analyses by nickel species or by cumulative exposure.

In the Norwegian study, Andersen et al (1996) reported a dose-response relationship between both cumulative exposure to water-soluble nickel and nickel oxide and the risk of nasal cancer. The risk was the highest in the group of highest cumulative exposure to soluble nickel compounds (SIR 81.7; 95% CI 45 – 135). For workers with the highest cumulative exposure to nickel oxide the SIR was 36.6 (95% CI 19.5- 62.5). See Table 48.

Anttila et al (1998) found an increased risk of nasal cancer among Harjavalta refinery workers exposed mainly to water-soluble nickel salts. The SIR was 67.1 (95% CI 8.12 – 242, based on 2 cases) when a latency time of at least 20 years from first exposure was applied. There were no cases in the smelter of the same facility where exposure levels were lower and mainly to poorly soluble nickel compounds. In the most recent follow-up of the same cohort the risk of nasal cancer was similar as in the follow-up of Anttila et al when all the exposed workers were considered (Pavela et al. 2017, see Table 48). There were again no cases in the smelter workers, while 3 of the cases were in the refinery workers and one case in a maintenance worker who had repeated refinery exposure. The four cases of nasal cancer had started their employment in 1960 or earlier, i.e. they had been employed since the beginning of nickel production.

Clearly increased risks of nasal cancer have been reported in the Clydach nickel refinery (Easton et al 1992, Sorahan and Williams 2005, Grimsrud and Peto 2006, See Table 48). Easton et al. (1992) fitted the mortality and exposure data of men employed before 1935 to a statistical model adjusted for age at first exposure and found indication that exposure to soluble nickel was the only significant factor for risk of nasal cancer. However, as explained in the chapter for metallic nickel and lung cancer, the authors concluded that their method had likely “overestimated the risk for metallic (and possibly soluble) nickel and underestimated those for sulphide and/or oxides”.

The risk of nasal cancer was also investigated in different facilities of the INCO Ontario nickel refinery (ICNCM 1990). The risk was increased in the Copper Cliff sinter facility and

Port Colborne leaching, calcining and sintering facility where high exposures predominantly to oxidic and sulfidic nickel occurred while there were no cases in the Coniston sinter facility and Port Colborne electrolysis department where exposure to both soluble and insoluble nickel were lower. The latest follow-up by Seilkop et al 2016 (see Table 48) confirmed an increased risk for the Copper Cliff sinter facility and Port Colborne leaching, calcining and sintering facilities, while no cases or deaths were observed in the Conister sinter facility. There were no cases of nasal cancer among the Port Colborne electrolysis workers who had started employment in 1960 or later.

In the cohort of Oak Ridge Gaseous Diffusion Plant workers exposed to metallic nickel at concentrations below 1 mg/m^3 there were no cases of nasal cancer vs. 0.22 expected (ICNCM 1990).

In a cohort of 869 Swedish Ni-Cd battery factory workers there were three nasal cancer cases observed vs 0.36 expected (SIR = 8.32; 95% CI 1.72 – 24.3) (Järup et al 1998). Two of these cases occurred among workers exposed to greater than 2 mg/m^3 nickel (SIR = 10.8; 95% CI 1.31 – 39.0), while a similar SIR was observed also when analysing the highest category of Cd exposure.

All in all there is epidemiologic evidence of nasal carcinogenic effects of both water soluble and insoluble nickel species, while not convincing evidence of such properties for metallic nickel. It is to be noted that even in high risk cohorts nasal cancer is by far less common than lung cancer. The low observed absolute numbers of cases make nasal cancer less amenable to quantitative dose response assessment. However, comparing the studies described for lung cancer and nasal cancer in Summary tables of cohort studies

Table 47and Table 48 indicates that there is no cohort were the risk of nasal cancer would be statistically significantly increased if the risk of lung cancer was also not statistically significantly increased.

Reviews on the roles of different nickel species in the epidemiological data

The above-mentioned analyses of Grimsrud et al (2002) in the Kirstiansand cohort and Easton et al (1992) in the Clydach cohort are the only ones that have tried to analyse the roles of different nickel species by incorporating individual worker level exposure metrics of those in the same statistical model. In the Kristiansand analysis also adjustment for smoking was included.

International Committee on Nickel Carcinogenesis in Man (ICNCM 1990) concluded that based on their assessment of the cohort studies available "*The evidence suggests that respiratory cancer risks are primarily related to exposure to soluble nickel at concentrations in excess of 1 mg/m^3 and to exposure to less soluble forms at concentrations greater than 10 mg/m^3.*" There have been recent attempts to analyse these effects at group level using all the cohorts reported by ICNCM (1990) and their more recent follow-ups and refined exposure assessments. Goodman et al (2011) compared the ranges and averages of exposure to sulfidic, oxidic, soluble and metallic nickel in 22 process areas of the existing 13 cohorts and assigned them to subgroups. E.g. high exposure to soluble and high exposure to insoluble nickel or high exposure to soluble and low exposure to insoluble nickel. This matrix was then linked with lung cancer risk estimates from these process areas. It was concluded that there is a strong possibility that risks attributed to water-soluble nickel could in fact be due to another form of nickel or that water-soluble nickel accentuated the risks of other nickel forms, acting through non-genotoxic mechanism. However the final conclusion was that epidemiologic data alone are not robust enough to assess this in humans.

Oller et al (2014) continued the work of Goodman by plotting the lung cancer risk estimates by the cohort's estimated exposure level for soluble nickel separately for cohort's were exposure to sulfidic nickel was either above or below 0.2 mg/m^3. Similarly the lung cancer risk estimates were plotted by the cohort's estimated exposure level to oxidic nickel separately for cohorts with sulfidic nickel exposure below 0.2 mg/m^3 and

soluble nickel exposure below 0.1 mg/m^3 and cohorts were either sulfidic nickel exposure was above 0.2 mg/m^3 or soluble nickel exposure above 0.1 mg/m^3. The authors concluded that in the absence of sulfidic nickel exposure above 0.2 mg/m^3 there was no cohort with a significantly increased lung cancer risk with estimated exposure to soluble nickel below 0.1 mg/m^3. As regards oxidic nickel it was concluded that in the absence of sulfidic nickel exposure below 0.2 mg/m^3 and soluble nickel exposure below 0.1 mg/m^3 there was no cohort exposed to oxidic nickel showing a statistically significantly increased risk of lung cancer and the cohort with highest exposure was estimated to have exposure level around 2 mg/m^3. All the exposures were expressed as mg/m^3 Ni (inhalable fraction). This analysis suggests that if the threshold proposed by Oller et al (2014) for water soluble nickel (below 0.1 mg/m^3) would be applied for total nickel, then exposure to sulfidic nickel and oxidic nickel would by default be below the above "thresholds" for those species (0.2 mg/m^3 and 2 mg/m^3, respectively). It is worth noting that the above analysis or the statistical analyses in the Kirstiansand cohort do not indicate sulfidic nickel showing the highest carcinogenic potency in humans as suggested in the animal studies performed with nickel subsulphide. However, there is no nickel species specific information on exposure to particles of respirable fraction in the human studies available. For total nickel the respirable fraction accounted for usually for10%-20% of the inhalable fraction in the few studies available in nickel smelting and refining industry (Oller and Oberdorster 2010).

Temporal trends in nickel refinery processes, monitoring arrangements and respiratory cancer

Clydach cohort

Nickel production in Clydach started in 1902. The process used is still the Mond nickel carbonyl process. However, major process changes have been described for 1923, 1930, 1937, 1949, 1958, and 1969 (ICNCM 1990 and Sorahan et al 2005). These included important changes for example concerning the calcining, milling and grinding processes (1930-36), gradually moving to use of oxide material only and thus eliminating the need for sulfur elimination (completed in 1949) and termination of smelting operations (1958).

No measurements of the actual concentrations, let alone nickel species, exist for any of the plant operations prior to 1950 (ICNCM 1990). For more recent years measurements were available for nickel, copper and occasionally sulfur. These measurements were used in conjunction with knowledge of the chemistry in industrial processes to estimate the concentration of airborne nickel species to which the workers were exposed. These more modern estimates were combined with historical information about the industrial processes to estimate nickel species concentrations in earlier years. Even when measurements were available, they were often taken with different types of devices which sampled different fractions of the particle size distribution (e.g. konimeters, high-volume samplers and personal gravimetric samplers as described in the Appendix of ICNCM 1990). Estimated exposure levels over time are presented in Table 49.

Among the workers with more than 5 years of employment in the Clydach nickel refinery the mortality from lung cancer (as compared to the general population) has decreased form about 6-fold among those hired in 1902-1919 to about 1.4 among those hired after 1953. The mortality from nasal cancer decreased from about 380-fold to about 10-fold over the same period of first employment (Table 48).

Harjavalta cohort

The nickel production in Harjavalta started in 1960 and the most important process change was in 1973 when the leaching and grinding operations were moved to a separate building from the electrolytic operations. The cancer follow-up studies have not reported cancer risk by level of exposure. Neither have they specifically assessed temporal trends in the risk of respiratory cancers. However, as regards the four cases of nasal cancer observed in the cohort, it is known that their employment had started in 1960 or earlier (Pavela et al 2017), i.e. they had been employed since the beginning of nickel production.

Kristiansand cohort

The nickel production in Kirstiansand started in 1910. Process changes have been described for 1915, 1952 and 1967 (Grimsrud et al 2000 and 2003). The most important process change was the abandonment of the Hybinette process and start of the chlorine leach process in 1978 (Grimsrud et al 2000). This lead among others to reduction of some process steps with highly contaminated roasting and smelting activities.

Very few readings of atmospheric nickel concerntrations in the plant were available before the early 1970s (ICNCM 1990, Grimsrud et al 2000). All exposures to total nickel before 1973 were estimated through retrograde calculation with multiplication factors. This was based on 500 stationary dust or nickel measurements before 1973 and 5900 personal measurements in 1973-1994 of total nickel in the breathing zone, a few analyses of nickel species in dust samples and aerosols in 1990s and historical process information. Important changes in production technology and chemistry as well as ventilation and other environmental improvements had been described by experienced engineers and the corresponding influence on exposures had been discussed and summarised by an expert panel by the time shifts available and treating departments of the plant separately (Grimsrud et al 2000). For the most heavily contaminated departments, 24-hour stationary measurements for 1969-1972 were available ranging from 37 to 166 per department. The nickel species distribution was based on measurements in the refinery and some measurements from a similar refinery in Russia. However for departments with process steps unique to the old Hybinett process speciation analyses had never been performed and estimations were necessary. Typically the multiplication factors applied to convert from more recent measurements to older time periods were of the order of 1.5 to 2. At the most 5 such multiplication factors were introduced for a single department during the period 1910 to 1972.

The latest cancer follow-up does not indicate a clear reduction in the risk of lung cancer for workers with first employment after 1978 as compared to those with earlier start of employment (Grimsrud et al 2003). Yet, the number of cases is quite small for that part of the cohort (see Summary tables of cohort studies

Table 47). No temporal trends have been published for the risk of nasal cancer.

Ontario cohorts

A number of important process changes in the Copper Cliff and Coniston sinter plants, in the Port Colborne leaching, calcining and sintering department and Port Colborne electrolysis department were described in the appendix of the ICNCM (1990). Even in the latest follow-up no analyses are presented by cumulative exposure or other quantitative exposure metric because “the existing workplace nickel exposure estimates were considered to be too imprecise (and in some cases perhaps unrealistically high) for use in analyses based on cumulative exposure” (Seilkop et al 2016). Instead analyses were presented by departments and also whether sinter work was involved or not. Consequently the process changes and exposure measurements are not further described here apart from the fact that the sintering operations have been closed: Copper Cliff sinter plant in 1963, Port Colborne leaching, calcining and sintering department in 1958 and Coniston sinter plant in 1972 (Seilkop et al 2016). Estimated exposure levels over time are presented in Table 49.

In the latest follow-up until the end of 2000 the lung cancer mortality was statistically significantly increased among workers ever having worked in sinter operations (Seilkop et al 2016) although the risk estimates (SMR) were slightly lower than in the ICNCM 1990 report: Copper Cliff (2.1 vs 3.1), Port Colborne (1.8 vs 2.4), Coniston (2.3 vs 2.9). A similar pattern was seen for nasal cancer mortality in comparison to ICNCM (1990): Copper Cliff (30 vs 36), Port Colborne (62 vs 78). There continued to be no nasal cancer deaths in the Coniston sinter workers.

Among those Port Colborne electrolysis department workers without any sinter work history the lung cancer mortality was only marginally increased (SMR 1.23; 95% CI 0.95 – 1.56). This applied also to all Ontario cohort workers never having worked in sintering operations (SMR 1.11: 95% CI 1.05 – 1.17). However, this latter group contained a lot of underground miners with an exposure profile quite different from refinery workers. The risk estimates were not adjusted for smoking but the authors provided some evidence that the increases were within what one could expect for blue collar workers who are more frequently smokers than white collar workers. Also some evidence was cited that smoking was more prevalent in the region around the refineries than in Ontario in general which formed the reference population for mortality figures. Further evidence for the slight increase in lung cancer risk not being due to factors at work was that the risk did not show an increasing trend by increasing duration of employment. As regards nasal cancer those never having worked in sintering operations did not have a significantly increased risk (SMR 1.29; 95% CI 0.59 – 2.44). The nasal cancer mortality was not increased in the Port Colborne electrolysis department. However, quantitative risk estimates were not disclosed due to the Statistics Canada data confidentially rules not allowing reporting separately numbers of deaths lower than 3. However, it was reported that no deaths from nasal cancer were observed in workers having started employment in 1960 or later.

Industry level general information

Symanski et al (2000) reported an annual decrease in geometric mean exposure levels to total nickel of 7% per year in refining and 9% per year in smelting from 1970s to 1990s. In the US nickel alloy industry Sivulka and Seilkop (2009) reported that in melting the mean of total nickel exposures (mg Ni/m^3) decreased from 2.22 in 1940s/1960s to 0.18 in early 1970s, 0.05 in late 1970s, 0.04 in 1980s and 0.03 in 1990s and later. I.e. the multiplication factor for back-extarpolation 1940s/1960s vs early 1970s would be 12.3 (=2.22/0.18) in US alloy industry. A similar comparison is not available for refining and smelting operations for this time period.

Conclusions on temporal trends

It is noted that important process changes have occurred in each of these cohorts. These most led not only to reduction of overall exposure levels (Table 49), but also involved changes in how much each of the different nickel species contributed to the overall nickel exposure and most likely also influenced the particle size distribution affecting estimation of inhalable and respirable fractions of exposure. The exposure assessment in the cohorts consequently involves expert judgement in extrapolating results of measurements to times and circumstances for which measurements were not available. The validation of the assumptions made is complicated by the fact the older processes were not anymore existing when regular monitoring of exposure levels became a practice. This introduces some uncertainty to the quantitative dose-response information and nickel species specific information available in the epidemiological studies.

Parallel to the process improvements there were also changes in the sampling and analytical techniques used to monitor exposure. These apply, at varying quantitative impacts, to dust overall (see Chapter 5.3.2) but also more specifically to nickel species. Based on studies by Tsai *et al (1995 and 2001)* in a number of work sites in nickel mining, smelting and refining Oller and Oberdörster (2010) have pointed out that comparisons of measurements in various nickel industries using the old 37 mm sampler and the IOM sampler indicate that the 37 mm sampler captured on average about half of the nickel mass captured by the IOM inhalable sampler. Thus a correction factor of 2 would be needed when 37 mm sampler had been used in assessing exposure in the epidemiological cohorts which would have underestimated the exposure levels linked to the identified risk levels. Based on Tsai et al 1995 and 2001 the factor would typically range between 1.7 to slightly above 3 with and overall range from 1.2 to 4.9. It is to be noted that for many of the earlier studies described it was not explicit which sampler/exact method had been used in the measurements forming the basis of the cohort's exposure estimation. As mentioned earlier, however, in the summary analysis by Oller et al. 2014 all the exposures were

expressed as inhalable aerosol fraction. Furthermore, for the Kristiansand cohort Grimsrud et al (2000) specifically reported that all available historical personal measurements that were used to generate the individual exposure estimates of the cohort members were performed with a 37 mm filter cassette.

A need for a correction factor of 2 was also acknowledged by the EU RAR (2008) of nickel and its compounds, but finally not used as the risk assessment was done in terms of orders of magnitude: "*The exposure level for the exposurescenarios in the table is given in the metric "inhalable dust" which numerically is about twice as high a value as the same exposure level given in the metric "total dust" (section 4.1.1.2.1.2). If correction for this relationship should be made then the lifetime risks in the table should be approximately 50% lower. However, a correction of this magnitude would not lead to any significant changes in the evaluations of the risk levels as the indicated levels more properly should be interpreted as orders of magnitude rather than exact values.*"

Other cancers

Some studies have found indications of an elevated risk for cancers other than lung or nasal cavities, e.g. buccal cavity (ICNCM 1990), stomach (Anttila et al 1998, Pang et al. 1996) or colon (Arena et al 1998). However, there is currently no consistency in the epidemiological data to suggest that nickel compounds cause cancer at sites other than lung or nasal cavities (IARC 2012).

Since the IARC assessment an update has been published for the Ontario nickel refinery cohort (Seilkop et al. 2016) repeating the earlier observations that there was no increase in mortality from laryngeal cancer. The latest update also analysed incidence and found no increase. There was also no increase in pharyngeal cancer mortality or incidence among the non-sinter workers. However, there was an increase in mortality and incidence among the Port Colborne leaching, calcining and sintering workers. In the absence of increased risk observed in any other sub-cohort of Ontario nickel refinery workers and the high risk of nasal cancer mortality in this Port Colborne department, the authors considered this finding possibly due to misdiagnosed nasal cancers. In the latest update of the Harjavalta cohort there was again an increase in the incidence of stomach cancer which was, however, not statistically significant (Pavela et al 2017). Stomach cancer incidence or mortality was not increased in the latest update of the non-sinter workers of the Ontario nickel refineries (Lightfoot et al 2016).

All in all there is no convincing evidence of a carcinogenic potential of any nickel species as regards cancers other than lung and nasal cavities.

Conclusions human data

The human cancer data set on nickel compounds is extensive covering about 100 000 exposed workers from various populations.

Altogether epidemiological evidence points towards a dose-related carcinogenic potential (lung and nasal cancer) of water soluble nickel compounds. Especially when considering the Kristiansand cohort, where the lung cancer analyses allowed assessment of the roles of the different nickel species together with adjustment for smoking. There is also epidemiological evidence of carcinogenic effects (lung and nasal cancer) of insoluble oxidic and sulfidic nickel species, especially in the various subcohorts of the Ontario cohort exposed to high levels of these nickel species.

Overall, there seems to be some variation in the epidemiological estimates on whether exposure to soluble or non-soluble nickel is the main contributor to the increase of risk of respiratory tract cancer. The Ontario cohort data have linked the risk to insoluble nickel exposure while the Kristiansand data indicate soluble nickel exposure as the main contributor. It must be noted that the epidemiological evaluation of the carcinogenic risk for different nickel species has limitations. Notably, there are no cohorts available exclusively exposed to a single nickel species. Furthermore assessments of the relative contribution of the diverse nickel species far back in time depend largely on exposure

estimates such as job history in combination with assumptions made to extrapolate from recent (species) measurements to historical situations, which introduces uncertainty. Finally, combination effects either with confounding factors or between water soluble and water insoluble nickel species cannot be excluded.

Concerning metallic nickel there is less epidemiologic evidence than for water-soluble nickel compounds or for oxidic/sulfidic nickel. However, based on the epidemiological data alone it is not possible to definitively rule out a human carcinogenic effect in the respiratory tract for exposure to metallic nickel. Nevertheless the epidemiological evidence seems to be in line with the negative animal data.

The epidemiological data are not robust enough to definitively identify or to exclude a threshold for these carcinogenic effects of the different nickel species. The analysis by Oller et al (2014) does provide some evidence of a threshold. However, epidemiology is not a sensitive tool to detect slightly increased risks that would still represent a toxicologically relevant effect, but would not reach statistical significance due to the size of the population studied. Although some of the nickel cohorts, like the nickel alloy worker cohort and some sub-cohorts in the Ontario cohort are large and consequently have quite narrow confidence intervals for lung cancer mortality/incidence estimates, many of the other cohorts still have quite wide confidence intervals for the risk estimates. All in all the epidemiological data are in line with animal data, with the exception that the epidemiological data clearly suggest a respiratory carcinogenic role for water soluble nickel as well.

7.7.2 Animal data

Table 38: Summary table of long term / carcinogenicity tests in animals

Method, guideline, deviations, duration of exposure, species, strain, sex, no/group	Test substance, dose levels	Observations	Ref
2y study inhalation, F344/N rats, 65m/65f per group Interim evaluation after 7m and 15m	**Nickel oxide** 0, 0.62, 1.25, 2.5 mg NiO/m^3 (0, 0.5, 1.0, 2.0 mg Ni/m^3) 6 h/day, 5 d/week	**2y survival rate**: male: 14/54, 15/53, 15/53,12/52 female: 21/53, 26/53, 20/53, 26/54 **Body weight:** male: 2.5 mg/m^3 slightly lower than controls female: 1.25 and 2.5 mg/m^3 slightly lower than controls **Non neoplastic findings**: Lung: Chronic inflammation: male: 28/54, 53/53, 53/53, 52/52 female: 21/53, 26/53, 20/53, 26/54 Pigment: male: 1/54, 53/53, 53/53, 52/52 female: 0/53, 52/53, 53/53, 54/54 Bronchial LN: Lymphoid hyperplasia: male: 0/52, 7/51, 10/53, 18/52 female: 1/49, 5/50, 20/53, 13/52 Pigment: male: 0/52, 45/51, 51/53, 51/52 female: 0/49, 43/50, 52/53, 47/52 Adrenal medulla:	NTP 1996a

Method, guideline, deviations, duration of exposure, species, strain, sex, no/group	Test substance, dose levels	Observations	Ref
		Hyperplasia: female: 8/51, 12/52, 14/53, 22/53 **Neoplastic findings**: Lung: Alveolar/bronchiolar carcinoma or adenoma or squamous cell carcinoma (m only): male: 1/54, 1/53, 6/53, 4/52 female: 1/53, 0/53, 6/53, 5/54 Adrenal medulla: benign or malignant (m only) pheochromocytoma: male: 27/54, 24/52, 27/53, 35/52 female: 4/51, 7/52, 6/53, 18/53 **Tumour incidences,** overall rate **:** **2.5 mg/m³:** Lungs: Alveolar/bronchiolar adenoma (2m/4f), alveolar/bronchiolar carcinoma incl squamous differentiation: 8%m/9%f; controls: 2%m/2%f Adrenal glands: Benign pheochromocytoma: 62%m/34f; controls: 50%m/8%f; malignant pheochromocytoma: 12%m/0%f; controls: 0%m/0%f **1.25 mg/m³:** Lung: alveolar/bronchiolar adenoma (3m/1f), alveolar/bronchiolar carcinoma incl squamous differentiation: 11%m/11%f; controls: 2%m/2%f Adrenal glands: benign pheochromocytoma: 2%m/11%f; controls: 50%m/8%f **0.62 mg/m³:** alveolar/bronchiolar adenoma:2%m/0%f; controls: 2%m/2%f	
2y study, inhalation, B6C3F mice, 76-79m/74-76f Interim evaluation after 7m and 15m	**Nickel oxide** 0, 1.25, 2.5, 5 mg NiO/m³ 6 h/day, 5 days/week	**2y survival rate**: male: 19/57, 23/67, 29/66, 23/69 female: 41/64, 40/66, 42/63, 38/64 **Body weight:** female: 5 mg/m³ slightly lower than controls **Nonneoplastic findings**: Lung: Bronchialization: male: 0/57, 24/67, 40/66, 40/69 female: 0/64, 35/66, 39/63, 40/64 proteinosis: male: 0/57, 12/67, 22/66, 43/69 female: 0/64, 8/66, 17/63, 29/64 Chronic inflammation: male: 0/57, 21/67, 34/66, 55/69 female: 7/64, 43/66, 53/63, 52/64 Pigment:	NTP 1996a

Method, guideline, deviations, duration of exposure, species, strain, sex, no/group	Test substance, dose levels	Observations	Ref
		male: 0/57, 65/67, 66/66, 68/69 female: 0/64, 64/66, 61/63, 64/64 Bronchial LN: Lymphoid hyperplasia: male: 5/45, 18/56, 28/61, 33/62 female: 14/54, 37/63, 40/59, 44/62 Pigment: male: 0/45, 55/56, 61/61, 60/62 female: 0/54, 58/63, 56/59, 60/62 **Neoplastic findings**: none **Uncertain findings:** Lung: Alveolar/bronchiolar adenoma: female: 2/64, 4/66, 10/63, 3/64 bronchiolar adenoma and carcinoma: female: 6/64, 15/66, 12/63, 8/64 **Tumour incidences, overall rate :** **5 mg/m³:** Alveolar/bronciolar adenoma and carcinoma: 20%m/13%f; control: 16%m/9%f **2.5 mg/m³:** Alveolar/bronciolar adenoma and carcinoma: 23%m/19%f; control: 16%m/9%f **1.25 mg/m³:** Alveolar/bronciolar adenoma and carcinoma: 21%m/23%f; control: 16%m/9%f	
2y study, inhalation, F344/N rats, 63m/63f per group Interim evaluation after 7m and 15m	**Nickel subsulfide**, 0, 0.15, 1.0 mg Ni_3S_2/m^3 (0, 0.11, 0.73 mg Ni/m^3) 6h/day 5 days/week	**2y survival rate**: male: 13/53, 21/53, 18/53 female: 25/53, 25/53, 28/53 **Body weight:** 1 mg/m^3: lower than controls (m/f) **Nonneoplastic findings**: Lung: Chronic active inflammation: male: 9/53, 53/53, 51/53 female: 7/53, 51/53, 51/53 Focal alveolar epithelial hyperplasia: male: 2/53, 6/53, 11/53 female: 2/53, 10/53, 11/53 Macrophage hyperplasia: male: 9/53, 48/53, 52/53 female: 8/53, 51/53, 52/53 Fibrosis: male: 2/53, 48/53, 40/53 female: 0/53, 50/53, 44/53 Nose: Chronic active inflammation:	NTP 1996b

Method, guideline, deviations, duration of exposure, species, strain, sex, no/group	Test substance, dose levels	Observations	Ref
		male: 12/53, 10/53, 18/52 female: 7/53, 51/53, 51/53 Olfactory epithelial atrophy: male: 2/53, 1/53, 9/52 female: 0/53, 0/53, 16/52 <u>Adrenal medulla:</u> Hyperplasia: female: 5/53, 11/53, 16/53 **Neoplastic findings**: <u>Lung:</u> alveolar/bronchiolar adenoma: male: 0/53, 3/53, 6/53 female: 2/53, 5/53, 5/53 alveolar/bronchiolar carcinoma: male: 0/53, 3/53, 7/53 female: 0/53, 0/53, 4/53 squamous cell carcinoma: female: 0/53, 1/53, 0/53 alveolar/bronchiolar adenoma and carcinoma or squamous cell carcinoma (f only): male: 0/53, 6/53, 11/53 female: 2/53, 6/53, 9/53 <u>Adrenal medulla:</u> benign pheochromocytoma: male: 13/53, 30/52, 38/53 female: 2/53, 7/53, 36/53 malignant pheochromocytoma: male: 0/53, 2/52, 10/53 benign or malignant pheochromocytoma: male: 14/53, 30/52, 42/53 **Tumour incidences, overall rate :** **1 mg/m³:** Lung: carcinoma/adenoma 21%m/17%f; control:0%m/4%f **0.15 mg/m³:** Lung: carcinoma/adenoma 11%m/11%f; control:0%m/4%f <u>Adrenal glands:</u> Benign pheochromocytoma 70%m/68%f; in control: 25%m/4%f, malignant pheochromocytoma 21%m/2%f; control: 0%m/2%f	
2y study, inhalation, B6C3F mice, 80m/80f per group Interim evaluation after 7m and 15m	**Nickel subsulfide**, 0, 0.6, 1.2, mg Ni_3S_2/m^3 (0, 0.44, 0.88 mg Ni/m³) 6 h/day, 5 days/week	**2y survival rate**: male: 26/61, 25/60/ 26/60 female: 36/58, 34/60, 38/60 **Body weight:** 0.6 and 1.2 mg/m³ lower than controls (m/f) **Nonneoplastic findings**: <u>Lung:</u> Chronic active inflammation: male: 1/61, 52/59, 53/58 female: 1/58, 46/59, 58/60 Bronchialization:	NTP 1996b

Method, guideline, deviations, duration of exposure, species, strain, sex, no/group	Test substance, dose levels	Observations	Ref
		male: 3/61, 53/59, 54/58 female: 3/58, 53/59, 58/60 Macrophage hyperplasia: male: 6/61, 57/59, 58/58 female: 5/58, 57/59, 60/60 Fibrosis: male: 0/61, 3/59, 16/58 female: 058, 7/59, 17/60 <u>Nose:</u> acute inflammation: male: 0/61, 0/59, 3/59 female: 0/58, 11/59, 14/60 Olfactory epithelial atrophy: male: 1/61, 27/59, 55/59 female: 1/58, 11/59, 41/60 **Neoplastic findings**: none	
2y study, inhalation, F344/N rats, Main group: 63-65m/63-64f per group Interim evaluation after 7m and 15m	**Nickel sulphate hexahydrate**, 0, 0.12, 0.25, 0.5 mg $NiSO_4$ $6H_2O/m^3$ (0, 0.03, 0.06, 0.11 mg Ni/m^3) 6 h/day, 5 days/week	**2y survival rate**: male: 16/54, 16/53, 18/53, 21/53 female: 22/53, 17/53, 28/54, 29/55 **Body weight:** 0.5 mg/m^3 lower than controls (f) **Nonneoplastic findings**: <u>Lung:</u> Chronic active inflammation: male: 14/54, 11/53, 42/53, 46/53 female: 14/52, 13/53, 49/53, 52/54 Macrophage hyperplasia: male: 7/54, 9/53, 35/53, 48/53 female: 9/52, 10/53, 32/53, 45/54 Alveolar proteinosis: male: 0/54, 0/53, 12/53, 41/53 female: 1/52, 0/53, 22/53, 49/54 Fibrosis: male: 3/54, 6/53, 35/53, 43/53 female: 8/52, 7/53, 45/53, 49/54 <u>Bronchial lymph node:</u> male: 0/51, 0/49, 3/47, 10/52 female: 2/50, 1/52, 0/51, 11/49 <u>Nose:</u> Olfactory epithelial atrophy: male: 0/54, 0/52, 3/53, 7/53 female: 0/51, 1/52, 1/53, 7/54 **Neoplastic findings**: none	NTP 1996c
2y study, inhalation, B6C3F mice,	**Nickel sulphate hexahydrate,** Main group:	**2y survival rate**: male: 26/61, 23/61, 24/62, 25/62 female: 34/61, 39/60, 45/60, 37/60 **Body weight:** male: 1 mg/m^3 lower than controls females: exposed groups lower than controls	NTP 1996c

Method, guideline, deviations, duration of exposure, species, strain, sex, no/group	Test substance, dose levels	Observations	Ref
80m/80f per group Interim evaluation after 7m and 15m	0, 0.25, 0.5, 1 mg $NiSO_4$ $6H_2O/m^3$ (0, 0.6, 1.1, 2.2 mg Ni/m^3) 6 h/day, 5 days/week	**Nonneoplastic findings**: Lung: Chronic active inflammation: male: 1/61, 2/61, 8/62, 29/61 female: 1/61, 7/60, 14/60, 40/60 Bronchialization: male: 1/61, 4/61, 19/62, 39/61 female: 0/61, 9/60, 32/60, 45/60 Macrophage hyperplasia: male: 6/61, 9/61, 35/62, 59/61 female: 7/61, 24/60, 53/60, 59/60 Interstitial infiltration: male: 1/61, 0/61, 3/62, 17/61 female: 0/61, 4/60, 16/60, 39/60 Alveolar proteinosis: male: 0/61, 0/61, 0/62, 42/61 female: 0/61, 0/60, 11/60, 45/60 Bronchial lymph node: lymphoid hyperplasia male: 2/46, 4/49, 2/45, 17/54 female: 15/50, 9/54, 16/58, 26/56 macrophage hyperplasia: male: 0/46, 0/49, 8/45, 39/54 female: 2/50, 0/54, 14/58, 37/56 Nose: Olfactory epithelial atrophy: male: 0/61, 0/61, 12/61, 37/60 female: 23/61, 2/59, 1/60, 17/60 **Neoplastic findings**: none	
2y study, plus up to 11m recovery Inhalation Wistar rat Core study: 50m/50f Satellite group for Ni lung burden /hematology / BALF: 22m/22f	**Nickel metal powder** 0, 0.1, 0.4, 1 mg Ni/m^3 6 h/day, 5 days/week	**2y survival rate**: 1 mg/m^3 high mortality, early terminated. No data available for this dose group male: 41/50, 41/50, 36/50 female: 38/50, 38/50, 24/50 **Body:** male: BW lower in dose groups females: 0.4 and 1 mg/m^3 BW lower **Nonneoplastic findings**: Lung: Chronic inflammation: male: 14/50, 44/50, 41/50 female: 16/50, 45/50, 45/54 Bronchiolar-alveolar proteinosis: male: 0/50, 50/50, 50/50 female: 8/50, 50/50, 54/54 Alveoplar histiocytosis: male: 28/50, 50/50, 44/50 female: 26/50, 50/50, 50/54 Bronchial lymph node: histiocyte infiltrate: male: 4/50, 24/50, 27/50	Oller et al 2008

Method, guideline, deviations, duration of exposure, species, strain, sex, no/group	Test substance, dose levels	Observations	Ref
		female: 2/50, 32/50, 22/54 <u>Spleen:</u> Extramedulare hematopoesis: male: 16/50, 16/50, 28/50 female: 26/50, 28/50, 34/50 <u>Femoral bone marrow:</u> Hypercellularity male: 10/50, 11/50, 26/50 female: 18/50, 23/50, 36/50 **Neoplastic findings**: <u>Adrenal gland:</u> Benign pheochromocytomas: males: 0/50, 5/50, 19/50 females: 0/50, 5/49, 3/53 Malignant pheochromocytomas: males: 0/50, 0/50, 5/50 Combined malignant and begnin pheochromocytomas: males: 0/50, 5/50, 21/50 females: 0/50, 5/49, 3/53 <u>Adrenal cortex:</u> Adenona males: 1/50, 3/50, 2/50 females: 1/50, 2/49, 4/54 Carcinoma: females: 1/50, 0/49, 3/54 **Tumour incidences:** **0.4 mg/m³:** Combined malignant and begnin pheochromocytomas: 42%m/6%f; control: 0%m/0%f Adrenal cortex malignant and begnin tumor: 2%m/7%f; control: 2%m/4%f **0.1 mg/m³:** Combined malignant and begnin pheochromocytomas: 10%m/10%f; control: 0%m/0%f Adrenal cortex malignant and begnin tumor: 6%m/4%f; control: 2%m/4%f	
78 weeks study, plus 30w recovery period Inhalation F344 rat 108-110m/98-107f	**Ni subsulfite** 6 h/day, 5 days/week 0, 73 mg/m³ (0, 0.97 mg Ni/m³) 6 h/day, 5 days/week	**Nonneoplastic lung findings**: Exposed animals showed higher pulmonary hyperplastic and neoplastic lesions originating from the bronchial and bronchilo-alveloar segments and pulmonary inflammatory reactions **Neoplastic lung findings**: Dose group: 15/208 Adenome 13/208 Karzinome 1/208 Sarkom	Ottolenghi et al 1975

Method, guideline, deviations, duration of exposure, species, strain, sex, no/group	Test substance, dose levels	Observations	Ref
		Controls: 1/215 Adenom 1/215 Karzinom **Lungtumor incidence** 14% in exposed animals, 1% in controls	
2y study, Oral, gavage F344 rats, 60m/60f per group	**Nickel sulphate hexahydrate,** 0, 10, 30, 50 mg $NiSO_4$ $6H_2O$/kg bw (0, 2.2, 6.7, 11 mg Ni/kg bw) daily	**2y survival rate**: male: 24/60, 31/60, 30/60, 26/60 female: 46/60, 40/60, 34/60, 33/60 **Body weight:** sightly (≥10%) reduced bw in 30 mg/kg (m) and 50 mg/kg (m/f) dose groups **Nonneoplastic findings**: none **Neoplastic findings**: none	Heim et al 2007
30 months Intra-tracheal instillation 1/ week for 10 to 20 weeks Wistar rat females only 32-47f/ group	**Nickel powder** 20 x 0.3 mg/rat, 32 rats 10 x 0.9 mg/rat, 32 rats **Ni oxide** 10 x 5 mg/rat, 34 rats 10 x 15 mg/rat, 37 rats **Ni subsulfide** 15 x 0.063 mg/rat, 47 rats 15 x 0.125 mg/rat, 45 rats 15 x 0.25 mg/rat, 47 rats	**Nickel powder:** Lung carcinomas and adenomas, incl. incidences: Control:0/40 (0%) 0.3 mg group:10/39 (25.6%) 0.6 mg group:8/32 (25%) Tumours: one adenoma, four adenocarcinomas, 12 squamous-cell carcinomas, one mixed tumour **Ni oxide:** Induction of lung tumour (27%, 31.6%) **Ni subsulfide:** Induction of lung tumour (15%, 28.9%)	Pott et al 1987
Intra-peritoneal injection weekly for 1 to 10 weeks	**Nickel powder** 10 x 7.5 mg Ni/rat, 48 rats	Animals developed sarcoma, mesothelioma or carcinoma in abdominal cavity **Nickel powder:** Tumours incidence 95.8%	Pott et al 1987

Method, guideline, deviations, duration of exposure, species, strain, sex, no/group	Test substance, dose levels	Observations	Ref
Wistar rat females only 42-48f/group Lifelong post exposure time, up to man 2.5 years	**Ni oxide** 2 x 500 mg Ni/rat, 47 rats **Ni subsulfide** 1 x 25 mg Ni/rat, 42 rats	**Ni oxide:** Tumours incidence 97.9% **Ni subsulfide:** Tumours incidence: 64.3% Tumour controls: 5/204 control rats (incidence 2.5%)	

There are several lifetime carcinogenicity studies in rats and mice available with 4 different nickel substances covering different routes of exposure (inhalation, oral, intra-peritoneal and intra-tracheal instillation), as summarised in the table above.

In the inhalation toxicity studies in rodents, the animals were exposed to nickel monoxide, nickel subsulphide, nickel sulphate or nickel metal powder (only rats) (NTP 1996a,b,c; Oller et al 2008; Ottolenghi et al 1975).

Chronic exposure to nickel sulphate, nickel subsulfide, or nickel oxide resulted in chronic active lung inflammation in rats and mice. The particle sizes of the aerosols used in the animal inhalation bioassays were quite small, with most measures near a mass median aerodynamic diameter (MMAD) of 2 µm.

Rats exposed to nickel subsulphide were clearly positive for lung tumors at all dose levels tested (0.1 and 0.7 mg Ni/m^3 in NTP 1996b; 0.97 mg Ni/m^3 in Ottolenghi et al 1975). At nickel subsulphide exposure levels, nickel was able to reach nuclear sites of target cells in sufficient amounts to induce tumors in a dose dependent manner after 2 years of exposure. Nickel subsulphide is partially soluble in lysosomal fluid and this allows for the particles to be taken up by epithelial cells (e.g., facultative phagocytosis) and to release high amounts of nickel ions once inside the cells.

Exposure to nickel oxide induced some tumors in rats (NTP, 1996a), although with 1 and 2 mg Ni/m^3 at higher exposure levels than nickel subsulphide. The lowest exposure level to nickel oxide (0.5 mg Ni/m^3) was at or below the threshold for lung tumors. Nasal tumours were not observed in the nickel subsulfide and nickel oxide studies, but in rats exposed to nickel subsulfide inflammatory reaction in the nose were observed.

Adrenal medulla hyperplasia and increased incidences of benign pheochromocytoma were observed in female rats exposed to 2 mg Ni/m^3 as nickel oxide (NTP 1996a). Significant increases in the incidence of benign or malignant pheochromocytoma in the adrenal medulla of rats were also observed in males at 0.11 or 0.73 mg Ni/m^3 and females at 0.73 mg Ni/m^3 as nickel subsulfide (NTP 1996b). Pheochromocytomas are relatively common spontaneous neoplasms in chronic studies with F344 rats, especially in males. Pheochromocytomas appear to be secondary to the lung toxicity associated with the exposure rather than being related to a direct nickel effect on the adrenal glands. Pheochromocytomas are observed in numerous carcinogenicity studies and occur with relatively higher frequency in male rats, especially when the following conditions are involved: hypoxia, uncoupling oxidative phosphorylation, disturbance of the hypothalamic-endocrine axis and disturbance in calcium homeostasis with involvement of catecholamine

synthesis, receptor tyrosine kinase (RET) and hypoxia-inducible factor (HIF) among others (Greim et al., 2009; Ozaki et al., 2002). Moreover, to date there is no indication that substances inducing pheochromocytomas in animal experiments also induce corresponding tumors in humans.

The most soluble of the nickel compounds (nickel sulphate) did not induce tumors at any of the three exposure levels tested, including the maximum tolerated dose (MTD) of 0.1 mg Ni/m^3 (NTP, 1996c), whereas at the same exposure level nickel subsulphide did induce tumors. This indicates that nickel sulphate is either not carcinogenic in rats (and mice) or it has a threshold for lung tumors and at the MTD exposure level it was not able to deliver nickel to target sites above the threshold needed for the tumor development. However, nickel sulphate showed clear inflammatory effects in the lungs and nose at 0.1 mg Ni/m^3 (MTD). The NOAEC of 0.03 mg Ni/m^3 was identified based on pronounced inflammatory reaction at the next higher dose (NTP, 1996c).

Nickel metal did not induce tumours in the inhalation study at any of the 3 exposure levels tested, including the MTD 0.4 mg Ni/m^3 (Oller et al 2008). This can be interpreted that either nickel metal is not carcinogenic or nickel metal has a threshold and at the MTD exposure it was not able to deliver sufficient nickel to target sites above the threshold needed for the lung tumour adverse outcome pathway (AOP) events. However, in the intra-tracheal instillation study with nickel metal (Pott et al 1987) lung carcinomas and adenomas were induced, but no clear dose response was observed (25.6% lung adenoma or carcinoma in the low–dose group and 25.0% in the high-dose group, 0% tumors in saline control). The mortality due to respiratory toxicity was not increased in this study which was inconsistent with the toxicity observed in the inhalation study with metallic nickel (Oller et al., 2008), and suggested localized dose deposition. Intratracheal instillation can be assumed to produce hotspots and therefore result in false positive tumor outcomes. The highest mean nickel lung burdens that could be achieved (even with increased mortality) in rats exposed to nickel metal by inhalation were under ~60 µg/ lung after one or two years of daily 6-hour exposure to the maximum tolerated concentration of 0.4 mg Ni/m^3 (Oller et al., 2008). In contrast, the localized lung doses in the Pott et al. (1987) study after single or multiple intratracheal instillation would have been 5-15- fold or higher (≥ 300 and 900 µg nickel metal) which could not be achieved in vivo via inhalation. Additionally, there has not been a positive association between exposure to metallic nickel and increased cancer risk in epidemiological studies (even among workers with predominant and high metallic nickel exposures, ICNCM, 1990; Redmond et al., 1995). Therefore, the argument of the lack of carcinogenicity of nickel metal is rather strong.

However, nickel metal induced significant increase in pheochromocytomas of the adrenal medulla in male rats as well as a significant increase in combined adenomas and carcinoma of the adrenal cortex in female rats (Oller et al 2008). While the pheochromocytomas may have been treatment-related in the nickel metal study, it is unlikely that they were nickel -related. This is because in a rat oral cancer study with nickel sulphate, where higher blood nickel levels than in the nickel metal study were achieved, neither pheochromocytomas nor adrenal cortical tumors were observed (Heim et al., 2007; Oller et al., 2008). The incidence of combined (only) cortical tumors among females exposed to 0.4 mg Ni/m^3 fell within the historical control range. For this reason, as well as the absence of these tumors in the Heim et al. (2007) study with higher nickel blood levels, the elevated cortical tumors in female rats are considered of uncertain relationship to the nickel metal exposure.

One additional cancer study in rats was conducted with nickel sulphate via the oral route (Heim et al 2007). In this study, no increased tumors were observed at doses up to 11 mg Ni/kg body weight/day. In all the rat studies described above, nickel levels in the lungs and/or blood/urine were measured, demonstrating that nickel was delivered to the organs.

Three inhalation carcinogenicity studies were conducted in mice (nickelmonoxide, nickel subsulphide, nickel sulphate) (NTP 1996a,b,c). None of these studies were clearly positive for lung tumors. While nickel sulphate and nickel subsulphide had no evidence of

carcinogenic activity, nickel oxide had equivocal evidence in female mice. This could be interpreted as mice not being susceptible to the carcinogenicity of nickel or as mice having higher thresholds for the AOPs leading to tumour formation. However, mice exposed to nickel subsulphide and nickel sulphate developed inflammatory reactions in lung and nose.

7.7.3 Summary

In the inhalation carcinogenicity studies in rats and mice, nickel subsulphide and nickel oxide were clearly positive for lung tumours in rats but not in mice, demonstrating that the rat is a good animal model to detect the carcinogenicity of nickel compounds. Same effects have been seen in humans in several epidemiological studies, but indicating different carcinogenic potencies in different nickel species. Exposure to nickel oxide in rats induced lung tumours at 10 times higher exposure levels than nickel subsulphide. The lowest exposure level in the rat study with nickel oxide (0.5 mg Ni/m^3) was below the threshold for lung tumours. This might demonstrate a higher sensitivity for lung tumours in rats induced by nickel subsulphide compared to nickel oxide. However, this effect could not be observed in humans, as shown in epidemiology data.

Nickel sulphate is the most soluble nickel compound. It did not induce tumors via inhalation in rats and mice nor in rats via the oral route. Nickel sulphate represents the most systemically bioavailable of the nickel substances. The combination of high lung toxicity, extracellular factores like metal ion chelators (see chapter 7.9) and rapid lung clearance may have result in insufficient amount of nickel at rat target sites for tumor formation.

When the inhalation and oral studies with nickel sulphate are considered together, they show that the cancer effects of nickel are local (respiratory tract after inhalation) and that it is not enough for a substance to just contain or release nickel ions to induce tumors. In the rat nickel sulphate study (NTP 1996c) a NOAEC of 0.03 mg Ni/m^3 was identified based on pronounced inflammatory reaction at the next higher dose.

Human data shows an association between soluble nickel exposure and increased lung cancer risk. Therefore, a potential explanation for the negative rat study is the presence of a threshold. The combination of high lung toxicity and rapid lung clearance could have resulted in insufficient amount of nickel at rat target sites for tumor formation. However, in epidemilological studies the exposure has been often to a mixture of soluble and poorly souble nickel compounds and an increased risk with both poorly soluble and soluble nickel has been observed. Also there has been no indication that sulfidic nickel show the highest carcinogenic potency in humans as it might be suggested by animal data with nickel subsulphide.

Chronic inhalation exposure to nickel sulphate, nickel subsulfide, or nickel oxide resulted in chronic active lung inflammation in rats and mice. The LOAECs for chronic inflammation in rats increased with decreased solublility of the nickel compound (LOAEC for nickel sulphate 0.06 mg Ni/m^3, for nickel subsulfide 0.11 mg Ni/m^3, for nickel oxide 0.5 mg Ni/m^3. Nickel sulphate and nickel subsulfide induce inflammatory reactions also in the nose. However, increased tumour incidences in rats after chronic nickel subsulfide exposure where observed together with first signs of lung inflammation (0.11 mg Ni/m^3), but rats exposed to nickel oxide developed inflammatory signs in the respiratory tract at 2 times lower doses than increased tumours (1.0 mg Ni/m^3).

There is also epidemiologic evidence of the carcinogenic effects in the nose of insoluble oxidic and sulfidic nickel species as well as soluble nickelcompounds.

Nickel metal tested in rats did not induce tumours in the respiratory tract after inhalation at any of the tested dose levels, including the MTD of 0.4 mg Ni/m^3. Therefore, it can be argued that nickel metal is either not carcinogenic or has a threshold for lung tumors. However, there has also not been a positive association between exposure to metallic nickel and increased cancer risk in epidemiological studies and nickel metal induced in the rat malign lung tumours after intra-tracheal instillation.

In the animal inhalation bioassays with nickel subsulfide, nickel oxide, and nickel metal powder, increases in adrenal gland pheochromocytomas were observed. Goodman et al (2011) and Greim et al (2009) stated that these tumours, also observed in inhalation studies with talc and other compounds, were considered secondary to the respiratory toxicity and hypoxemia caused by the particulate nickel exposures. SCOEL (2011) stated to nickel metal powder that significance of these endpoints for human carcinogenicity is presently unknown and underlying mechanisms imply that comparatively high concentrations are required to exert these effects. Adrenal gland tumours have not been observed in any of the epidemiological studies of nickel workers.

Nickel and its compounds are not mutagenic, but weak genotoxicity is assumed and mechanistic data indicate an indirect genotoxic mode of action for carcinogenicity. For a quantitative cancer risk assessment it is important to identify if nickel and compounds induce cancer via a threshold or a non-threshold mode of action. Different approaches have been published, indicating that the available data does not give clear answer to this question.

7.8 Reproductive toxicity

7.8.1 Human data

In an earlier study Chashschin et al (1994) reported that a normal course of pregnancy was less common (29%) among Russian female nickel refinery workers as compared to female construction workers (39%). There was also a statistically significant increase in the incidence of spontaneous abortion (16% vs 9%) and structural malformations (17% vs 6%) among the nickel refinery workers. A number of methodological problems was pointed out for the study concerning selection of the reference population, lack of control for confounding, characterization of nickel exposure and classification of some of the studied health outcomes (Odland et al 1999, EU RAR 2008). Consequently a series of studies was published aiming at avoiding such methodological problems.

In these further studies the association between nickel exposure and reproductive health outcomes has been studied in the city of Monˇcegorsk with a population of about 66 000 in the Kola Peninsula in northwest Russia. In the period of 1973-1997 about 43% of the delivering women of the city were employed by the local nickel refinery and the Kola Birth Registry includes extensive data of about 98% of all live births, as well as still births of at least 28 weeks of gestation by citizens of Monˇcegorsk in 1973-2001 (Vaktskjold et al 2006, Odland et al 1999). Information about estimated exposure to soluble nickel compounds (inhalable fraction) and solvents according to occupation has been added for all delivering women. These data are based on the occupational information at the time when becoming pregnant. There were about 23 000 births available for analysis in the studies reported below. Nickel exposure estimation was partly based on urine biomonitoring samples. High exposure definition corresponded to $\geq$ 0.16 mg/m^3 and low as 0.02 – 0.16 mg/m^3 of water soluble inhalable subfraction.

Vaktskjold et al (2006) reported that the risk of delivering a newborn with genital malformations was not increased for the nickel-exposed women (OR = 0.81; 95% CI 0.52 – 1.26) when adjusted for parity (first delivery), maternal malformations, exposure to solvents at work and infectious diseases before or during early stages of pregnancy. Separate analyses were performed for undescended testes revealing no increase in risk (OR = 0.76; 95% CI 0.40 – 1.47). There was also no indication of a trend when dividing the nickel exposed to those with low and high exposure. Neither for all genital malformations nor for undescended testes.

Vaktskjold et al (2007) reported that the risk of delivering a newborn that was small for gestational age (SGA) was not increased among the nickel exposed (OR = 0.84; 95% CI 0.75 – 0.93). SGA was defined as a birth weight below the 10th percentile birth weight for gestational age in the local population. The analyses were adjusted for maternal age,

maternal height, smoking, previous induced abortions and obvious signs of alcohol abuse in pregnancy. The analyses excluded the 27 newborns with a diagnosis with chromosomal aberrations (trisomies 13, 18 and 21, and Turner's syndrome).

Vaktskjold et al (2008) reported that the risk of delivering a newborn with musculoskeletal defects was not increased for the nickel-exposed women (OR = 0.96; 95% CI 0.76 – 1.21). The analyses were adjusted for both high and low maternal age, first delivery, smoking, solvent exposure at work and alcohol abuse. Overall the study found an incidence of musculoskeletal malformations in Monče̊gorsk that was more than twice than that in the EUROCAT database. Among the nickel exposed workers there was a particularly high incidence among those who worked in the copper refinery department.

Vaktskjold et al (2008b) analysed the risk of spontaneous abortion among women from selected workplaces (with and without nickel exposure). There were 238 spontaneous abortion cases which were compared to 1981 controls, i.e. live births among women without previous spontaneous abortion. The unadjusted OR of spontaneous abortion among the nickel exposed was 1.38 (95% CI 10.4 – 1.84). When adjusted for maternal age, previous induced abortion, previous delivery, regular heavy lifting at work and exposure to solvents at work the OR was 1.14 (95% CI 0.95 – 1.37). In a subset of the study also adjustment for smoking could be performed but did not change the result (OR = 1.15, 95% CI 0.96 – 1.39). The authors acknowledged that the findings do not exclude the possibility of a weak excess risk, or a risk in the first weeks of pregnancy which would not be reliably captured in a study based on self-reporting.

7.8.2 Animal data

Several regulatory bodies have evaluated the reproductive toxicity of nickel and nickel compounds following exposure to rats, mice and dogs.

Effects on male sex organs in rats and mice have been reported in limited studies after oral, inhalation or subcutaneous administration of nickel chloride or nickel sulphate. The NOAEC for effects on male sex organs of 0.45 mg Ni /m^3 for inhalation exposure and the NOAEL of 2.2 mg Ni/kg bw/day for oral administration were identified (Danish EPA (2008).

CONTAM (EFSA, 2015) summarised 18 oral studies on reproductive toxicity and further 5 oral studies on developmental toxicity and concluded that in the rat reproductive toxicity studies and repeated dose toxicity studies, oral administration of soluble nickel compounds did not induce alterations in reproductive tissues and no adverse effects on fertility or reproductive performances were found and confirmed the lowest set NOAEL for effects on fertility in rats after oral exposure with 2.2 mg Ni/kg bw/d.

In mice effects on male sex organs weights, histopathological changes in these organs, disturbed spermatogenesis, decreased sperm motility and sperm damages have been reported in studies after oral exposure to doses ≥ 2.2 mg Ni/kg bw/d and could have been considered responsible for a decrease in fertility. However, several limitations were noted in these studies, such as number of animals and doses tested, and number of parameters investigated (EFSA, 2015; ATSDR, 2005; SCOEL, 2011).

CONTAM (EFSA, 2015) further stated that nickel crosses the placental barrier, affecting directly the developing embryo or fetus. There is consistent evidence of increased pup mortality (stillbirth or postimplantation/ perinatal lethality) after exposure of rats to nickel chloride or sulphate in several reproductive toxicity studies at doses ≥ 1.3 mg/kg bw/d.

Based on the increased post-implantation/perinatal lethality in F1 generation in an OECD TG 416 two-generation rat study at 2.2 mg Ni /kg bw/day, the unequivocal NOAEL used for developmental toxicity for regulatory purposes was set at 1.1 mg Ni/kg b.w. per day by the Danish EPA (EU RAR, 2008).
In mice exposed to nickel chloride, malformations, reduced ossification and increased incidence of skeletal anomalies were observed at doses ≥ 92 mg Ni/kg bw/d in the presence of maternal toxicity. Microphthalmia was observed in mice at 46 mg Ni/kg bw/d

in the absence of maternal toxicity. EFSA CONTAM panel (EFSA 2015) concluded that nickel is considered to be a developmental toxicant inducing fetotoxicity, embryotoxicity and teratogenicity.

The EFSA CONTAM panel set a tolerable daily intake (TDI) of 2.8 µg Ni/kg bw/d for the general population (EFSA 2015). The TDI was derived from a lower 95 % confidence limit for a benchmark dose at 10 % extra risk (BMDL10) of 0.28 mg/kg bw for post-implantation fetal loss in rats by applying a 100-fold safety factor. More recently, Haber et al (2017) derived a TDI value of 20 µg Ni/kg bw/day, starting with the same animal studies but using different effects for modelling (number of affected pups within each litter based onthe nested data from different studies vs number of affected litters used by EFSA) and focusing the best fitted model (instead of the one showing the lowest BMDLs). This approach resulted in a $BMDL_{05}$ of 1.8 mg/kg, which was then used to derive a TDI by applying a standard AF of 100.

7.8.3 Summary

Data investigating nickel-induced reproductive/developmental effects in humans following inhalation exposure did not show any indication of reprotoxicity. However, several animal data show that nickel can be considered as developmental toxicant inducing fetotoxicity, embryotoxicity and teratogenicity.

Soluble nickel compounds are classified with Repro 1B under CLP.

7.9 Mode of action (MoA) considerations

An integrating consideration of the relevant cellular and biochemical findings allows the conclusion that the presence of nickel ions at target cellular sites is responsible for the inflammatory, genotoxic and/or carcinogenic effects of nickel compounds. Additionally, the long half live in the lung (nickel oxide: > 100d) of insoluble particles may contribute to adverse effects in the lung due to the longer retention time and thus longer time for interactions with target cells. (SCOEL 2011).

There is a fundamental difference between soluble and insoluble nickel compounds in their kinetic pattern and extracellular and intracellular bioavailability. The soluble nickel salts are rapidly cleared from the body and enter cells only to a limited degree where they become bioavailable only at higher dose levels and with continuous exposure. Insoluble nickel compounds such as nickel oxide and nickel subsulfide have a higher tendency to be retained at their site of application. They enter cells via active phagocytosis and achieve higher and long-lasting bioavailability. Particle size and surface charge are important factors for the induction of phagocytosis.

7.9.1 Nickel ion bioavailability

Goodman et al (2011) postulated the nickel ion bioavailability model taking into account various factors that determine the bioavailability of the nickel ion at nuclear sites of target epithelial cells. The bioavailability after inhalation depends on the interaction of different factors (respiratory toxicity, clearance, target cell uptake, intracellular dissolution), which differ among the various forms of nickel. The tolerable exposure levels (level which induces no or minimal toxicity) will affect the deposited doses in the lungs and subsequently influence the amount of nickel available for cellular uptake (provided that particle size distribution are the same for all nickel compounds). The particle size of nickel compounds determines the deposition fraction in the respiratory tract of rats and humans. The particle sizes of the aerosols used in the animal inhalation bioassays were near a mass median aerodynamic diameter (MMAD) of 2 µm. The human deposition characteristics of aerosols indicate that virtually all of these particles would be of respirable size in humans (Oller and Oberdorster 2010).

The toxicity of some forms of nickel is correlated with solubility (nickel ion release) in the respiratory tract. Compared to nickel sulphate, nickel subsulfide released 16-fold less nickel, nickel metal powder released 310-fold less nickel, and nickel oxide was virtually insoluble (689-fold less nickel release) in synthetic lung fluid after 24 hours (Oller et al 2009). With the exception of nickel metal powder, nickel compounds with greater solubility in the respiratory tract are more toxic.

Nickel lung burden, as a measure of retained dose, is a function of exposure, particle size, and clearance. Retention half-times in rats are 1 to 2 days for nickel sulphate hexahydrate, about 5 days for nickel subsulfide, between 30 and 50 days for nickel metal powder, and greater than 100 days for nickel oxide subsulfide (Goodman et al 2011). For nickel sulphate hexahydrate, high toxicity and rapid clearance are two factors that lead to low retained doses and can explain the lack of carcinogenicity in animals. For nickel subsulfide, nickel metal powder and nickel oxide the differences in carcinogenicity cannot be explain alone on the retained dose differences. Subsequent steps involving particle uptake and intracellular dissolution must also be considered.

Both water-soluble and poorly soluble nickel species are taken up by cells, in the form of ion channels and are transported, the latter by phagocytosis (see figure below). Both water-soluble and insoluble nickel compounds result in an increase in nickel ions in the cytoplasm and the nucleus (IARC 2012). *In vitro* studies suggest that the relative extent of cellular uptake of various nickel-containing substances is likely to follow the general trend: water-soluble nickel < metallic nickel < amorphous nickel sulfide < nickel oxide < nickel-copper oxides < crystalline nickel sulfide < crystalline nickel subsulfide (Goodman et al 2011).

The amount of nickel ions released from nickel-containing particles by dissolution after endocytosis depends on their physical and chemical properties. Nickel subsulphide is better soluble in lysosomal fluid than nickel oxide and this allows for the particles to release high amounts of nickel ions inside the cells. This could contribute to nickel oxide's lower carcinogenicity compared to nickel subsulfide (Goodman et al 2011).

The endocytotic uptake of Metallic nickel particles is poor and the intracellular dissolution rather slow, based on corrosion via oxidation, therefore the yield of intracellular nickel ions from metallic nickel particles is expected to be low (Oller et al., 2009). Water-soluble Nickel salts can enter the cell and nucleus via ion channels. But extracellular amino acids will bind nickel ions, and other divalent cations may compete for cellular uptake. The majority of free nickel ions entering the cell might also bind to intracellular ligands, such as proteins, which increases cytotoxicity and severely limits the amount of nickel ions entering the nucleus (Haber et al., 2000).

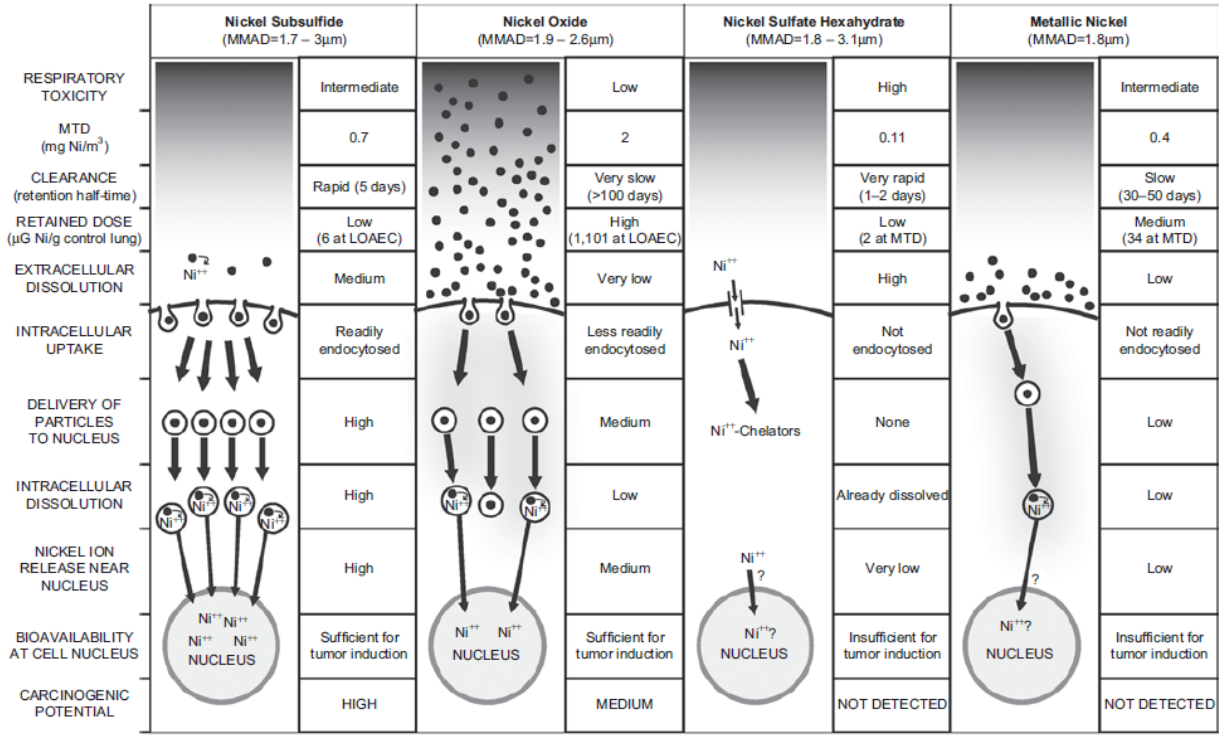


Figure 1: Lung cells bioavailability model

Lung cells bioavailability model explains the tumorigenic potential of nickel substances after inhalation (corresponding to Fig 1 of Goodman et al 2011). The delivery of Ni(II) ion from inhaled nickel substances to nuclear sites of target cells is visualized here as the result of an interplay between systemic toxicity, particle clearance and extracellular dissolution, and cellular uptake and intracellular dissolution.

It is only if the nickel ion reaches the nucleus in sufficient amounts, and the cell survives, that it can ultimately lead to carcinogenesis. This implies the existence of a threshold for the initiation of carcinogenicity, even if the effects of the nickel ion in the nucleus are assumed to be genotoxic (Goodman et al 2011).

7.9.2 Mechanisms of carcinogenicity

The mechanism of nickel carcinogenicity has not been firmly established; it is likely that the carcinogenic effects result from a variety of mechanisms. The available evidence suggests that, mechanistically, nickel carcinogenicity is probably the result of genetic factors and/or direct (e.g., conformational changes) or indirect (e.g., generation of oxygen radicals) epigenetic factors. Additionally, certain nickel compounds promote cell proliferation, which would convert repairable DNA lesions into non-repairable mutations.

Furthermore, it can be assumed that an inflammatory reaction triggered by the intrinsic cytotoxicity of the nickel compounds, via oxidative DNA damage and regenerative processes, promote tumor formation (AGS, 2017).

Efremenko et al. (2014) reported the results from a lung tissue-specific gene expression analysis in rats exposed to nickel subsulfide via inhalation to different dose-levels. Also BALF analysis and histopathology were made to record inflammatory lung effects. The study indicated that the pathways affected by nickel exposure primarily reflected responses to toxicity, including inflammatory and proliferative signalling. Most importantly, pathways related to the DNA damage not induced except possibly at the two highest dose levels after 4 weeks exposure. The results supported an indirect genotoxic mode of action (driven by chronic toxicity, inflammation and proliferation, leading to mis-replication, rather than by direct genotoxicity). An exposure level of 0.04 mg Ni/m^3 (respirable

fraction) was identified as the lowest BMD after 4 weeks of exposure (using benchmark dose analysis).

A more recent paper from Efremenko et al. (2017) reported the results from a similar study with nickel sulfate hexahydrate and compares the toxicogenomic responses with nickel subsulfide. The cellular responses to nickel sulfate were highly similar to those reported for nickel subsulfide. However, several key differences in the immune responses were identified that may result from the differential intracellular disposition of nickel from nickel sulfate entering the cell as an ion rather than as a slowly soluble nickel subsulfide particle. After four weeks of inhalation exposure, the category with the lowest BMD (0.05 mg Ni/m^3) was again the immune response. When comparing gene expression responses at different exposure levels, the study identified a dose-dependent transition in the mode of action at the higher exposure level of nickel subsulfide that was associated with up-regulation of immune signaling. The authors concluded that the ultimate tumour outcome for a given nickel compound may depend on the extent to which the compound is able to deliver sufficient nickel ion to critical cellular targets, at exposure levels that lack overt toxicity (e.g., this may not be feasible for nickel sulfate). The No Observed Transcriptional Effect Level (NOTEL) for repeated exposure to both nickel sulfate and nickel subsulfide was 0.03 mg Ni/m^3 (respirable fraction).

A weight of evidence analysis indicates that the mode of action of nickel for tumor induction is an indirect genotoxic mode of action and is through a variety of threshold effects like inflammation, and genotoxic and epigenetic effects that are dependent on the delivery of sufficiently high Ni(II) levels to nuclear sites of target cells.

In a recent paper Scanlon et al (2017) stated: “Unlike many other environmental carcinogens, however, nickel does not directly induce DNA mutagenesis, and the mechanisms of nickel-related carcinogenesis remains incompletely understood. Cellular nickel exposure leads to signalling pathway activation, transcriptional changes and epigenetic remodeling, processes also impacted by hypoxia, which itself promotes tumor growth without causing direct DNA damage. One of the mechanisms by which hypoxia contributes to tumor growth is the generation of genomic instability via down-regulation of high-fidelity DNA repair pathways”.

7.9.3 Mechanisms of indirect genotoxicity

The overall evidence strongly supports that the mutagenicity of nickel compounds is weak and that there is an indirect genotoxic mode of action for carcinogenicity. Thus, a mode of action for nickel compounds through indirect mechanisms can be proposed and as reported by EFSA (2015) on the basis of the current literature, three predominant mechanisms emerge: 1) interference with cellular redox regulation and induction of oxidative stress; 2) inhibition of DNA repair systems; 3) dysregulation of signalling pathways and alteration of the epigenetic landscape.

Oxidative stress

Treatment with soluble and insoluble nickel causes increases in reactive oxygen species (ROS) in many cell types and in animal models. ROS induction seems to be responsible of increased DNA SSBs, DNA-protein cross-links and SCEs.

Kawanishi et al. (2002) investigated the participation of ROS in nickel-induced DNA damage by incubating calf thymus DNA with Ni(II) plus H_2O_2 which induced increased levels of 8-OH-dG with increasing H_2O_2 concentration. In contrast, H_2O_2 or Ni(II) alone induced little or no 8-OH-dG increase. Rats were exposed to 1 mg of various nickel compounds and formation of 8-OH-dG in the lungs was measured. The potency for lesion formation was Ni_3S_2 > NiO (black) = NiO (green) > $NiS0_4$. Exposure to 0.5 mg Ni_3S_2 and NiO (black) also induced 8-OH-dG, but not exposure to NiO (green) or $NiS0_4$. These results suggest that Ni(II) reacts with H_2O_2 and produces ROS causing oxidative DNA damage. The authors proposed that there is an indirect, inflammation related generation of

oxidative damage in vivo by all nickel compounds and a direct generation of oxidative damage by Ni_3S_2 which is seen *in vitro*.

In another *in vivo* study Mayer et al. (1998) reported increased mutation frequency by nickel subsulphide in a lacI transgenic embryonic fibroblast cell line. Rats were exposed for 2hrs via inhalation to 24-352 mg /m^3 of nickel subsulfide, DNA damage was measured by the Comet assay in lung and nasal cells and mutations were measured at the LacI transgene. After 2hrs inhalation at approximately 300 mg/m^3 nickel subsulfide, nasal nickel levels were elevated by 37-fold and in lung tissue an order of magnitude higher at 370-fold even though DNA damage was more pronounced in nasal tissue. It was noted that the DNA damage in lungs was minimal or absent. Similarly, after 2hrs inhalation at approximately 200 mg/m^3 nickel subsulfide, no significant elevation of lacI frequency in lung or nasal cells of exposed animals was observed. DNA SSBs (single strand breaks) were detected in a dose-dependent manner in both cell types. These results support a non-genotoxic model of nickel carcinogenesis, which acts through gene silencing via DNA methylation and chromatin condensation.In *in vitro* studies by Chen et al (2003a) concluded that there was a dose-dependent association between generation of OH radical and DNA strand breakage and that the generation of OH radical is likely to be responsible for nickel chloride -induced DNA strand breakage. Chen et al (2010) also analysed the effects on cell cycle and apoptosis of nickel chloride and reported that nickel induced cytotoxicity in NRK cells involves generation of ROS, oxidative stress, DNA strand breaks, and apoptosis.

It has been reported (ATSDR 2005) that the binding of nickel to the histone protein within heterochromatin could result in the generation of oxygen radicals. These oxygen radicals could subsequently induce damage bases, DNA strand breaks, and DNA protein crosslinks (Costa et al. 1994; Oller et al. 1997). However, although the available evidence suggests that this mechanism would play a minor role in nickel carcinogenicity, the damage would be confined to heterochromatin regions of DNA, which lack active genes (Oller et al. 1997).

Nickel ions can complex with a number of cellular ligands including amino acids, peptides, and proteins resulting in the generation of oxygen radicals. The reactive oxygen species (ROS) generated could non-selectively damage DNA, possibly resulting in genetic changes in active genes (Kasprzak et al. 2003; Oller et al. 1997).

Inhibition of DNA repair

The treatment of cells with soluble Ni(II) increases the DNA damage and mutagenicity of several agents most likely via inhibition of DNA repair (nucleotide excision repair, base excision repair and O^6-methylguanine-DNA methyltransferase).

There is evidence that nickel ions inhibit DNA repair (Hartwig et al. 1994) which showed that Ni(II) interferes with the incision step in nucleotide excision repair in mammalian cells. The effect of Ni(II) on the damage recognition step of the repair process was also specifically investigated by applying a gel-mobility-shift assay in HeLa nuclear extracts (Hartmann and Hartwig, 1998) and concluded that nickel disturbs DNA-protein interactions essential for the initiation of nucleotide excision repair most likely by the displacement of essential metal ions.

It has been reported (ATSDR 2005) that nickel enhances the genotoxicity of ultraviolet light, x-rays, *cis*- and *trans*-platinum, and mitomycin C. *In vitro* studies in HeLa cells suggest that nickel inhibits the incision step in excision repair (Hartwig et al. 1994), while studies using Chinese hamster ovary cells suggest that nickel inhibits the ligation step of excision repair (Lee-Chen et al. 1994).

The underlying mechanism of how nickel affects DNA repair is unclear. Sunderman and Barber (1988), Sunderman (1989b), and Hartwig et al. (1994) suggest that nickel ions may compete with zinc ions for binding to zinc-finger DNA binding proteins, resulting in structural changes in DNA that prevent repair enzymes from binding. Nickel may also directly interact with enzymes required for DNA repair (Hartwig et al. 1994).

Epigenetic mechanisms

Both water-soluble and water insoluble nickel compounds are able to cause gene silencing. As described (IARC 2012, EFSA 2015), this effect was first reported when mutations in the transgenic *gpt* gene in a Chinese hamster cell line (G12) were found to be epigenetically silenced rather than mutated (Lee at al 1995, Klein and Costa, 1997). Genes that are located near heterochromatin are subject to such inactivation by nickel. The *gpt* gene was silenced by DNA methylation.

Although nickel has a relatively weak affinity for DNA, it has a high affinity for chromatin proteins, particularly histones and protamines (Costa et al. 1994; Kasprzak et al. 2003b; Oller et al. 1997). Nickel's preferential and stronger interaction with proteins than DNA, is noted by the relatively low Ni(II) binding constants of 6.7 X 10^{-1} M^{-1} for adenosine and 7.3 X 10^{2} M^{-1} for DNA. In contrast, binding constants of 4.37 X 10^{9} M-1 for cysteine, 1.9 X 109 M-1 for histidine or 1-5 X 105 M-1 for other amino acids have been reported (Biggart and Costa, 1986). The complexing of nickel ions with heterochromatin results in a number of alterations including condensation, DNA hypermethylation, gene silencing, and inhibition of histone acetylation. These alterations have been shown to disturb gene expression (Costa et al. 1994; Kasprzak et al. 2003b; Lee et al. 1995; Oller et al. 1997; Zoroddu et al. 2002). Methylation of DNA may result in critical genes becoming incorporated into heterochromatin where they can no longer be expressed (Costa 1995).

The strongest epigenetic effects on nickel have been associated with HIF-1. The HIF-1 transcription factor is involved in the regulation of hypoxia-inducible genes involved in cell transformation, tumor promotion, and progression, angiogenesis, altered metabolism, and apoptosis. HIF-1α, one of the HIF-1 subunits, is over-expressed in both primary and metastatic tumors. It is induced in response to hypoxia and exposure to nickel (Li et al. 2004; Salnikow et al. 2000b). Both soluble and insoluble nickel compounds have also been shown to induce Cap43 (also called NDRG2) gene expression, which requires HIF-1α activation (Costa et al. 2003; Li et al. 2004; Salnikow et al. 2000b).

Modification of histones by nickel has been reported in several studies in human cells in culture. Ke et al. (2006) was the first study to show that nickel compounds increase histone ubiquitination in cells. Other studies (Karaczyn et al. 2006, Kang et al. 2003, Ke et al., 2008) also modified histone activity.

Ji et al (2008) investigated epigenetic alterations in a set of DNA repair genes in NiS-transformed human bronchial epithelial (16HBE) cells. The silencing of the O(6)-methylguanine DNA methyltransferase (MGMT) gene locus and upregulation of DNMT1 expression was specifically detected in these cells. Moreover, epigenetic alterations including DNA hypermethylation, reduced histone H4 acetylation and a decrease in the ratio of Lys-9 acetylated/methylated histone H3 at the MGMT CpG island in NiS-transformed 16HBE cells were noted.

In a study in occupationally exposed subjects (Arita et al. 2012) it was observed that H3K4me3 was significantly elevated in nickel subjects compared with referents, and H3K9me2 was decreased. H3K4me3 was positively and H3K9ac was negatively associated with urinary Ni.

Recent studies have reported that miRNAs may play a role in nickel-induced cell transformation. Zhang et al. (2013) reported that expression of miR-222 was significantly up-regulated in rat rhabdomyosarcomas and observed that there was a strong downregulation of miR-203. Ji et al. (2013) reported that miR-152, a tumour suppressor microRNA targeting DNMT1, was significantly down-regulated in nickel sulphide-transformed 16HBE cells.

7.9.4 Summary

A weight of evidence analysis indicates that the mode of action of nickel for tumor induction is an indirect genotoxic mode of action and is through a variety of threshold effects like

inflammation, and genotoxic and epigenetic effects that are dependent on the delivery of sufficiently high Ni(II) levels to nuclear sites of target cells.

7.10 Lack of specific scientific information

Although the current data seem to support the nickel ion bioavailability model (Goodman et al 2011) further data to improve the understanding of the processes that affect the bioavailability of the nickel ion from nickel-containing substances in respiratory epithelial cells are needed in order to limit the current uncertainties related to the model.

8. Cancer Risk Assessment and exposure limit values

8.1 Published approaches for cancer risk assessment

Different approaches have been published and are summarised below.

8.1.1 US-EPA

Overview

The US EPA has estimated cancer risk from exposure to nickel refinery dust with the midpoint 2.4 x 10^{-4}/µg/m^3 of the range from 1.1 x 10^{-5} to 4.6 x 10^{-4}/ µg/m^3 based on human data (US EPA, 1991a). Additionally, the US EPA has estimated the lifetime cancer risk from exposure to nickel subsulfide as a major component of nickel refinery dust. Nickel subsulfide has been shown to produce the highest incidence of tumours for nickel compounds in animals (NTP 1996b). The incremental unit risk estimate of nickel refinery dust of 2.4x10^{-4}/ µg/m^3 was used with a multiplication factor of 2 to account for the roughly 50% nickel subsulfide composition. An inhalation unit risk in the general population of 4.8x10^{-4}/ µg/m^3 (range 2.2x10^{-5} – 9.2x10^{-4}) was thus obtained for nickel subsulfide (US EPA, 1991b).

Discussion / Points of concern

US-EPA derived unit risks for the general population by using occupational cohort dataexposure and animal data. However, the methodology and the data source (epidemiological data) used are not described.

Additionally, a lifetime cancer risk for the general population from exposure to nickel subsulfide was estimated. Risk estimates for the general population are not within the scope of occupational protection.

8.1.2 CEPN

Overview

The Centre d´Etude sur l´Evaluation de la Protection dans le domaine Nucléaire (CEPN) performed a risk assessment for nickel based upon respiratory cancer in humans and animals. The epidemiological studies of occupational exposure led to a unit risk estimate of 2.5 x 10^{-4} / µg/m³ by using a linear non-threshold approach (Lepicard et al., 1997). To account for the physical and chemical differences between nickel refinery workers and the general population, adjustments were made to this value using the results of animal studies. In the view of the CEPN authors, this permitted to distinguish between nickel oxide and nickel subsulfide. They derived unit risk estimates for lung cancer due to nickel oxide exposure of 4.0 x 10^{-5}/ µg/m³ and 3.0 x 10 -4 / µg/m³ for nickel subsulfide (quoted from European Commission, 2000).

Discussion / Points of concern

CEPN estimated a lifetime cancer risk for the general population from exposure to nickel subsulfide and nickel oxide by using epidemiological studies of occupational exposure and

animal data. However, the methodology and the data sources used are not sufficiently described. Additionally, risk estimates for the general population are not within the scope of occupational protection.

8.1.3 WHO

Overview

An estimate of the unit risk was made by WHO (2000) on the basis of the report of lung cancer in nickel refinery workers in Norway first employed between 1968 and 1972 and followed through 1987 from Andersen et al (1996). Using the estimated risk of 1.9 for this group and an exposure of 2.5 mg/m^3, a lifetime exposure of 155 µg/m^3 and a unit risk of 3.8 x 10^{-4}/µg/m^3 for general population were calculated, which was also accepted by the CSTEE in their opinion on the Commission Ambient Air Position Paper (CSTEE 2001). It is to be noted that these estimates were based on total nickel exposure without considering the data by different nickel species or the revised exposure estimates of the Norwegian refinery cohort.

Based on the WHO excess risk estimate of 3.8 x 10^{-4} per µg/m^3 an occupational excess risk of 95 x 10^{-3} per mg/m^3 was calculated for a 40 years occupational exposure correcting for the difference between continuous general population exposure and occupational exposure (EU RAR 2008). This occupational excess risk of about 1 x 10^{-1} per mg/m^3 (or 1 x 10^{-4} per µg/m^3) was not corrected for the fact that the exposure estimates in the epidemiological study used were based on total dust measurements instead of the currently used metric of inhalable dust. Nevertheless EU RAR (2008) acknowledged that with the correction the risk would be approximately 50% lower.

Discussion / Points of concern

WHO estimated a lifetime cancer risk for the general population. These estimates were based on total nickel exposure without considering the data by different nickel species or the revised exposure estimates of the Norwegian refinery cohort and commented by EU RAR (2008). However, risk estimates for the general population are not within the scope of occupational protection.

8.1.4 SCOEL

Overview

According to the SCOEL categorisation scheme[11] (see Appendix 2), nickel and nickel inorganic compounds are considered a carcinogen Group C: Genotoxic carcinogens for which a **practical threshold** is supported.

SCOEL (2011) stated in the recommendation for nickel and inorganic compounds that mechanistic data indicate an indirect genotoxic mode of action. From a mechanistic point of view, nickel and nickel compounds are not directly mutagenic and based on cellular investigations, at low concentrations nickel ions do not directly interact with DNA but rather exert indirect genotoxic effects such as interference with DNA repair systems and DNA methylation patterns, which lead to clastogenicity and increased genomic instability. These effects are mediated by nickel ions, even though it cannot be excluded that on conditions of particle overload chronic inflammation may contribute to the carcinogenicity.

Therefore, nickel was considered as carcinogen group C (carcinogen with a practical threshold; acc to SCOEL classification system).

The proposed OELs are based on protection from inflammatory effects in the lungs seen in rat studies, which should also protect against carcinogenic effects.

In an inhalation study in rats with soluble nickel sulphate (NTP 1996c) a NOAEC of 0.027 mg Ni/m^3 rounded to 0.03 mg Ni/m^3 was identified based on pronounced inflammatory reaction at the next higher dose. Differences between rats and humans were considered by assuming an equivalent human concentration (EHC) of 0.016 mg/m^3. The EHC was taken from the publication Oller and Oberdoerster, 2010. However, since this conversion did not take the long-term chronic retained dose as well as potential toxicodynamic differences into account, an 8 h OEL of 0.005 mg Ni/m^3 for the respirable fraction (taking into account the respirable particle size of nickel sulphate of 2.5 µm MMDA) was proposed. Inflammatory reactions including fibrosis were also seen with poorly soluble nickel subsulphide (NTP 1996b) at 0.11 mg Ni/m^3 and with nickel oxide (NTP 1996a) at 0.5 mg Ni/m^3 and, in form of alveolar proteinosis, alveolar histocytosis and chronic inflammation with metallic nickel at 0.1 mg/m^3. In all three cases this was the lowest concentration applied and no NOAEC could be identified. SCOEL argued that due to the severe lung damage or chronic inflammation observed at these concentrations, the 2-3-fold higher deposition of nickel after exposure to nickel oxide in humans (as compared in rats) and the estimated longer retention half-times in humans for Ni_3S_2 and NiO (Oller and Oberdoerster), an **OEL of 0.005 mg/m^3 (respirable fraction)** was proposed for poorly soluble nickel compounds and metallic nickel.

SCOEL stated since epidemiological evidence suggests additional to lung tumours also the induction of nasal tumours, and particles at the workplace are not limited to the respirable fraction, exposure towards inhalable nickel particles needed to be limited for carcinogenic nickel species as well. Both water soluble and poorly water soluble, particulate nickel compounds have been considered as carcinogenic in humans, whereas no epidemiological studies indicate any carcinogenic potential of metallic nickel.

However, SCOEL emphasized that epidemiological data alone are not considered sufficient to exclude any nickel species such as metallic nickel from further considerations, since there are no cohorts that have been exclusively exposed to one nickel species.

However, animal long-term inhalation studies revealed carcinogenicity in the lung in case of poorly soluble nickel compounds (nickel oxide: 1.0 mg Ni/m^3; nickel subsulphide: > 0.11 mg Ni/m^3), but not in one inhalation study with water soluble nickel compounds, which appears to contradict the carcinogenic activity of water soluble nickel compounds in humans. SCOEL speculates that this might be due to the high toxicity and resulting limitations in exposure concentrations. Metallic nickel caused malignant tumours after intratracheal instillation and intraperitoneal injection in rats, but no significant increase in lung tumours was observed in a rat inhalation study.

The International Committee on Nickel Carcinogenicity in Man (ICNCM, 1990) concluded that the increase in cancers of the nasal cavity (ethmoïd) and lungs (bronchi, etc.) among workers in nickel refineries was associated with a minimum exposure of 1 mg/m^3 for water soluble salts and 10 mg/m^3 for insoluble compounds (sulphides, oxide, etc.) of nickel and that an excess of bronchial cancer and two cancers of the sinuses (nasal cavity) among workers exposed to concentrations of about 0.25 mg/m^3 water soluble nickel salts (sulphate) has been revealed (Anttila, 1998). A significant increase in cancer incidence for water soluble nickel was observed in the Kristiansand cohort at a cumulative exposure of 1.6 mg/m^3 x years, equivalent to 0.04 mg Ni/m^3 when calculated for 40 years exposure (Grimsrud et al., 2002). However, SCOEL indicated that this would resemble a conservative estimate, since current evidence strongly suggests indirect mechanisms with sublinear dose-response relationships in the low concentration range.

To protect from nickel-induced carcinogenicity observed in workers, SCOEL proposed an **OEL of 0.01 mg Ni/m^3 for the inhalable fraction** of water soluble as well as poorly water soluble nickel compounds, but not for metallic nickel. SCOEL argued that neither animal data nor epidemiological data point towards a carcinogenic action of nickel metal.

SCOEL stated further that this value should also protect against nickel-induced indirect genotoxicity, including chromosomal damage and that the value is below DNA repair inhibitory concentrations in experimental systems in vitro. . SCOEL considered this value as conservative estimate, since evidence strongly suggested indirect mechanisms with sublinear dose-response relationships in the low concentration range. The OEL for the inhalable fraction was also considered to provide sufficient protection of the reproductive system.

SCOEL also stated that exposure to nickel and nickel salts at workplaces might evoke contact sensitization and – in rare cases – also sensitization of the respiratory tract although it was recognized that soluble nickel compounds carry a CLP classification as Resp. Sens. 1; H334, these effects were not taken into account by setting the OEL.

Proposed health based OELs

SCOEL stated that exposure to nickel compounds is associated with an increased cancer risk in the lung and nasal cavity, as well as with inflammatory responses/fibrosis in the lung. The proposed OELs were based on protection from inflammatory effects in the lung, but according to available evidence should also protect against carcinogenic effects.

SCOEL proposed for the **respirable fraction** of poorly soluble nickel compounds and metallic nickel an OEL of 0.005 mg Ni/m^3 based on the rounded NOAEC of 0.03 mg Ni/m^3 identified in the chronic inhalation study in rats with soluble nickel sulphate (NTP 1996c), by using the published EHC of 0.016 mg/m^3 and taking into account the 2-3-fold higher deposition of nickel after exposure to nickel oxide and the estimated longer retention half-times in humans as compared in rats. SCOEL argued that this respirable OEL is valid for poorly water soluble nickel compounds and metallic nickel recognising that the LOAECs in respective chronic rat studies are based on inflammatory reactions in the lungs.

To protect from nickel-induced carcinogenicity observed in workers, SCOEL proposed an OEL of 0.01 mg Ni/m^3 for the **inhalable fraction** of water soluble as well as poorly water soluble nickel compounds, but not for metallic nickel, since neither animal data nor epidemiological data point towards a carcinogenic action of nickel metal. This OEL is derived on the basis of the significant increase in cancer incidence for water soluble nickel observed in epidemiological data at a cumulative exposure of 1.6 mg/m^3 x years and calculated for 40 years exposure (0.04 mg Ni/m^3 ;Grimsrud et al., 2002) and supported by in vitro genotoxicity data.

Discussion / Points of concern

SCOEL referred for deriving the OEL of 0.005 mg/m^3 for the **respirable fraction** to an EHC as published in Oller and Oberdoerster (2010). More recent data show that the EHC calculation had been based on data that had later been revised (in 2011) because newer information on the respiratory tract surface area in rats and humans had become available. Additionally, no quantitative assessments of human equivalent retained doses for various forms of nickel were undertaken.

Additionally, SCOEL based the lung cancer practical threshold (OEL of 0.01 mg Ni/m^3 for the inhalable fraction) on one cohort (5,000 workers) where exposures were collected with a 37-mm sampler, which is known to undersample the nickel mass in the inhalable aerosol fraction. SCOEL reported exposures both in terms of 37-mm samplers and equivalent inhalable samplers, but did not consider that these samplers differ by about 2-fold in sampling efficiency. Therefore, the final OEL did not incorporate a conversion to inhalable aerosol.

8.1.5 NiPERA

Overview

NiPERA (2017) has derived one respirable and two inhalable exposure limits (respirable guidance value for all nickel compounds including nickel metal and inhalable DNELs, one for nickel compounds and one for nickel metal) corresponding to respirable and inhalable OELs for all nickel compounds based upon the conclusions of SCOEL (2011) that carcinogenicity (and genotoxicity) exerted by nickel compounds is mediated by indirect mechanisms exhibiting a practical threshold. NiPERA integrated a high number of epidemiological data and reflected differences in sampling efficiency of different samplers used for aerosol collection at work place. These refinement factors influenced the calculation of the inhalable exposure limits. The exposure limits for nickel compounds were based jointly upon protection against human respiratory carcinogenicity and toxicity by using primarily human data but also considering in a complementary fashion the animal data.

The respirable exposure limit was derived by calculating the HEC from chronic rat data. NiPERAexplained that long-term respiratory (local) effects associated with inhalation exposures to nickel substances are considered related to the amount of nickel lung burden in the corresponding region of the respiratory tract. Lung inflammation and fibrosis were expected to be related to the retained nickel doses in the alveolar region, while lung tumours were considered to be related to the retained doses in trachea-bronchial and alveolar regions. Species specific differences in rodents and humans in physiology and anatomy in their respiratory tract resulted in differences in particle deposition, deposited dose, and retained doses in various regions of the respiratory tract, for different particle size distributions (PSDs). Also, the aerosols utilized in the animal studies (respirable aerosol) would have different PSDs from those to which humans are exposed in occupational environments (inhalable aerosols). Therefore, NIPERA stated further that for comparison of respiratory effects between rodents and humans the most relevant dose for the affected region, dose-metric (e.g., mass nickel/ alveolar surface area), particle density, as well as the clearance rate need to be considered. These factors should be taken into account by calculation a Human Equivalent Concentration (HEC) (with help of the Multiple Path Particle Deposition Model MPPD). NIPERA refined this calculation by using an updated value for the surface area of the rat pulmonary region.

The respirable guidance value of 0.01 mg Ni/m^3 for nickel metal and nickel compounds was derived by calculating HECs, derived from the animal data by using full dosimetric adjustments and for each group of nickel substances. Also nickel specific data for clearance rates and updated values for respiratory tract surface area in rats and humans were considered.

For the inhalable DNELs NIPERA considered 13 cohorts (> 100,000 workers) and exposure data reported in terms of inhalable aerosol fraction. In this calculation the exposures were converted to inhalable equivalents (37 mm sampler to inhalable sampler, factor 2) as described in Oller et al (2014) and Goodman et al (2011). Dosimetric adjustments were applied to the animal toxicity values for each group of nickel substances calculating HECs to animal exposure by considering workplace particle size distribution (PSD).

NiPERA argued that lung cancer appears to be a more sensitive endpoint observed with higher frequency that is amenable to accurate quantitative assessments of dose response, including efforts to identify a likely practical threshold for respiratory cancer risk. It should be noted that significant increased incidence of nasal tumours has not been observed in cohorts where the incidence of lung tumours is not significantly increased. Therefore, restricting inhalable nickel exposures to levels that prevent lung tumours is also expected to prevent nasal tumours.

NiPERA proposes inhalable DNELs of 0.05 mg Ni/m^3 for all nickel compounds and nickel metal, respectively based on respiratory cancer effects (not for nickel metal) in humans,

supported by animal data and respiratory toxicity effects base on animal data supported by human data.

Additionally, NiPERA stated that for nickel inhalable and respirable modified dose descriptors have been calculated based on retained doses and therefore no additional factor for toxicokinetic differences were needed. Epidemiological data indicate that humans are not more sensitive to respiratory toxicity effects of nickel than rats. Therefore the toxicodynamic component of the interspecies AF for nickel studies was set to 1. Dosimetric interspecies extrapolations replaced the use of default interspecies assessment factors.

Related to intra-human assessment factor for local respiratory effects after inhalation NiPERA stated that when HECs are calculated for nickel substances (based on animal data, local respiratory effects) and considering equivalent retained doses, these calculations already incorporate very conservative assumptions (most sensitive toxicity endpoint in most sensitive rodent species, retention T1/2 for nickel subsulfate, nickel oxide and nickel metal for rats are derived from studies conducted at exposure levels that are 3-fold higher than the calculated NAEC). For these additional reasons, and the fact that human data form several thousand workers is used in complementary fashion, applying an additional factor of 3 to the HEC values (corrected dose descriptors) based on animal data to account for intra-worker variability in the DNEL derivation is considered to be sufficiently conservative. It is additionally stated that when exposure levels from epidemiological studies were used as starting dose descriptors, adjustments for differences in length of exposure of the cohorts need to be considered.

NiPERA stated further that neither the inhalable DNELs of 0.05 mg Ni/m^3 for all nickel compounds and nickel metal nor the respirable guidance value of 0.01 mg Ni/m^3 were derived based on effects of nanoparticles.

Proposed health based OELs

The respirable guidance value of 0.01 mg Ni/m^3 for nickel metal and nickel compounds was derived by calculating HECs, derived from the animal data by using full dosimetric adjustments and for each group of nickel substances. Also nickel specific data for clearance rates and updated values for respiratory tract surface area in rats were considered.

Inhalable DNELs of 0.05 mg Ni/m^3 for all nickel compounds and nickel metal, respectively was proposed based on respiratory cancer effects (not for nickel metal) in humans and supported by animal data and respiratory toxicity effects base on animal data supported by human data.

Discussion / Points of concern

NiPERA considered a respirable guidance value and inhalable DNELs (for nickel compounds and nickel metal, respectively) in a comprehensive way by using the all available animal data to refine the derivation of HECs and considering the available human data in a weight of evidence approach.

However, on the basis of the current genotoxicity data, the genotoxicity of the nickel compounds is likely to be due to indirect effects. This principally would support the proposal of a threshold for tumour development induced by nickel compounds in animals and human. Nevertheless, since is cannot be demonstrated with certainty that the process has a clear threshold it is rather recommended to use, instead of the term DNEL or OEL, the term ‘practical’ OEL, indicating although weak, but remaining uncertainties.

8.1.6 The German AGS Approach

Overview

In the most recent publication by the German Federal Ministry of Labor and Social Affairs based on the opinion of the AGS (Ausschuss für Gefahrstoffe) "Begründung zu Nickelverbindungen in TRGS 910" (June 2017,

https://www.baua.de/DE/Angebote/Rechtstexte-und-Technische-Regeln/Regelwerk/TRGS/pdf/910/910-nickel.pdf?__blob=publicationFile&v=2)

the previous assessment on nickel metal (Begründung zu Nickelmetall in TRGS 900, November 2015) was consolidated and combined with an assessment of nickel compounds.

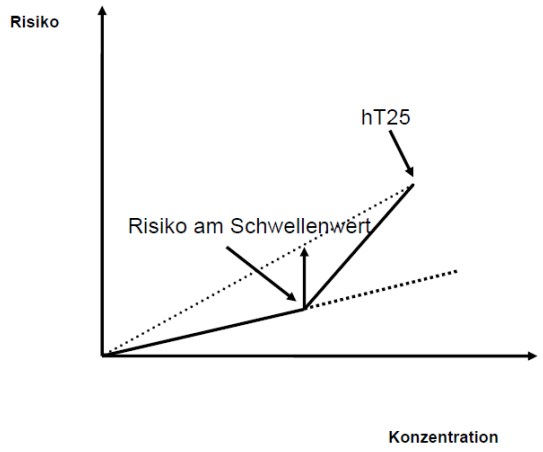
The derivation of a health based OEL (AGW) for nickel metal by AGS was based on the observed inflammatory processes in the lung of Wistar rats after chronic inhalation exposure (Oller et al 2008). AGS noted, that in this study only a LOAEC of 0.1 mg Ni/m^3 was observed. Overall the observed effects were however similar with those observed in NTP (1996c) after the inhalation exposure of F344/N rats to nickel sulphate. Therefore, the latter study was used to estimate a factor of 3 to extrapolate from the observed LOAEC in Oller (2008) to a rounded NOAEC of 0.03 mg Ni/m^3. This estimated NOAEC was used to calculate according to the AGS guidelines ("Guide for the quantification of substance-specific exposure-risk relationships and risk concentrations after exposure to carcinogenic hazardous substances at the workplace", (TRGS 910 Annex 3, 2013)) by employing the MPPD model 2.11 (2009) and the HEC concept a HEC-NOAEC of 0.018 mg Ni/m^3. With a reduced variability factor of 3 a health based OEL (AGW) of 6.1 µg Ni /m^3 was calculated. The reduced variability factor results from an analogy to soluble nickel compounds from comparative data from inhalation studies with repeated application for nickel chloride or nickel sulfate in rats, mice and rabbits. As the MMAD of the aerosol used in the chronic inhalation studies was about 2 µm, this OEL of **6 µg Ni/m^3** applies to the respirable particle fraction only.

For soluble nickel compounds ($NiSO_4$, $Ni(OH)_2$, $Ni(CO_3)_2$, $NiCl_2$, $NI(NO_3)_2$, $Ni(CH_3CO_2)_2$) the assessment was based on the chronic inhalation study, exposing rats to nickel sulfate (NTP 1996c), which allowed for the derivation of 0.027 mg Ni/m^3 (equivalent to 0.12 mg $NiSO_4$ * $6H_2O$ /m^3) as a NOAEC. As in the parallel experiment with mice higher doses were applied, this could not be used to calculate a NOAEC. The conclusion of AGS is based on the observation that in rats and mice the tumour incidence was not increased with regards to the control group, further evidenced by the outcome of the Oller et al study (2008) in which also no increase in tumour incidence could be observed. The observed effects in NTP 1996c of chronic inflammation, hyperplasia of macrophages, alveolar proteinosis and fibrosis were viewed by AGS as indicative of a threshold for the development of chronic inflammation. Further, AGS agreed with SCOEL (2011) that chromosomal aberrations are only observed in humans above concentrations of 0.5 mg Ni /m^3. Therefore the above estimated NOAEC was used to calculate according to their guidelines ("Guide for the quantification of substance-specific exposure-risk relationships and risk concentrations after exposure to carcinogenic hazardous substances at the workplace", (TRGS 910 Annex 3, 2013)) by employing the MPPD model a HEC-NOAEC of 65 µg $NiSO_4$ * $6H_2O$ /m^3, equivalent to 14.6 µg Ni/m^3. With an estimated reduced variability factor of 3 an analogous to a health based value, OEL of 4.9 µg Ni/m^3 was derived. As the MMAD of the aerosol used in the chronic inhalation studies was about 2 µm, this OEL of **5 ug Ni/m^3** applies to the respirable particle fraction only.

For less-soluble nickel compounds (Ni_3S_2, NiO, NiO_2, Ni_2O_3, NiS) an exposure risk relationship (ERB) was derived for the respirable particle fraction. AGS argued the available epidemiological human data do not allow the derivation of an ERB without doubt as it would not be possible to account for the effects of different nickel species in the data of the Kristiansand cohort. Therefore, the ERB was derived based inhalation studies in rats and mice with less-soluble nickel compounds (NTP 1996 a,b). In these chronic inhalation

studies with nickel oxide and nickel subsulfide a dose-dependent increase in the incidence of lung tumours was observed. From these studies a NOAEC could not be derived for the non-cancerogenous endpoints as even under the lowest dose effects were observed.

In the study with nickel sulphate (NTP 1996c) a NOAEC was derived. Further comparisons of the other above mentioned studies indicate that there is a threshold for the inflammatory reaction. AGS argued that an inflammatory reaction triggered by the intrinsic cytotoxicity of the nickel compounds (oxidative DNA damage, regenerative processes) promote tumour formation. Due to the indirect genotoxic effects of nickel, the fact that oxidative DNA damage leads to an increase in the mutation frequency and no tumours were observed below the cytotoxic region, an ERB was derived with a sublinear function (see figure below). This ERB takes the increase in risk by means of **indirect genotoxicity below the cytotoxic range** into account (flat part of the function), bends at the cytotoxicity threshold, and forms up to a T25 the steep part of the function in which the tumour promoting effect of cytotoxicity has been taken into account. A POD a HEC-hT25 of 491 µg Ni/m³ (for 40 years of working life) was calculated following the guidelines (TRGS 910 Annex 3) based on the calculated T25 in rats after exposure to nickel subsulfide (NTP, 1996b). The chronic nickel oxide rat study (NTP, 1996a) was not used for this calculation because no clear dose-response and not statistical significant effects in tumour development was found.



For the calculation of the T25 only animal data from Ni subsulfid were used, since data with Ni oxide did not result in a clear dose-response-relationship

The calculation was based on a threshold for cytotoxicity in the rat lung converted into the human equivalent concentration (HEC) for poorly soluble nickel compounds of 6 µg Ni / m³. This is equivalent to the HEC-AGW for nickel metal. The stepwise procedure for the calculations is explained in the guidelines (p. 50/51).

Based on the above assessment the following risk values have been calculated for the respirable fraction of less soluble nickel compounds:

Table 39: Derived exposure risk relationship for less soluble nickel compounds

Assumed excess cancer risk in humans at work place	ug Ni / m³
4 : 100 000	0.8
4 : 10 000	6
4 : 1 000	13

There are information that AGS is further in the process of developing inhalable risk values for nickel compounds, since in epidemiological studies, apart from lung tumours, also increased risks of nasal tumours have been found. However, at finalisation of this document AGS did not publish a proposal for inhalable OELs.

Proposed health based OELs

For nickel metal AGS derived a health based threshold of 0.006 mg Ni/m³ for the respirable particle fraction based exclusively on animal data on the assumption that the development of chronic inflammation found in animal studies after exposure to nickel metal and nickel compounds are indicative for a threshold.

For nickel compounds AGS derived an exposure risk relationship (ERB) for the respirable particle fraction based solely on animal data.

The above three approaches are summarised in one table, which depicts for the respirable fraction (taken from TRGS 910, June 2017, https://www.baua.de/DE/Angebote/Rechtstexte-und-Technische-Regeln/Regelwerk/TRGS/pdf/910/910-nickel.pdf?__blob=publicationFile&v=2):

Table 40: German legal entries for nickel and nickel compounds

Substance	Concentration [mg Ni/m³]	Risk
Nickel metal (entry in TRGS 900)	0.006	
Nickel compounds (entry in TRGS 910)	0.013	4 : 1 000
	0.006	4 : 10 000
	0.001	4 : 100 000

The excess risks (based on nickel subsulfide and applied to all nickel compounds) associated with exposure to respirable 1-13 µg Ni/m³ as shown in Table 40, represent a worst-case scenario for all “less soluble and soluble nickel compounds” since nickel subsulfide had 7-fold higher potency to induce tumors in rats than nickel oxide and no lung tumours have been observed in animals at the highest tolerated exposure levels.

Discussion / points of concern

AGS employed the threshold based approach for nickel metal for the respirable particle fraction but developed an exposure risk relationship (ERB) for nickel compounds, also for the respirable particle fraction, only. For both approaches AGS relied solely on animal data, arguing that (for nickel compounds) available epidemiological human data do not allow the derivation. AGS does not give a corresponding justification for the nickel metal OEL.

Additionally, AGS calculated an OEL of 0.005 mg Ni/m³ for the respirable particle fraction of soluble nickel compounds, which can be in practise considered as alomost the same.

There is no specific justification why AGS decided to use two different approaches for nickel metal and nickel compounds, threshold and exposure risk relationship (ERB), respectively. This is specifically surprising since AGS relied for the exposure risk relationship for nickel compounds also on the most sensitive endpoint lung inflammation and used for the calculations the NOAEC of the rat nickel sulfate study. However, AGS calculated additionally a T25 based in rat tumour data taken from the nickel subsulfide study but does not develop this approach further for proposing exposure risk relationships, but identifies in the curve a threshold for lung inflammation, far below the T25 concentration (see figure above).

The NOAEC of the rat nickel sulfate study is also used as POD for the AGS OEL proposal for soluble nickel compounds, whereas for nickel metal extrapolation from the LOAEC of the nickel metal study (Oller, 2008) to a NOAEC (->0.03 mg/m³) was calculated by using

a factor 3. This factor was considered as sufficiently justified by comparing the effects found at LOAEC in the nickel metal study to effects at the LOAEC of the $NiSO_4$ study in the rat (NTP, 1996c), which were considered similar. Furthermore AGS argued that there is a threshold for the inflammatory reaction and that an inflammatory reaction triggered by the intrinsic cytotoxicity of the nickel compounds (oxidative DNA damage, regenerative processes) promote tumour formation. In the assessment report also indirect genotoxic effects of nickel are recognize along with the fact that oxidative DNA damage leads to an increase in the mutation frequency and no tumours were observed below the cytotoxic region.

AGS did not publish an inhalable OEL for nickel and compounds. This may results in insufficient health protection since several epidemiological studies indicate that nose tumours appear in humans after exposure to different nickel compounds. Although effects in the nose of rats and mice are seen after chronic exposure to nickel compounds, nose tumour formation is only reported in humans. It can be argued that rodents are not sensitive for nose tumours. However, animals received under experimental conditions test substance aerosols with a MMAD of about 2 µm which is much lower than the particle sizes workers are exposed to. It might be assumed that the deposition of nickel compounds in the nose of workers is due to higher particle sizes and that tumour development solely found in humans is related to this difference in exposure. This indicates that the animal studies are not suitable for developing the inhalable OEL (protective also for nose tumours) and that more detailed evaluation of the available epidemiological data is needed in order to gain sufficient health protection.

8.2 Exposure Limit Values

8.2.1 Occupational Exposure Limits (OELs)

Different approaches on health based limit value setting for nickel and nickel compounds have been developed.

It is assumed that nickel compounds can produce *in vitro* effects that could contribute to the appearance of respiratory tumours. Generally, there is consensus by different regulatory bodies that nickel and compounds are not directly mutagenic but can cause genotoxicity via indirect genotoxic mode of action such as interference with DNA repair systems and DNA methylation patterns as well as oxidative stress, which lead to clastogenicity and increased genomic instability (SCOEL 2011; EFSA 2015). IARC (2012) stated that based on the update and distribution in cells as described, the ultimate genotoxic agent is nickel (II). However, direct reaction of nickel (II) with DNA does not seem to be relevant under realistic exposure conditions.

Based on the assumption that genotoxicity as well as carcinogenicity of nickel compounds are likely to be due to indirect effects SCOEL and NiPERA developed limit values for the inhalable and respirable fractions of nickel compounds assuming that the inflammatory and possible also the tumorigenic effects found in animals and humans (only tumours seen) are most likely threshold dependent for all nickel compounds including nickel metal. SCOEL and NiPERA relied in their assessment on animal and human data, although to different extent. However, SCOEL used for the respirable OEL calculation a published EHC which had been based on respiratory tract surface area in rats and humans that was later revised (in 2011) and for the inhalable OEL human exposure data which were not converted to most recent sample technic. Both limitations from the SCOEL calculations have been reflected by NiPERA. Additionally, NiPERA used for the inhalable limit value data from an extended human database (13 cohorts), including data for nasal cancer and lung tumours.

In contrast to this the most recent German AGS approach assumed threshold based effects (lung inflammation) for nickel metal and soluble nickel compounds, but developed an exposure risk relationship for the respirable fraction of poorly soluble nickel compounds

based on a non-linear assumption of the dose-response. German model assumes also that there is still a risk for indirect genotoxicity below the levels causing inflammation (cytotoxicity) in lungs. The German approach relied solely on animal data and indicated that the available epidemiological human data do not allow the [limit value] derivation. The POD for OEL for nickel metal setting was the LOAEC from which AGS extrapolated to a NOAEC by applying an assessment factor (AF) 3. This proposed AF 3 based on comparison to a chronic rat study with nickel sulfate in which the LOAEC was identified at a 3x higher dose level than the NOAEC with comparable inflammatory effects in the respirable tract. In the German assessment limit values only for the respirable aerosols factions have been developed stating that there are no robust data for a quantitative assessment of the inhalable fraction available.

The lack of an inhalable limit value may results in insufficient health protection since several epidemiological studies indicate that nose tumours appear in humans after exposure to different nickel compounds.

The available toxicity information indicates that the key events of nickel metal and nickel compounds toxicity (inflammatory effects and tumour development) in the respiratory tract (lung and nose) might be threshold dependent. Nickel compounds are not directly mutagenic and also, there is evidence showing that mechanisms, for which a threshold can be assumed play a major role in the nickel caused genotoxicity (see Section 7.9 Mode of Action). One of the major mechanisms resulting in DNA damage caused by nickel compounds is the generation of reactive oxygen species (ROS). These can be generated by the reaction of Ni^{2+} with H_2O_2 resulting in or caused by inflammation. The mechanisms are likely to show a threshold; the first one is dependent on the antioxidative capacity present in the cells and the second one is dependent on the induction of inflammation. *In vivo*, the inflammatory mechanism for oxidative effects and DNA damage seems to be critical as suggested by the studies by Kawanishi et al. (2002) and Efremenko et al. (2014, 2017).

The particle size of nickel compounds determines the deposition fraction in the respiratory tract of rats and humans. The particle sizes of the aerosols used in the animal inhalation bioassays were small, with most measures near a mass median aerodynamic diameter (MMAD) of 2 µm. The human deposition characteristics of aerosols indicate that all of these particles would be of respirable size in humans (Oller and Oberdorster, 2010). Nickel containing aerosols with larger particles (e.g., >20 µm MMAD), such as those in workplaces, contain a relatively smaller proportion of respirable-size nickel. Human occupational exposure concentrations were often much higher than those tested in the inhalation bioassays, but resulted in equivalent exposures to respirable-size nickel as in the animal bioassays (i.e., resulted in the same deposited dose in the pulmonary region per unit of surface area) (Goodman et al 2011). Therefore, two different mode-of-action based exposure limits, for the inhalable and the respirable fraction, respectively are proposed in order to give sufficient worker protection.

Respirable fraction

A practical approach is proposed for OEL setting for nickel metal and all nickel compounds based on the most sensitive endpoint in animal data which is inflammatory reactions in the lungs. In the inhalation toxicity study in rats with nickel sulfate a NOAEC of 0.027 (≈0.03) mg Ni/m^3 for inflammatory effects were observed. However, for less soluble nickel subsulfide and nickel oxide, a LOAEC of 0.11 and 0.05 mg Ni/m^3, respectively, were identified for inflammatory effects and lung fibrosis and, for nickel subsulfide for tumor formation in NTP (1996) studies, but no NOAEC. Also for metallic nickel a LOAEC of 0.1 mg Ni/m^3 for inflammation in the lung was observed (Oller et al 2008).Inflammatory effects in the respiratory tract are not seen in humans. Therefore the PODs (Points of Departure) are the NAEC-HECs (No Adverse Effect Concentration –Human Equivalent Concentration) for soluble and poorly soluble nickel compounds as well as for nickel metal, as calculated by NiPERA (2017). This approach is based on multiple path particle deposition model (MPPD, Asgharian et al, 1999), which was used to predict the deposition of particles

in the alveolar and trachea-bronchial region. MPPD model is a model validated for human and rat lung deposition and clearance of spherical particles. It takes into account particle characteristics, breathing frequency and pattern, exposure concentration and duration and predicts total, regional and airway specific lung doses. This 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, also retained doses were calculated on the basis of retention T½ for nickel particles with different solubility in animal studies.

Predicted deposited doses for rats and humans and measured (rats) or calculated (humans) retained doses are presented in the following table (Table 41). For the calculation of HECs retained doses are used, since it is considered that retained dose is more relevant for chronic lung toxicity. In addition, the use of retained doses seem to result in more conservative HECs in the case of nickel subsulfide and oxide than the use of deposited doses.

Table 41: Deposited and retained doses used in human equivalent concentration calculation

Substance	Animal data					Human data				
	Particle Size	Exposure level (mg Ni/m³)[a]	Rat Daily Deposited Dose (ng Ni/cm²)[b]	Rat Total Retention T1/2 (days)[c]	Calculated Rat Retained dose 2 y (ng Ni/cm²)[d]	Human Daily Deposited Dose (ng Ni/cm²)[b]	Human Total Retention T1/2 (days)[c]	Calculated Human Retained Dose at 40 y (ng Ni/cm²)[d]	Ratio of Retained Doses (rat/human)[e]	Respirable HEC to N(L)OAEC or NAEC Based on Long-term Retained Dose (mg Ni/m³)
Nickel Sulphate										
NOAEC	MMAD=2.5 GSD=2.38	0.03	0.033	4.2	0.140	0.035	4.5	0.151	0.93	**0.03**
Nickel Subsulphide										
LOAEC	MMAD=2.17 GSD=2.34	0.11	0.154	28	4.434	0.157	43	6.39	0.693	0.08
Calculated NAEC		0.04								**0.03**
Nickel Oxide										
LOAEC	MMAD=2.21 GSD=1.97	0.5	0.653	116	76.81	0.775	700	514.3	0.149	0.08
				500	213.5		5000	3188.2	0.067	0.03
Calculated NAEC		0.17		116			700			**0.03[f]**
Metallic Nickel										
LOAEC	MMAD=1.8 GSD=2.4	0.1	0.175	39	5.62[g]	0.166	78	12.26	0.458	0.05
Calculated NAEC		0.03								**0.02**

a. An assessment factor of 3 was applied to convert LOAEC to NAEC, where relevant
b. Deposited dose calculated using the MPPD model
c. Retention T1/2 data based on experimental data in rats
d. Calculated long-term retained dose; for the calculation it was assumed that clearance by dissolution is the same in animals and humans and mechanical clearance half-time was assumed to be 70 d in rats and 700 days in humans based on existing general data on mechanical particle clearance.
e. For nickel oxide, 2 ratios were calculated based on different combinations of clearance rates (days) for rats and humans
f. The HEC to the NAEC for Ni oxide was calculated using the combination of retention T1/2s of 116 days for rats and 700 days for humans as this is considered to be the more relevant combination for non toxic exposure levels
g. Thirty months (2.5 years) observation period

An assessment factor (AF) of 3 is applied for the LOAECs of 0.11, 0.05 and 0.1 mg Ni/m³ for nickel subsulfide nickel oxide and nickel metal, respectively, and HECs are calculated for soluble and poorly soluble nickel compounds resulting in a HEC of ca 0.03 mg Ni/m³ for respirable particles.

Table 42: Limit values for respirable fraction of different nickel species

	Respirable acceptable exposure limits (mg Ni/m³) based on inflammatory effects			
	Ni metal	**Ni oxide**	**Ni subsulfide[a]**	**Ni sulfate**
Calculated NAEC-HEC[b]	**0.02**	**0.03**	**0.03**	**0.03**
Respirable acceptable exposure limits (accounting for intraworker differences by applying AF 3 and AF 2 for the severity of toxic endpoint)	**0.004**	**0.006**	**0.006**	**0.006**

[a] Rats exposed to nickel subsulfide show at LOAEC lung inflammation and tumours

The HEC calculations already take possible differences in toxicokinetics into account and an additional AF for toxicokinetic differences is therefore not considered. Regarding AF for toxicodynamic part of interspecies extrapolation, rat is generally the most sensitive species for the local lung effects of particulates (Oberdoerster 1995, Mauderly 1997), which is supported by the difference seen in long term inhalation effects of nickel 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 effects of nickel lung toxicity and carcinogenicity. 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). Semi-quantitative comparisons between the exposures resulting in increased cancer indicence in humans and rats does not show that humans are more sensitive to carcinogenic effects of nickel compounds either (see further chapter "Sensitivity analysis of the OEL approach used for respriratory fraction). Therefore, it can be concluded that AF of 1 for interspecies toxicodynamic differences is sufficient.

Chapter R8 of the ECHA Guidance on IR &CSA (2008)[12] provides guidance on default assessment factors (AF). Default factor for intra-worker variation is 5. However, in the case of nickel compounds human data is used as a supporting data for the setting an OEL. This human database includes 13 cohorts and up to 100000 workers. Therefore, factor of 3 is considered sufficient to cover possible inter-worker variability. It should be noted that human epidemiological studies report exposure as inhalable exposure to soluble Ni. Convertion of this to respirable exposure includes some uncertainties, which are also considered to be covered by this AF of 3. In addition, additional AF of 2 for the severity of the toxic endpoint (cancer) is applied. This results in the value of 0.005 mg Ni/m³ for nickel compounds.

For metallic nickel there is no need for additional AF of 2 for the severity of the toxic endpoint and therefore only an assessment factor of 3 is applied for calculated HEC of 0.02 mg/m³. This results in an OEL of 0.0067 mg/m³. This is rounded down to 0.005 mg/m³ and the value of **0.005 mg Ni/m³ is recommended by the dossier submitter ECHA as an OEL for the respirable fraction of both nickel metal and nickel compounds**. The choice of 0.005 mg Ni/m³ instead of 0.0067 mg/m³ for metallic nickel is also in accordance with the general practise of OEL setting which usually uses the decimals of the integers 1, 2 or 5 ppm or mg/m³, if scientific reasons do not suggest a more specific value (further see SCOEL key documentation from 2013). This avoids giving wrong impression

12 https://echa.europa.eu/documents/10162/13632/information_requirements_r8_en.pdf/e153243a-03f0-44c5-8808-88af66223258

on the preciseness in cases in which uncertainties related to the limitations of the database do not justify such a precision.

Although nickel compounds are considered to have a practical threshold for its carcinogenicity, it should be noted that the residual cancer risk cannot to be totally excluded at the exposure levels below the proposed occupational exposure level of 0.005 mg Ni/m^3.

Inhalable fraction

Since nickel compounds have shown to increase also the risk of sinonasal cancer in humans, an OEL for inhalable fraction is considered appropriate. Anttila (1998) found in Finnish workers exposed to concentrations of ca. 0.25 mg/m^3 soluble nickel sulphate an excess of bronchial cancer and two cancers of the sinuses in the nasal cavity. However, the low observed absolute numbers of cases make nasal cancer less amenable to quantitative dose response assessment. Comparing the overall lung and nasal cancer incidence/mortality in the available cohort studies (see Tables 44 and 45) indicates that there is no cohort were the risk of nasal cancer would be statistically significantly increased if the risk of lung cancer was also not statistically significantly increased. Consequently the quantitative dose-response for lung cancer can be used as a surrogate. In epidemiological data from Norwegian refinery workers (Kristiansand cohort) a significant increase in lung cancer incidence for water soluble nickel is observed at a cumulative exposure of 1.6 mg/m^3 x years. Since the average exposure of the cohort was 13 years, this corresponds an average exposure to 0.123 mg Ni/m^3 (Grimsrud et al., 2002; 2003). 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. A standard AF 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 sampler efficiency is applied (all personal measurements in the Kristiansand cohort were peformed with the 37 mm filter cassette) this results in the lowest inhalable exposure 0.027 mg/m^3.

However, it is to be noted that exposure in Kristiansand was to several nickel species and the above cumulative risk estimate of 1.6 mg/m^3 x years for soluble nickel was not adjusted for the effect of other nickel species. The final model indicated that in addition to the dose-dependent risk (for soluble nickel) there was an additional dichotomous risk component (exposure yes/no, OR=1.5) which the authors suggested representing exposure to other nickel species that was correlated to exposure to soluble nickel (See chapter 7.7.1). This means that the exposure to total nickel resulting in the statistically significantly increased risk was higher than 1.6 mg/m^3 x years. Consequently, the calculated 0.027 mg/m^3 is a conservative estimate. According to the tabular data of Grimsrud et al (2002 and 2003) the fraction of soluble nickel of total nickel was about 10% in crushing/grinding, old smelter building, calcining smelting department and roasting, about 50% in copper leaching and copper cementing and 80-90% in copper electrolysis, electrolyte purification and nickel electrolysis. A simple arithmetic average of those data for these 9 departments allows rough estimation of the levels of insoluble (sulfidic + oxidic, excluding metallic) nickel in comparison to soluble nickel in the cohort: airborne concentration of insoluble nickel would have been on the average 3.5 times that of soluble nickel and Total nickel thus 4.5 times that of soluble nickel. As there is indication from animal and human data that the sulfidic and oxidic nickel species increase the risk of cancer, the effect from them should not be ignored. Unfortunately there is no risk estimate available combining the effect of all relevant nickel species.

The starting point represents the lowest estimate for an increased nasal cancer risk and it is derived from the epidemiological data from a large worker cohort (5 300 workers) as conservatively selected from various cohorts including altogether around 100 000 workers, and it is therefore considered to adequately address the variability among workers. Thus, no additional AF for interindividual variation is considered to be required. As the value of 0.027 mg/m^3 is based on conservative assumptions it can be rounded to 0.03 mg/m^3. In this regards it is noted that this rounding by 10% would assume water soluble nickel

having accounted for about 90% of total nickel. As explained in the previous paragraph, water soluble nickel usually accounted for much less of the total nickel in the various departments of this refinery. Thus, **the value of 0.03 mg/m³ is proposed by the dossier submitter ECHA as an OEL for inhalable fraction.**

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

EFSA CONTAM panel derived a TDI of 2.8 µg Ni/kg bw/d for general population (lifelong exposure 7days/week). If this is converted as occupational inhalation exposure occurring 5 days per week, it corresponds an air level of 27 µg Ni/m³ (0.027 mg Ni/m³) as 8 h TWA. Therefore, it is assumed that the proposed OELs are likely to protect also from reproductive effects.

Sensitivity analysis of the OEL approach used for respiratory fraction

As described in the previous chapter a statistically significant increase in the risk of lung cancer (OR = 2.5) was observed at cumulative dose of 1.6 mg/m³ soluble nickel in the Kristiansand cohort (Grimsrud et al 2002). Based on the correction factor of 2 for the 37 mm sampler efficiency, average duration of exposure of 13 years in the cohort, assuming respirable fraction being 10-20% of inhalable and the above estimate that total nickel concentration was 4.5 times that of soluble nickel results in this increased risk being linked to a respirable concentration of Total nickel of 0.11-0.22 mg/m³ (= 1.6*2*4.5*(0.1 or 0.2)/13). As explained above for the inhalable fraction it should be noted that the Grimsrud et al (2002) analysis identifed at zero soluble nickel levels an OR of 1.5, which was likely due to exposure to other nickel species not further quantified in that analysis.

Applying similar estimations of respirable fraction concentrations of total nickel based on effect levels identified by Oller et al (2014) (> 0.1 mg/m³ for soluble nickel, > 0.2 mg/m³ for sulfidic Ni, > 2.0 mg/m³ for oxidic Ni) or ICNCM (1990) (> 1.0 mg/m³ for soluble nickel, > 10 mg/m³ for insoluble nickel) would result in clearly higher estimates. Consequently, the Grimsrud et al. (2002) based calculations above would represent a conservative approach.

In animal experiments the exposure was not to mixture of nickel species. A carcinogenic effect was observed at dose 0.11 mg/m³ of nickel in a carcinogenicity assay with nickel subsulfide of respirable particle size. There were 12 lung tumours in 106 animals in that dose and 2 lung tumours in 106 control animals corresponding to a 6-fold relative risk. By linear extrapolation a risk of 2.5 (i.e. the risk that was observed in humans above) would have been observed at a dose of 0.046 mg/m³ of nickel (0.11*2.5/6). Comparison of this dose to the estimated respirable fraction dose levels above calculated for the human data from Grimsrud et al (2002), Oller et al (2014) or ICNCM (1990) seem to indicate that humans are not more sensitive than rats to lung carcinogenic effects of nickel compounds.

There is no clear human evidence for lung fibrosis induced by nickel compounds based on mortality and chest X-ray studies in workers with high exposure (see Ch 7.3.1) while increased risks of lung cancer have been observed in numerous cohorts with similar exposure. In animals lung inflammation seems to occur at doses lower than those inducing lung tumours. This seems to indicate that humans are not more sensitive than rats for non-malignant pulmonary toxicity.

The above considerations represent a semi-quantitative assessment relying on several assumptions and can therefore not serve as calculations quantitatively demonstrating a difference between rats and humans. However they provide support for applying an AF of 1 for toxicondynamic difference (humans seem not to be more sensitive than rats). They also provide support for reducing the default AF of 5 for intraspecies difference with the

argument that the same extensive data set was considered as for inhalable fraction, however, without having direct measured data regarding respirable fraction.

8.2.2 Short Term Exposure Limits (STELs)

SCOEL (2011) did not propose a STEL for nickel metal and inorganic nickel compounds.

For nickel metal and inorganic nickel compounds there are not toxicological effects known which could pose risk to worker after short term exposure. This group of substances is neither know to be acutely toxic nor irritating. **Therefore a STEL is not proposed by the dossier submitter ECHA**.

However, the organic nickel compound nickel carbonyl is known to be the most toxic of all nickel compounds. It has been estimated to be lethal in man at atmospheric exposures of 30 ppm for 20 min (Doull, J et al, 1980). Nickel carbonyl appears to be exceptionally toxic by inhalation as evidenced by a number of human poisoning accidents (NiPERA, 1996). Due to this several EU member states have derived a short term exposure level (STEL), see Table 6 in section 4 with limits ranging from 0.05 mg/m^3 to 0.24 mg/m^3 as nickel. However, nickel as carbonyl has the oxidation state Ni^0 and is unlikely to express carcinogenic potential. Due to the high toxicity it is not relevant for long term exposure and not within the scope of the COM request of OEL setting.

8.2.3 Biological Limit Value (BLV)

The use of a biological limit value for nickel in urine may not be feasible when setting an OEL around 10 µg/m^3 or lower as the levels in urine from workers may not be significantly different from those of the general population (see section 6.2.1). **Therefore a BLV is not proposed by the dossier submitter ECHA.**

8.2.4 Biological Guidance Value (BGV)

Due to the high variability between populations of the levels of nickel in urine, it is proposed not to set a biological guidance value (see section 6.2.2). **Therefore a BGV is not proposed by the dossier submitter ECHA.**

8.3 Notation

Nickel and its compounds are well documented skin sensitisers and many are also respiratory sensitisers. Nickel and its compounds are all classified as skin sensitisers therefore the dossier submitter ECHA proposes that a “sensitisation notation” is warranted. See section 7.5 for full details.

The available data indicate that absorption of nickel following dermal contact to various nickel compounds is low and to a limited extent with a large part of the applied dose remaining on the skin surface or in the stratum corneum. Therefore, the proposal from the dossier submitter ECHA is that nickel and its compounds do not warrant a skin notation.

There are no available human or animal data that indicate auditory effects and therefore the proposal of the dossier submitted ECHA is that nickel and its compounds do not warrant a noise notation.

9. Groups at Extra Risk

A susceptible population will exhibit a different or enhanced response to nickel than will most persons exposed to the same level of nickel in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). Both for smokers and non-smokers not-occupationally exposed to nickel, exposure by inhalation may be expected in general to represent a negligible or minor addition to the daily exposure via the diet.

Individuals sensitized to nickel may be unusually susceptible (to allergic symptoms) because exposure to nickel by any route may trigger an allergic response. It has been reported (ATSDR 2005, EFSA 2015) that individuals sensitised to nickel through dermal contact and who have allergic contact dermatitis (estimated prevalence in the general population to be up to 15 %, but frequently remaining undiagnosed), may be unusually susceptible because exposure to nickel by any route may trigger an allergic response. Epidemiology studies indicate that African-Americans have a higher nickel sensitivity than Caucasians and that women of both racial groups have higher reaction rates than men (Nethercott and Holness 1990; North American Contact Dermatitis Group 1973; Prystowsky et al. 1979). The incidence of reactions may be higher in women because they generally wear more metal jewelry than men. Further studies are required to determine if there are true gender and racial differences in nickel sensitivity, or if it is indeed a difference in exposure.

A relationship between HLA (human leucocyte antigen) and nickel sensitivity was observed in individuals who had a contact allergy and positive results in a patch test for nickel (Mozzanica et al. 1990). The nickel-sensitive group had a significant elevation in HLA-DRw6 antigen, compared to controls with no history of atopy or contact dermatitis. The relative risk for individuals with DRw6 to develop a sensitivity to nickel was approximately 3.3. The presence of DRw6 may be monitored to determine the potential risk of individuals to become sensitized to nickel.

Other populations with potentially high exposure (and therefore potentially higher risk) include patients who have nickel containing joint prostheses, sutures, clips, and screws for fractured bones either from corrosion of these implants leading to elevated nickel levels in the surrounding tissue and to the release of nickel into extracellular fluid (IARC 1990; Ries et al. 2003; Sunderman 1989a; Sunderman et al. 1986, Sunderman et al. 1989c) or short-term elevations in nickel concentrations measured in blood and urine, seen in patients receiving knee and hip protheses within 1–2 days of implant (Sunderman et al. 1989c).

It is reported (ATSDR 2005) that for people in the US who live near or work at facilities that produce stainless steel and other nickel-containing alloys, oil-fired or coal-fired power plants, refuse incinerators, or waste sites for nickel using and producing industries .These people have a greater potential to be exposed to levels of nickel in airborne dust, soil, and vegetation that are greater than those for the general population by virtue of their proximity to these sites.

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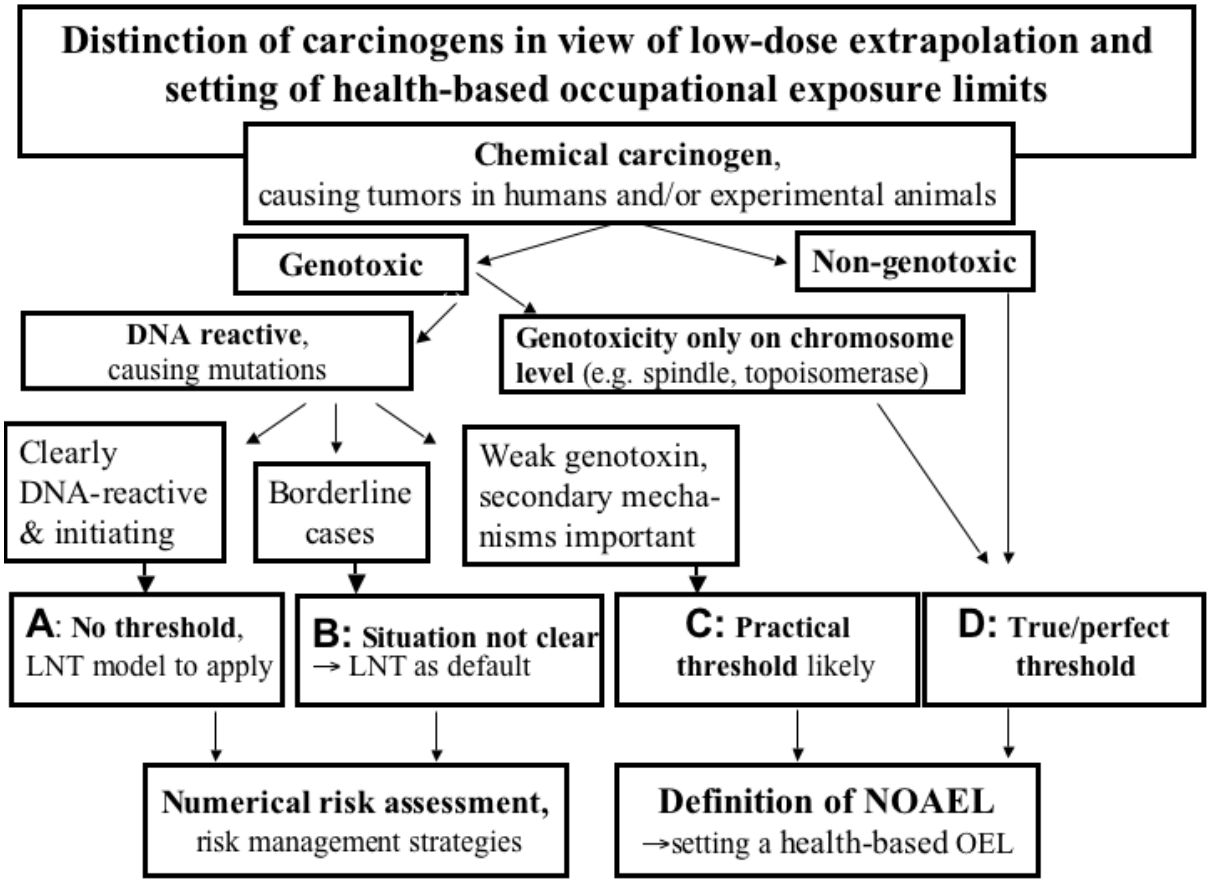
Appendix 1. SCOEL categorisation of carcinogens

Taken from current SCOEL 'Methodology for the Derivation of Occupational Exposure Limits' (SCOEL, 2013; version 7[13]),



Group A: Non-threshold genotoxic carcinogens; for risk low-dose assessment the linear non-threshold (LNT) model appears appropriate.

Group B: Genotoxic carcinogens, for which the existence of a threshold cannot be sufficiently supported at present. In these cases the LNT model may be used as a default assumption, based on the scientific uncertainty.

Group C: Genotoxic carcinogens for which a practical threshold is supported.

Group D: Non-genotoxic carcinogens and non-DNA reactive carcinogens; for these compounds a true ("perfect") threshold is associated with a clearly founded NOAEL.

[13] Available on Commission webpage on SCOEL [http://ec.europa.eu/social/main.jsp?catId=148&intPageId=684&langId=en]

Appendix 2. Tabulated Summaries for Substance identification and Physico-chemical properties of nickel compounds

Table 43: Substance identification for nickel compounds

Inorganic nickel compounds

	Substance	CAS No	EC/list No. [14]	Description	Molecular formula
UVCB	Slags, ferronickel-manufg.	69012-29-9	273-729-7	By-product from the production of ferronickel from a complex ore. Consists primarily of oxides of aluminum, iron, magnesium and silicon.	
	Matte, nickel	69012-50-6	273-749-6	Product of blowing smelted nickel ore in a converter to lower the iron content.	
	Speiss, lead, nickel-contg.	98246-91-4	308-765-5	Product obtained and separated during the melting of nickel and other non-ferrous metals containing raw materials. Consists primarily of antimonides and arsenides of copper and nickel.	
	2-Butenedioic acid (2Z)-, reaction products with ammonium di-µ3-hydroxyhexacosa-µ-oxododecaoxododecatungstate(6-) (6:1), ammonium octa-µ-oxodi-µ3-oxo-µ4-oxododecaoxoheptamolybdate(6-) (6:1), nickel(2+) nitrate (1:2) and nickel(2+) sulphate (1:1)	1351378-24-9	800-777-3	Mixed metal oxides produced by thermal decomposition	(Ni)z(Mo)x(W)yO (13 – 20)x
	Reaction product of soluble nickel salt, cobalt salt, manganese salt with alkalines	-	931-895-4	a mixture of different grades and types of nickel, cobalt, manganese hydroxides and oxides	

[14] Number starting with the digits 2 or 3 are listed on **EINECS** (European INventory of Existing Commercial chemical Substances) as published in O.J. C 146A, 15.6.1990.

Numbers starting with the digit 4 are listed on **ELINCS** (European LIst of Notified Chemical Substances) in support of Directive 92/32/EEC, the 7th amendment to Directive 67/548/EEC.

Numbers starting with the digits 6,7,8,9 are assigned by ECHA and have no legal status.

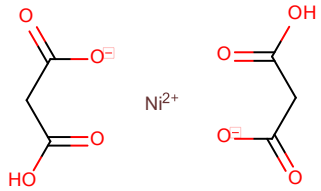
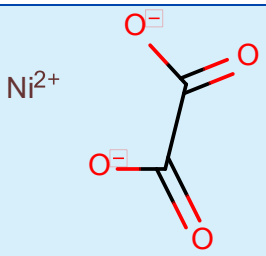
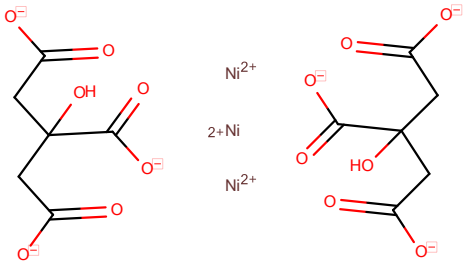
	Substance	CAS No	EC / list No. [14]	Description	Molecular formula
	Residues, copper-iron-lead-nickel matte, sulfuric acid-insol.	102110-49-6	310-050-8		
Oxide	Nickel iron chromite black spinel	71631-15-7	275-738-1	This substance is identified in the Colour Index by Colour Index Constitution Number, C.I. 77504.	(Ni,Fe)(Fe,Cr)2O4
	Antimony nickel titanium oxide yellow	8007-18-9	232-353-3	This substance is identified in the Colour Index by Colour Index Constitution Number, C.I. 77788.	(Ti, Sb, Ni) O2
	Nickel tungsten tetraoxide	14177-51-6	238-032-4		NiWO4
	Molybdenum nickel tetraoxide	14177-55-0	238-034-5		NiMoO4
	cobalt lithium nickel oxide	-	442-750-5		
	Reaction mass of aluminium fluoride and aluminium oxide and chromium (III) oxide and nickel dichloride	-	909-803-9		AlF3.Al2O3.Cr2O3.NiCl2
	Reaction mass of nickel monoxide and silicon dioxide	-	910-417-8		NiO.SiO2
	Lithium Nickel Cobalt Aluminium Oxide	-	700-042-6		AlCoLiNiO4
	Reaction mass of diiron trioxide and divanadium pentaoxide and nickel monoxide	-	909-880-9		Fe2NiO9V2
	cobalt lithium manganese nickel oxide	-	480-390-0		CoLiMnNiO2
	Dialuminium nickel tetraoxide	12004-35-2	234-454-8		Al2O3.NiO
	Nickel monoxide	1313-99-1	215-215-7		NiO
hydroxide	Pentanickel octahydroxide carbonate	-	941-652-4		NiCO3.(Ni(OH)2)4

	Substance	CAS No	EC / list No. [14]	Description	Molecular formula
	Nickel hydroxide oxide (Ni (OH) O (1:1:1))	55070-72-9[15]	700-710-7		NiO(OH)
	[carbonato(2-)]tetrahydroxytrinickel	12607-70-4	235-715-9		NiCO3.(Ni(OH)2)2
	Nickel dihydroxide	12054-48-7	235-008-5		Ni(OH)2
sulfide	Reaction mass of cobalt sulphide and nickel sulphide and trinickel disulphide	-	910-663-6		CoS.Ni3S2.NiS
	Trinickel disulphide	12035-72-2	234-829-6		Ni3S2
	Nickel sulphide	16812-54-7	240-841-2		NiS
halogenide	Nickel difluoride	10028-18-9	233-071-3		NiF2
	Reaction mass of aluminium fluoride and chromium trifluoride and nickel difluoride	-	914-309-1		AlCrF8Ni
	Nickel dichloride	7718-54-9	231-743-0		NiCl2
	Reaction mass of aluminium fluoride and aluminium oxide and chromium (III) oxide and nickel dichloride	-	909-803-9		Al3Cl2Cr2F3NiO6
misc	Nickel bis(dihydrogen phosphate)	18718-11-1	242-522-3		Ni(H2PO3)2
	Nickel bis(sulphamidate)	13770-89-3	237-396-1		Ni(SO3NH2)2
	Nickel sulphate	7786-81-4	232-104-9		NiSO4
	Nickel dinitrate	13138-45-9	236-068-5		Ni(NO3)2

[15] The CAS number is for a related substance with unspecified ratio.

	Substance	CAS No	EC/list No. [14]	Description	Molecular formula
metallic	Aluminium, compound with nickel (1:1)	12003-78-0	234-439-6		AlNi

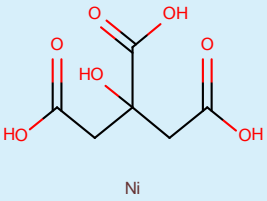
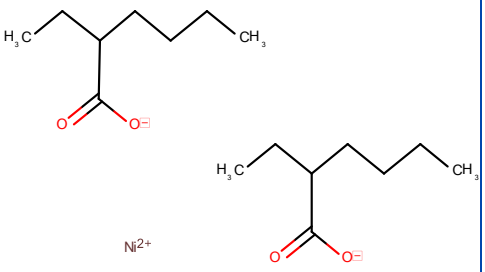
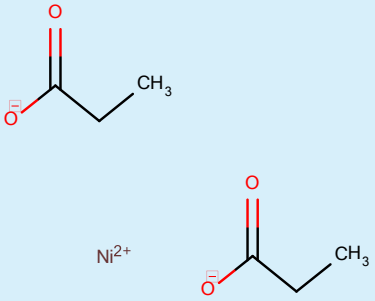
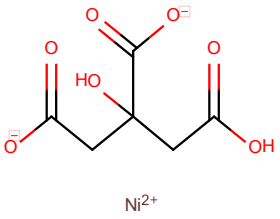
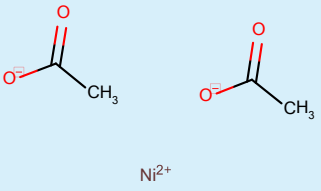
Organic nickel compounds

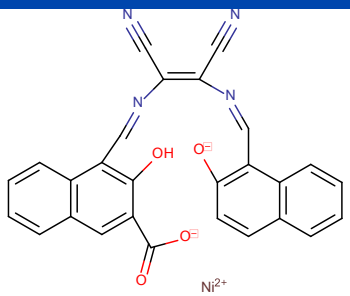
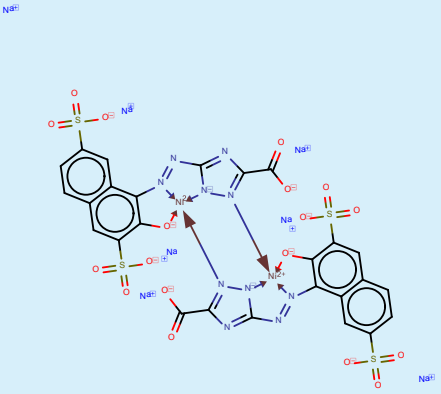
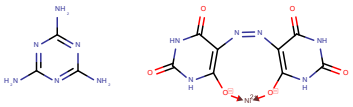
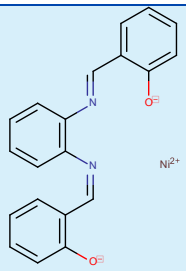
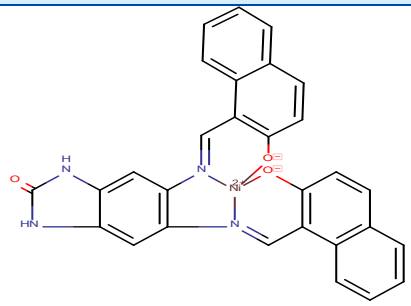
	Substance	CAS No.	EINECS/ EC-list No.[16]	Molecular formula
carboxylate	nickel(2+) bis(2-carboxyacetate)	936644-67-6	931-258-0	
	Nickel oxalate	547-67-1	208-933-7	
	Trinickel dicitrate	6018-92-4	227-873-2	

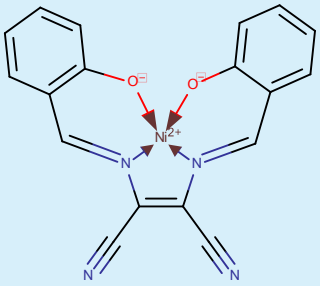
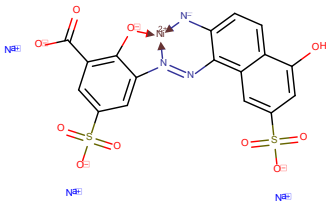
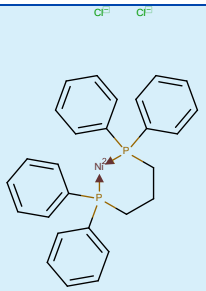
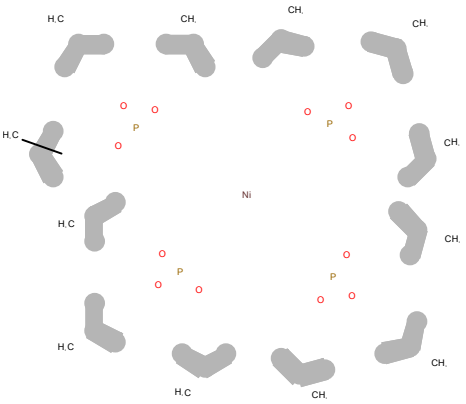
[16] Number starting with the digits 2 or 3 are listed on **EINECS** (European INventory of Existing Commercial chemical Substances) as published in O.J. C 146A, 15.6.1990.

Numbers starting with the digit 4 are listed on **ELINCS** (European LIst of Notified Chemical Substances) in support of Directive 92/32/EEC, the 7th amendment to Directive 67/548/EEC.

Numbers starting with the digits 6,7,8,9 are assigned by ECHA and have no legal status.

	Substance	CAS No.	EINECS / EC-list No.[16]	Molecular formula
	Nickel(2+) hydrogen citrate	18721-51-2	242-533-3	
	Nickel bis(2-ethylhexanoate)	4454-16-4	224-699-9	
	Nickel(2+) propionate	3349-08-4	222-102-6	
	Citric acid, nickel salt	22605-92-1	245-119-0	 Unspecified ratio
	Nickel di(acetate)	373-02-4	206-761-7	

	Substance	CAS No.	EINECS / EC-list No.[16]	Molecular formula
Aromatic alcohol	(3-carboxy-1,1'-(1,2-dicyanovinylenebis(nitrilomethylidyne)-2,2'-dinaphtholato)nickel (II)	205057-15-4	403-550-3	
	sodium μ-[5-{[7-(hydroxy-1κO)-2,6-disulfo-1-naphthyl]diazenyl-1κN}-1H-1,2,4-triazole-3-carboxylato(2-)-1κN$^{1'}$:2κN$^{2'}$]-μ-[5-{[7-(hydroxy-2κO)-2,6-disulfo-1-naphthyl]diazenyl-2κN}-1H-1,2,4-triazole-3-carboxylato(3-)-1κN$^{2'}$:2κN$^{1'}$]dinickelate(1-)	738587-10-5	443-510-2	
	{5,5'-[(E)-diazenediyl]bis[6-(hydroxy-kO)pyrimidine-2,4(1H,3H)-dionato](2-)}nickel compound with melamine		939-379-0	
	[2,2'-[1,2-phenylenebis(nitrilomethylidyne)]-bis(phenolato)]-N,N',O,O'-nickel(II)	-	400-870-5	
	[1,3-dihydro-5,6-bis[[(2-hydroxy-1-naphthyl)methylene]amino]-2H-benzimidazol-2-onato(2-)-N5,N6,O5,O6]nickel	42844-93-9	255-965-2	

	Substance	CAS No.	EINECS / EC-list No.[16]	Molecular formula
	[2,3'-bis[[(2-hydroxyphenyl)methylene]amino]but-2-enedinitrilato(2-)-N2,N3,O2,O3]nickel	64696-98-6	265-022-7	
	Trisodium (1-(3-carboxylato-2-oxido-5-sulfonatophenylazo)-5-hydroxy-7-sulfonatonaphthalen-2-amido)nickel(II)	480445-87-2	407-110-1	
phosphorous	Bis-DPP Nickel(II)chloride	55659-60-4	467-300-5	
	Tetrakis(tritolyl phosphite)nickel[17]	35884-66-3	252-777-2	

[17] This substance is used only as in-situ produced intermediate and has therefore not been considered further in this proposal.

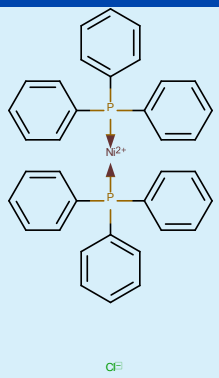
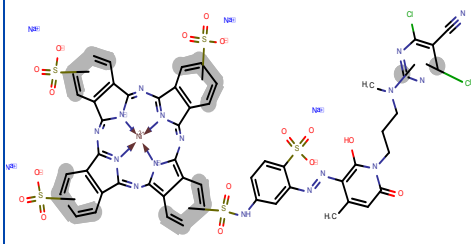
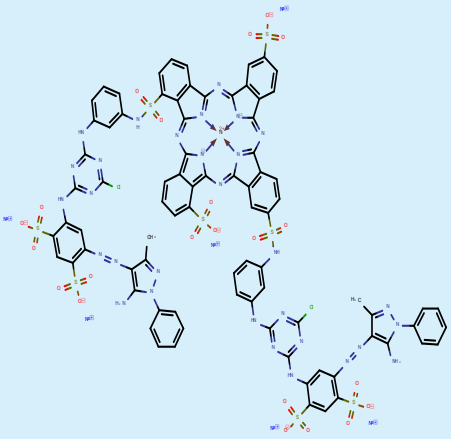
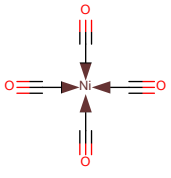
	Substance	CAS No.	EINECS / EC-list No.[16]	Molecular formula
	bis(triphenylphosphine)nickel(II) chloride	14264-16-5	238-154-8	
phthalocyanate	Tetrasodium (c-(3-(1-(3-(e-6-dichloro-5-cyanopyrimidin-f-yl(methyl)amino)propyl)-1,6-dihydro-2-hydroxy-4-methyl-6-oxo-3-pyridylazo)-4-sulfonatophenylsulfamoyl)phthalocyanine-a,b,d-trisulfonato(6-))nickelato II, where a is 1 or 2 or 3 or 4,b is 8 or 9 or 10 or 11,c is 15 or 16 or 17 or 18, d is 22 or 23 or 24 or 25 and where e and f together are 2 and 4 or 4and 2 respectively	148732-74-5	410-160-7	
	hexasodium (di-[N-(3-(4-[5-(5-amino-3-methyl-1-phenylpyrazol-4-yl-azo)-2,4-disulfo-anilino]-6-chloro-1,3,5-triazin-2-ylamino)phenyl)-sulfamoyl](di-sulfo)-phthalocyaninato)nickel	151436-99-6	417-250-5	
	Nickel tetracarbonyl	13463-39-3	236-669-2	

Table 44: Physical and chemical properties for nickel compounds

Inorganic nickel compounds[18]

	Substance name	EC / list number	Physical state	Density [g/cm³ at 20°C]	Melting point [°C]	Water Solubility	additional data
UVCB	Slags, ferronickel-manufg.	273-729-7	solid granules	1.5-2 (bulk) 2-5	> 600.0	Ph: 11.61, $1 \cdot 10^{-6}$ g Ni/L Ph: 8.93, $58 \cdot 10^{-3}$ g Ni/L	
	Matte, nickel	273-749-6	solid granules	5.64 (high copper) 7.2 (metallic) 6.02 (low copper)	> 360	Ph: 7.1, $1.1 \cdot 10^{-3}$ g total metal /L (metallic) Ph: 6.5, $6.4 \cdot 10^{-4}$ g total metal /L (high copper) Ph: 6.5, $33 \cdot 10^{-3}$ g total metal/L (low copper)	
	Speiss, lead, nickel-contg.	308-765-5	solid granules	7.75	700	$5.0 \cdot 10^{-4}$ g Ni /L	
	2-Butenedioic acid (2Z)-, reaction products with ammonium di-µ3-hydroxyhexacosa-µ-oxododecaoxododecatungstate(6-) (6:1), ammonium octa-µ-oxodi-µ3-oxo-µ4-oxododecaoxoheptamolybdate(6-) (6:1), nickel(2+) nitrate (1:2) and nickel(2+) sulphate (1:1)	800-777-3	solid grained	3.43	> 1100.0	7.15-38.62 g Ni /L	
	Reaction product of soluble nickel salt, cobalt salt, manganese salt with alkalines	931-895-4	solid powder	2	234 - 355 (decomp)		

[18] All values are taken from the corresponding registration dossier(s) published on https://echa.europa.eu/information-on-chemicals/registered-substances unless otherwise indicated.

	Substance name	EC / list number	Physical state	Density [g/cm³ at 20°C]	Melting point [°C]	Water Solubility	additional data
	Residues, copper-iron-lead-nickel matte, sulfuric acid-insol.	310-050-8					
Oxide	Nickel iron chromite black spinel	275-738-1	solid black powder	5.16	> 1000.0	$3.5 \cdot 10^{-6}$ g Ni/L	
	Antimony nickel titanium oxide yellow	232-353-3	solid powder	4-5	> 2000.0	Ph: 7.0 , < $0.1 \cdot 10^{-3}$ g/L	
	Nickel tungsten tetraoxide	238-032-4					
	Molybdenum nickel tetraoxide	238-034-5	solid powder	3.37		Ph: 7.0 , 4.65 g/L	
	cobalt lithium nickel oxide	442-750-5					
	Reaction mass of aluminium fluoride and aluminium oxide and chromium (III) oxide and nickel dichloride	909-803-9					
	Reaction mass of nickel monoxide and silicon dioxide	910-417-8					
	Lithium Nickel Cobalt Aluminium Oxide	700-042-6	solid black powder				

	Substance name	EC / list number	Physical state	Density [g/cm³ at 20°C]	Melting point [°C]	Water Solubility	additional data
	Reaction mass of diiron trioxide and divanadium pentaoxide and nickel monoxide	909-880-9					
	cobalt lithium manganese nickel oxide	480-390-0	solid black powder	4.63	>360.0	Ph: 7.05 , $18.2 \cdot 10^{-6}$ g Ni/L	
	Dialuminium nickel tetraoxide	234-454-8	solid powder	3.44	> 400.0	Ph: 6.0 , $28.95 \cdot 10^{-6}$ g Ni/L	
	Nickel monoxide	215-215-7	solid granules	6.75	1984.0	Ph: 6.9 , $27.1 \cdot 10^{-6}$ g Ni/L	
hydroxide	Pentanickel octahydroxide carbonate	941-652-4	solid powder	2.96	350.0 (decomp)	Ph: 7.65 , $6.35 \cdot 10^{-3}$ g Ni/L	
	Nickel hydroxide oxide (Ni (OH) O (1:1:1))	700-710-7	solid grey powder	3.8	200 (decomp)	Ph: 7.4 , $14.36 \cdot 10^{-3}$ g/L	
	[carbonato(2-)]tetrahydroxytrinickel	235-715-9	solid powder	2.6	240 (decomp)	Ph: 6, 42-46·10^{-3} g/L Ph: 8, 5.5-9.3·10^{-3} g/L	vp: $4.86 \cdot 10^{-4}$ Pa, 25.0 °C
	Nickel dihydroxide	235-008-5	solid powder	3.8	200 (decomp)	Ph: 8.3 , $68 \cdot 10^{-6}$ g Ni/L	
sulfide	Reaction mass of cobalt sulphide and nickel sulphide and trinickel disulphide	910-663-6	solid black powder	5.45 - 5.98	> 600.0		bp: > 600.0 °C

	Substance name	EC / list number	Physical state	Density [g/cm³ at 20°C]	Melting point [°C]	Water Solubility	additional data
	Trinickel disulphide	234-829-6	solid powder	5.98	> 360	Ph: 7.2 , $11.6 \cdot 10^{-3}$ g Ni/L	
	Nickel sulphide	240-841-2	solid powder	5.66	> 360	Ph: 6.2, $57 \cdot 10^{-3}$ g Ni/L	
halogenide	**Nickel difluoride**	233-071-3	solid yellow to green powder	4.63 [19]	1000.0 (sublim)	Ph: 5.0 , 40.0 g/L	bp: 1001.0 °C (subl)
	Reaction mass of aluminium fluoride and chromium trifluoride and nickel difluoride	914-309-1					
	Nickel dichloride	231-743-0	solid crystalline	3.55 [19]	1001 [19]	642 g/L [19]	bp: 973 (subl) [19]
	Reaction mass of aluminium fluoride and aluminium oxide and chromium (III) oxide and nickel dichloride	909-803-9					
misc	Nickel bis(dihydrogen phosphate)	242-522-3	liquid solution	1.47		Ph: 1.4, >500.0 g/L (miscible)	
	Nickel bis(sulphamidate)	237-396-1	solid crystalline	2.25	142 (decomp)	Ph: 1.35 , >500 g/L	

[19] David R Lide (ed.), *Handbook of Chemistry and Physics, 75th Edition*, CRC Press Inc., Boca Rator, Ann Arbor, London, Tokyo, **1995**.

	Substance name	EC / list number	Physical state	Density [g/cm³ at 20°C]	Melting point [°C]	Water Solubility	additional data
	Nickel sulphate	232-104-9	solid crystalline	3.68 (anhyd) 2.07 (hexaqua) 1.95 (heptaqua)	840.0 848.0 °C (decomp) >53.0 (hexaqua) >99.0 (heptaqua)	293 g/L (anhyd) 625.0 g/L (hexaqua) 756 g/L (heptaqua)	
	Nickel dinitrate	236-068-5	solid crystalline	2.05 (hexaqua)	56.7 (hexaqua)	2385.0 g/L	bp: 136.7 °C (hexaqua) vp: $3.4 \cdot 10^{-3}$ Pa, 25.0 °C
metallic	Aluminium, compound with nickel (1:1)	234-439-6	solid grey powder	5.85	1380		

Organic nickel compounds

	Substance name	EC/list number	Physical State	Density [g/cm³ at 20°C]	Melting point [°C]	Water solubility	additional data (bp: boiling point vp: vapor pressure)
carboxylate	nickel(2+) bis(2-carboxyacetate)	931-258-0					
	Nickel oxalate	208-933-7	solid green/ blue powder	2.07		Ph: 6.0 , 475·10⁻⁶ g Ni/L	bp: 258-365 °C (decomp) vp: < 1.47·10⁻³ Pa, 20.0 °C
	Trinickel dicitrate	227-873-2	solid powder	1.85	> 365.0 (decomp)	Ph: 4.5 , 34.73 g/L	vp: 1.29·10⁻⁴ Pa, 20.0 °C
	Nickel(2+) hydrogen citrate	242-533-3	solid powder	1.85	> 365.0 (decomp)	Ph: 4.5 , 34.73 g/L	vp: 1.29·10⁻⁴ Pa, 20.0 °C
	Nickel bis(2-ethylhexanoate)	224-699-9	semi-solid green paste	0.78	< -50.0 °C	Ph: 5.9, 110·10⁻³ g/L	bp: 326 - 328 °C (decomp ?) vp: 9.2·10⁻⁵ Pa, 25.0 °C log(P_{ow}): -0.33 , Ph: 6.2

	Substance name	EC/list number	Physical State	Density [g/cm³ at 20°C]	Melting point [°C]	Water solubility	additional data (bp: boiling point vp: vapor pressure)
	Nickel(2+) propionate	222-102-6					
	Nickel di(acetate)	206-761-7	solid crystalline	1.78	> 360	177.0 g/L	
aromatic alcohol	(3-carboxy-1,1'-(1,2-dicyanovinylenebis(nitrilomethylidyne)-2,2'-dinaphtholato)nickel(II)	403-550-3	solid powder	1.61	> 320	Ph: 6.1 , Solubility: $7 \cdot 10^{-6}$ g/L	
	sodium μ-[5-{[7-(hydroxy-1κO)-2,6-disulfo-1-naphthyl]diazenyl-1κN}-1H-1,2,4-triazole-3-carboxylato(2-)-1κN1′:2κN2′]-μ-[5-{[7-(hydroxy-2κO)-2,6-disulfo-1-naphthyl]diazenyl-2κN}-1H-1,2,4-triazole-3-carboxylato(3-)-1κN2′:2κN1′]dinickelate(1-)	443-510-2	solid red-brown powder	1.79	> 300	Ph: 7.75 , 405 g/L	bp: > 420.0 °C vp: $<5.0 \cdot 10^{-4}$ Pa, 25.0 °C log(P_{ow}): -3.2 , Ph: 7.75
	{5,5'-[(E)-diazenediyl]bis[6-(hydroxy-kO)pyrimidine-2,4(1H,3H)-dionato](2-)}nickel compound with melamine	939-379-0	solid yellowish powder (nanomaterial)	0.385 (bulk)	200-350 (decomp)	Ph: 6.2 , $80 \cdot 10^{-6}$ g/L	bp: 200-350 °C (decomp) vp: 0.0 Pa , 25.0 °C (calc) log(P_{ow}): -2.63 (calc)

	Substance name	EC/list number	Physical State	Density [g/cm³ at 20°C]	Melting point [°C]	Water solubility	additional data (bp: boiling point vp: vapor pressure)
	[2,2'-[1,2-phenylenebis(nitrilomethylidyne)]-bis(phenolato)]-N,N',O,O'-nickel(II)	400-870-5		1.58	> 300	< $30 \cdot 10^{-6}$ g/L	
	[1,3-dihydro-5,6-bis[[(2-hydroxy-1-naphthyl)methylene]amino]-2H-benzimidazol-2-onato(2-)-N5,N6,O5,O6]nickel	255-965-2	solid powder	1.61	> 450	Ph: 6.2 , $12.5 \cdot 10^{-6}$ g/L	log(P_{ow}): 1.2, Ph: 6.2
	[2,3'-bis[[(2-hydroxyphenyl)methylene]amino]but-2-enedinitrilato(2-)-N2,N3,O2,O3]nickel	265-022-7	solid brown powder	0.46 (bulk) 1.61	> 356 (decomp)	Ph: 7.0 , $6.4 \cdot 10^{-6}$ g/L	log(P_{ow}): 2.59 , Ph: 7.0
	Trisodium (1-(3-carboxylato-2-oxido-5-sulfonatophenylazo)-5-hydroxy-7-sulfonatonaphthalen-2-amido)nickel(II)	407-110-1					
phosphorous	Bis-DPP Nickel(II)chloride	467-300-5	solid powder	1.47		Ph: 6.0 , Solubility: $61 \cdot 10^{-6}$ g/L	bp: 592.5 °C (calc) vp: < $1.0 \cdot 10^{-6}$ Pa, 25.0 °C (calc)

	Substance name	EC/list number	Physical State	Density [g/cm³ at 20°C]	Melting point [°C]	Water solubility	additional data (bp: boiling point vp: vapor pressure)
	Tetrakis(tritolyl phosphite)nickel[17]	252-777-2	red liquid	1.1	< -150.0		bp: > 42.0 °C (decomp) vp: < 0.001.47·10^{-3} Pa, 20.0 °C log(P_{ow}): 7.0, Ph: 7.0 (calc)
	bis(triphenylphosphine)nickel(II) chloride	238-154-8			247-250 °C[20]		
phthalocyanine	Tetrasodium (c-(3-(1-(3-(e-6-dichloro-5-cyanopyrimidin-f-yl(methyl)amino)propyl)-1,6-dihydro-2-hydroxy-4-methyl-6-oxo-3-pyridylazo)-4-sulfonatophenylsulfamoyl)phthalocyanine-a,b,d-trisulfonato(6-))nickelato II, where a is 1 or 2 or 3 or 4,b is 8 or 9 or 10 or 11,c is 15 or 16 or 17 or 18, d is 22 or 23 or 24 or 25 and where e and f together are 2 and 4 or 4and 2 respectively	410-160-7					

20

	Substance name	EC/list number	Physical State	Density [g/cm³ at 20°C]	Melting point [°C]	Water solubility	additional data (bp: boiling point vp: vapor pressure)
	hexasodium (di-[N-(3-(4-[5-(5-amino-3-methyl-1-phenylpyrazol-4-yl-azo)-2,4-disulfo-anilino]-6-chloro-1,3,5-triazin-2-ylamino)phenyl)-sulfamoyl](di-sulfo)-phthalocyaninato)nickel	417-250-5					
carbonyl	Nickel tetracarbonyl	236-669-2	liquid	1.32 [19]	-25 [19]	0.018 [19]	bp: 43 °C [19] vp: $17.07 \cdot 10^3$ Pa, 0 °C $77.68 \cdot 10^3$ Pa, 35.1 °C [21]

21

Appendix 3. CLH Tables

Table 45: EU classification: CLP (EC) 1271/2008, Annex VI listing of nickel and its compounds

Index No	International chemical ID	EC No	CAS No	Annex VI of CLP hazard class and category	Hazard statement code
028-002-00-7	nickel	231-111-4	7440-02-0	**Carc. 2** STOT RE 1 Skin Sens. 1	H351 H372** H317
028-001-00-1	Tetracarbonylnickel nickel tetracarbonyl	236-669-2	13463-39-3	Flam. Liq. 2 **Carc. 2** Repr. 1B Acute Tox. 2 * Aquatic Acute 1 Aquatic Chronic 1	H225 H351 H360D *** H330 H400 H410
028-002-01-4	nickel powder; [particle diameter < 1 mm]	231-111-4	7440-02-0	Carc. 2 STOT RE 1 Skin Sens. 1 Aquatic Chronic 3	H351 H372 ** H317 H412
028-003-00-2	nickel monoxide [1] nickel oxide [2] bunsenite [3]	215-215-7 [1] 234-323-5 [2]	1313-99-1 [1] 11099-02-8 [2] 34492-97-2 [3]	Carc. 1A STOT RE 1 Skin Sens. 1 Aquatic Chronic 4	H350i H372 ** H317 H413
028-004-00-8	nickel dioxide	234-823-3	12035-36-8	Carc. 1A STOT RE 1 Skin Sens. 1 Aquatic Chronic 4	H350i H372 ** H317 H413
028-005-00-3	dinickel trioxide	215-217-8	1314-06-3	Carc. 1A STOT RE 1 Skin Sens. 1 Aquatic Chronic 4	H350i H372 ** H317 H413
028-006-00-9	nickel (II) sulfide [1] nickel sulfide [2] millerite [3]	240-841-2 [1] 234-349-7 [2]	16812-54-7 [1] 11113-75-0 [2] 1314-04-1 [3]	Carc. 1A Muta. 2 STOT RE 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H341 H372 ** H317 H400 H410
028-007-00-4	trinickel disulfide; nickel subsulfide [1] heazlewoodite [2]	234-829-6 [1]	12035-72-2 [1] 12035-71-1 [2]	Carc. 1A Muta. 2 STOT RE 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H341 H372 ** H317 H400 H410
028-008-00-X	nickel dihydroxide [1] nickel hydroxide [2]	235-008-5 [1] 234-348-1 [2]	12054-48-7 [1] 11113-74-9 [2]	Carc. 1A Muta. 2 Repr. 1B Acute Tox. 4 * Acute Tox. 4 * STOT RE 1	H350i H341 H360D *** H332 H302 H372 **

Index No	International chemical ID	EC No	CAS No	Annex VI of CLP hazard class and category	Hazard statement code
				Skin Irrit. 2 Resp. Sens. 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H315 H334 H317 H400 H410
028-009-00-5	nickel sulfate	232-104-9	7786-81-4	Carc. 1A Muta. 2 Repr. 1B Acute Tox. 4 * Acute Tox. 4 * STOT RE 1 Skin Irrit. 2 Resp. Sens. 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H341 H360D *** H332 H302 H372 ** H315 H334 H317 H400 H410
028-010-00-0	nickel carbonate; basic nickel carbonate; carbonic acid, nickel (2+) salt [1] carbonic acid, nickel salt [2] [μ-[carbonato(2-)-O:O']] dihydroxy trinickel [3] [carbonato(2-)] tetrahydroxytrinickel [4]	222-068-2 [1] 240-408-8 [2] 265-748-4 [3] 235-715-9 [4]	3333-67-3 [1] 16337-84-1 [2] 65405-96-1 [3] 12607-70-4 [4]	Carc. 1A Muta. 2 Repr. 1B Acute Tox. 4 * Acute Tox. 4 * STOT RE 1 Skin Irrit. 2 Resp. Sens. 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H341 H360D *** H332 H302 H372 ** H315 H334 H317 H400 H410
028-011-00-6	nickel dichloride	231-743-0	7718-54-9	Carc. 1A Muta. 2 Repr. 1B Acute Tox. 3 * Acute Tox. 3 * STOT RE 1 Skin Irrit. 2 Resp. Sens. 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H341 H360D *** H331 H301 H372 ** H315 H334 H317 H400 H410
028-012-00-1	nickel dinitrate [1] nitric acid, nickel salt [2]	236-068-5 [1] 238-076-4 [2]	13138-45-9 [1] 14216-75-2 [2]	Ox. Sol. 2 Carc. 1A Muta. 2 Repr. 1B Acute Tox. 4 * Acute Tox. 4 * STOT RE 1 Skin Irrit. 2 Eye Dam. 1 Resp. Sens. 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H272 H350i H341 H360D *** H332 H372 ** H315 H318 H334 H317 H400 H410
028-013-00-7	nickel matte	273-749-6	69012-50-6	Carc. 1A STOT RE 1 Skin Sens. 1 Aquatic Acute 1	H350i H372 ** H317 H400

Index No	International chemical ID	EC No	CAS No	Annex VI of CLP hazard class and category	Hazard statement code
				Aquatic Chronic 1	H410
028-014-00-2	slimes and sludges, copper electrolytic refining, decopperised, nickel sulfate	295-859-3	92129-57-2	Carc. 1A Muta. 2 Repr. 1B Acute Tox. 4 * Acute Tox. 4 * STOT RE 1 Skin Irrit. 2 Resp. Sens. 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H341 H360D *** H332 H302 H372 ** H315 H334 H317 H400 H410
028-016-00-3	nickel diperchlorate; perchloric acid, nickel(II) salt	237-124-1	13637-71-3	Carc. 1A Muta. 2 Repr. 1B STOT RE 1 Skin Corr. 1B Resp. Sens. 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H341 H360D *** H372 ** H314 H334 H317 H400 H410
028-017-00-9	nickel dipotassium bis(sulfate) [1] diammonium nickel bis(sulfate) [2]	237-563-9 [1] 239-793-2 [2]	13842-46-1 [1] 15699-18-0 [2]	Carc. 1A Muta. 2 Repr. 1B Acute Tox. 4 * Acute Tox. 4 * STOT RE 1 Resp. Sens. 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H341 H360D *** H332 H302 H372 ** H334 H317 H400 H410
028-018-00-4	nickel bis(sulfamidate); nickel sulfamate	237-396-1	13770-89-3	Carc. 1A Muta. 2 Repr. 1B STOT RE 1 Resp. Sens. 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H341 H360D *** H372 ** H334 H317 H400 H410
028-019-00-X	nickel bis(tetrafluoroborate)	238-753-4	14708-14-6	Carc. 1A Muta. 2 Repr. 1B STOT RE 1 Resp. Sens. 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H341 H360D *** H372 ** H334 H317 H400 H410
028-021-00-0	nickel diformate [1] formic acid, nickel salt [2] formic acid, copper nickel salt [3]	222-101-0 [1] 239-946-6 [2]	3349-06-2 [1] 15843-02-4 [2] 68134-59-8 [3]	Carc. 1A Muta. 2 Repr. 1B STOT RE 1 Resp. Sens. 1 Skin Sens. 1	H350i H341 H360D *** H372 ** H334 H317

Index No	International chemical ID	EC No	CAS No	Annex VI of CLP hazard class and category	Hazard statement code
		268-755-0 [3]		Aquatic Acute 1 Aquatic Chronic 1	H400 H410
028-022-00-6	nickel di(acetate) [1] nickel acetate [2]	206-761-7 [1] 239-086-1 [2]	373-02-4 [1] 14998-37-9 [2]	Carc. 1A Muta. 2 Repr. 1B Acute Tox. 4 * Acute Tox. 4 * STOT RE 1 Resp. Sens. 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H341 H360D *** H332 H302 H372 ** H334 H317 H400 H410
028-024-00-7	nickel dibenzoate	209-046-8	553-71-9	Carc. 1A Muta. 2 Repr. 1B STOT RE 1 Resp. Sens. 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H341 H360D *** H372 ** H334 H317 H400 H410
028-025-00-2	nickel bis(4-cyclohexylbutyrate)	223-463-2	3906-55-6	Carc. 1A Muta. 2 Repr. 1B STOT RE 1 Resp. Sens. 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H341 H360D *** H372 ** H334 H317 H400 H410
028-026-00-8	nickel(II) stearate; nickel(II) octadecanoate	218-744-1	2223-95-2	Carc. 1A Muta. 2 Repr. 1B STOT RE 1 Resp. Sens. 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H341 H360D *** H372 ** H334 H317 H400 H410
028-027-00-3	nickel dilactate	-	16039-61-5	Carc. 1A Muta. 2 Repr. 1B STOT RE 1 Resp. Sens. 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H341 H360D *** H372 ** H334 H317 H400 H410
028-028-00-9	nickel(II) octanoate	225-656-7	4995-91-9	Carc. 1A Muta. 2 Repr. 1B STOT RE 1 Skin Corr. 1A Resp. Sens. 1 Skin Sens. 1 Aquatic Acute 1	H350i H341 H360D *** H372 ** H314 H334 H317 H400 H410

Index No	International chemical ID	EC No	CAS No	Annex VI of CLP hazard class and category	Hazard statement code
				Aquatic Chronic 1	
028-029-00-4	nickel difluoride [1] nickel dibromide [2] nickel diiodide [3] nickel potassium fluoride [4]	233-071-3 [1] 236-665-0 [2] 236-666-6 [3]	10028-18-9 [1] 13462-88-9 [2] 13462-90-3 [3] 11132-10-8 [4]	Carc. 1A Muta. 2 Repr. 1B STOT RE 1 Resp. Sens. 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H341 H360D *** H372 ** H334 H317 H400 H410
028-030-00-X	nickel hexafluorosilicate	247-430-7	26043-11-8	Carc. 1A Muta. 2 Repr. 1B STOT RE 1 Resp. Sens. 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H341 H360D *** H372 ** H334 H317 H400 H410
028-031-00-5	nickel selenate	239-125-2	15060-62-5	Carc. 1A Muta. 2 Repr. 1B STOT RE 1 Resp. Sens. 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H341 H360D *** H372 ** H334 H317 H400 H410
028-032-00-0	nickel hydrogen phosphate [1] nickel bis(dihydrogen phosphate) [2] trinickel bis(orthophosphate) [3] dinickel diphosphate [4] nickel bis(phosphinate) [5] nickel phosphinate [6] phosphoric acid, calcium nickel salt [7] diphosphoric acid, nickel(II) salt [8]	238-278-2 [1] 242-522-3 [2] 233-844-5 [3] 238-426-6 [4] 238-511-8 [5] 252-840-4 [6]	14332-34-4 [1] 18718-11-1 [2] 10381-36-9 [3] 14448-18-1 [4] 14507-36-9 [5] 36026-88-7 [6] 17169-61-8 [7] 19372-20-4 [8]	Carc. 1A STOT RE 1 Resp. Sens. 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H372 ** H334 H317 H400 H410
028-033-00-6	diammonium nickel hexacyanoferrate	-	74195-78-1	Carc. 1A STOT RE 1 Resp. Sens. 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H372 ** H334 H317 H400 H410
028-034-00-1	nickel dicyanide	209-160-8	557-19-7	Carc. 1A STOT RE 1 Resp. Sens. 1 Skin Sens. 1 Aquatic Acute 1	H350i H372 ** H334 H317 H400

Index No	International chemical ID	EC No	CAS No	Annex VI of CLP hazard class and category	Hazard statement code
				Aquatic Chronic 1	H410
028-035-00-7	nickel chromate	238-766-5	14721-18-7	Carc. 1A STOT RE 1 Resp. Sens. 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H372 ** H334 H317 H400 H410
028-036-00-2	nickel(II) silicate [1] dinickel orthosilicate [2] nickel silicate (3:4) [3] silicic acid, nickel salt [4] trihydrogen hydroxybis[orthosilicato(4-)]trinickelate(3-) [5]	244-578-4 [1] 237-411-1 [2] 250-788-7 [3] 253-461-7 [4] 235-688-3 [5]	21784-78-1 [1] 13775-54-7 [2] 31748-25-1 [3] 37321-15-6 [4] 12519-85-6 [5]	Carc. 1A STOT RE 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H372 ** H317 H400 H410
028-037-00-8	dinickel hexacyanoferrate	238-946-3	14874-78-3	Carc. 1A STOT RE 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H372 ** H317 H400 H410
028-038-00-3	trinickel bis(arsenate); nickel(II) arsenate	236-771-7	13477-70-8	Carc. 1A STOT RE 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350 H372 ** H317 H400 H410
028-039-00-9	nickel oxalate [1] oxalic acid, nickel salt [2]	208-933-7 [1] 243-867-2 [2]	547-67-1 [1] 20543-06-0 [2]	Carc. 1A STOT RE 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H372 ** H317 H400 H410
028-040-00-4	nickel telluride	235-260-6	12142-88-0	Carc. 1A STOT RE 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H372 ** H317 H400 H410
028-041-00-X	trinickel tetrasulfide	-	12137-12-1	Carc. 1A STOT RE 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H372 ** H317 H400 H410
028-042-00-5	trinickel bis(arsenite)	-	74646-29-0	Carc. 1A STOT RE 1 Skin Sens. 1	H350i H372 ** H317

Index No	International chemical ID	EC No	CAS No	Annex VI of CLP hazard class and category	Hazard statement code
				Aquatic Acute 1 Aquatic Chronic 1	H400 H410
028-043-00-0	cobalt nickel gray periclase; C.I. Pigment Black 25; C.I. 77332 [1] cobalt nickel dioxide [2] cobalt nickel oxide [3]	269-051-6 [1] 261-346-8 [2]	68186-89-0 [1] 58591-45-0 [2] 12737-30-3 [3]	Carc. 1A STOT RE 1 Skin Sens. 1	H350i H372 ** H317
028-044-00-6	nickel tin trioxide; nickel stannate	234-824-9	12035-38-0	Carc. 1A STOT RE 1 Skin Sens. 1	H350i H372 ** H317
028-045-00-1	nickel triuranium decaoxide	239-876-6	15780-33-3	Carc. 1A STOT RE 1 Skin Sens. 1	H350i H372 ** H317
028-046-00-7	nickel dithiocyanate	237-205-1	13689-92-4	Carc. 1A Muta. 2 Repr. 1B STOT RE 1 Resp. Sens. 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H341 H360D *** H372 ** H334 H317 H400 H410
028-047-00-2	nickel dichromate	239-646-5	15586-38-6	Carc. 1A Muta. 2 Repr. 1B STOT RE 1 Resp. Sens. 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H341 H360D *** H372 ** H334 H317 H400 H410
028-048-00-8	nickel(II) selenite	233-263-7	10101-96-9	Carc. 1A STOT RE 1 Resp. Sens. 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H372 ** H334 H317 H400 H410
028-049-00-3	nickel selenide	215-216-2	1314-05-2	Carc. 1A STOT RE 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H372 ** H317 H400 H410
028-050-00-9	silicic acid, lead nickel salt	-	68130-19-8	Carc. 1A Repr. 1A STOT RE 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H360Df H372 ** H317 H400 H410

Index No	International chemical ID	EC No	CAS No	Annex VI of CLP hazard class and category	Hazard statement code
028-051-00-4	nickel diarsenide [1] nickel arsenide [2]	235-103-1 [1] 248-169-1 [2]	12068-61-0 [1] 27016-75-7 [2]	Carc. 1A STOT RE 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H372 ** H317 H400 H410
028-052-00-X	nickel barium titanium primrose priderite; C.I. Pigment Yellow 157; C.I. 77900	271-853-6	68610-24-2	Carc. 1A STOT RE 1 Skin Sens. 1	H350i H372 ** H317
028-053-00-5	nickel dichlorate [1] nickel dibromate [2] ethyl hydrogen sulfate, nickel(II) salt [3]	267-897-0 [1] 238-596-1 [2] 275-897-7 [3]	67952-43-6 [1] 14550-87-9 [2] 71720-48-4 [3]	Carc. 1A Muta. 2 Repr. 1B STOT RE 1 Resp. Sens. 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H341 H360D *** H372 ** H334 H317 H400 H410
028-054-00-0	nickel(II) trifluoroacetate [1] nickel(II) propionate [2] nickel bis(benzenesulfonate) [3] nickel(II) hydrogen citrate [4] citric acid, ammonium nickel salt [5] citric acid, nickel salt [6] nickel bis(2-ethylhexanoate) [7] 2-ethylhexanoic acid, nickel salt [8] dimethylhexanoic acid nickel salt [9] nickel(II) isooctanoate [10] nickel isooctanoate [11] nickel bis(isononanoate) [12] nickel(II) neononanoate [13] nickel(II) isodecanoate [14] nickel(II) neodecanoate [15] neodecanoic acid, nickel salt [16] nickel(II) neoundecanoate [17] bis(.sc.d.sc.-gluconato-O1,O2)nickel [18] nickel 3,5-bis(tert-butyl)-4-hydroxybenzoate (1:2) [19] nickel(II) palmitate [20] (2-ethylhexanoato-O)(isononanoato-O)nickel [21] (isononanoato-O)(isooctanoato-O)nickel [22] (isooctanoato-O)(neodecanoato-O)nickel [23] (2-ethylhexanoato-O)(isodecanoato-O)nickel [24] (2-ethylhexanoato-O)(neodecanoato-O)nickel [25] (isodecanoato-O)(isooctanoato-O)nickel [26] (isodecanoato-O)(isononanoato-O)nickel [27] (isononanoato-O)(neodecanoato-O)nickel [28]	240-235-8 [1] 222-102-6 [2] 254-642-3 [3] 242-533-3 [4] 242-161-1 [5] 245-119-0 [6] 224-699-9 [7] 231-480-1 [8] 301-323-2 [9] 249-555-2 [10] 248-585-3 [11] 284-349-6 [12] 300-094-6 [13] 287-468-1 [14] 287-469-7 [15]	16083-14-0 [1] 3349-08-4 [2] 39819-65-3 [3] 18721-51-2 [4] 18283-82-4 [5] 22605-92-1 [6] 4454-16-4 [7] 7580-31-6 [8] 93983-68-7 [9] 29317-63-3 [10] 27637-46-3 [11] 84852-37-9 [12] 93920-10-6 [13] 85508-43-6 [14] 85508-44-7 [15] 51818-56-5 [16] 93920-09-3 [17] 71957-07-8 [18] 52625-25-9 [19] 13654-40-5 [20] 85508-45-8 [21] 85508-46-9 [22]	Carc. 1A Muta. 2 Repr. 1B STOT RE 1 Resp. Sens. 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H341 H360D *** H372 ** H334 H317 H400 H410

Index No	International chemical ID	EC No	CAS No	Annex VI of CLP hazard class and category	Hazard statement code
	fatty acids, C6-19-branched, nickel salts [29] fatty acids, C8-18 and C18-unsaturated, nickel salts [30] 2,7-naphthalenedisulfonic acid, nickel(II) salt [31]	257-447-1 [16] 300-093-0 [17] 276-205-6 [18] 258-051-1 [19] 237-138-8 [20] 287-470-2 [21] 287-471-8 [22] 284-347-5 [23] 284-351-7 [24] 285-698-7 [25] 285-909-2 [26] 284-348-0 [27] 287-592-6 [28] 294-302-1 [29] 283-972-0 [30]	84852-35-7 [23] 84852-39-1 [24] 85135-77-9 [25] 85166-19-4 [26] 84852-36-8 [27] 85551-28-6 [28] 91697-41-5 [29] 84776-45-4 [30] 72319-19-8 [31]		
028-055-00-6	nickel(II) sulfite [1] nickel tellurium trioxide [2] nickel tellurium tetraoxide [3] molybdenum nickel hydroxide oxide phosphate [4]	231-827-7 [1] 239-967-0 [2] 239-974-9 [3] 268-585-7 [4]	7757-95-1 [1] 15851-52-2 [2] 15852-21-8 [3] 68130-36-9 [4]	Carc. 1A STOT RE 1 Resp. Sens. 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H372 ** H334 H317 H400 H410
028-056-00-1	nickel boride (NiB) [1] dinickel boride [2] trinickel boride [3] nickel boride [4] dinickel silicide [5] nickel disilicide [6] dinickel phosphide [7]	234-493-0 [1] 234-494-6 [2]	12007-00-0 [1] 12007-01-1 [2] 12007-02-2 [3]	Carc. 1A STOT RE 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H372 ** H317 H400 H410

Index No	International chemical ID	EC No	CAS No	Annex VI of CLP hazard class and category	Hazard statement code
	nickel boron phosphide [8]	234-495-1 [3] 235-723-2 [4] 235-033-1 [5] 235-379-3 [6] 234-828-0 [7]	12619-90-8 [4] 12059-14-2 [5] 12201-89-7 [6] 12035-64-2 [7] 65229-23-4 [8]		
028-057-00-7	dialuminium nickel tetraoxide [1] nickel titanium trioxide [2] nickel titanium oxide [3] nickel divanadium hexaoxide [4] cobalt dimolybdenum nickel octaoxide [5] nickel zirkonium trioxide [6] molybdenum nickel tetraoxide [7] nickel tungsten tetraoxide [8] olivine, nickel green [9] lithium nickel dioxide [10] molybdenum nickel oxide [11]	234-454-8 [1] 234-825-4 [2] 235-752-0 [3] 257-970-5 [4] 268-169-5 [5] 274-755-1 [6] 238-034-5 [7] 238-032-4 [8] 271-112-7 [9]	12004-35-2 [1] 12035-39-1 [2] 12653-76-8 [3] 52502-12-2 [4] 68016-03-5 [5] 70692-93-2 [6] 14177-55-0 [7] 14177-51-6 [8] 68515-84-4 [9] 12031-65-1 [10] 12673-58-4 [11]	Carc. 1A STOT RE 1 Skin Sens. 1	H350i H372 ** H317
028-058-00-2	cobalt lithium nickel oxide	442-750-5	-	Carc. 1A Acute Tox. 2 * STOT RE 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H330 H372 ** H317 H400 H410
607-288-00-2	Tetrasodium (c-(3-(1-(3-(e-6-dichloro-5-cyanopyrimidin-f-yl(methyl)amino)propyl)-1,6-dihydro-2-hydroxy-4-methyl-6-oxo-3-pyridylazo)-4-sulfonatophenylsulfamoyl)phthalocyanine-a,b,d-trisulfonato(6-))nickelato II, where a is 1 or 2 or 3 or 4,b is 8 or 9 or 10 or 11,c is 15 or 16 or 17 or 18, d is 22 or 23 or 24 or 25 and where e and f together are 2 and 4 or 4 and 2 respectively	410-160-7	148732-74-5	Eye Irrit. 2 Skin Sens. 1 Aquatic Chronic 3	H319 H317 H412

Index No	International chemical ID	EC No	CAS No	Annex VI of CLP hazard class and category	Hazard statement code
611-103-00-0	trisodium (1-(3-carboxylato-2-oxido-5-sulfonatophenylazo)-5-hydroxy-7-sulfonatonaphthalen-2-amido)nickel(II)	407-110-1		Eye Dam. 1 Skin Sens. 1 Aquatic Chronic 2	H318 H317 H411
611-122-00-4	hexasodium (di[N-(3-(4-[5-(5-amino-3-methyl-1-phenylpyrazol-4-yl-azo)-2,4-disulfo-anilino]-6-chloro-1,3,5-triazin-2-ylamino)phenyl)-sulfamoyl](di-sulfo)-phthalocyaninato)nickel	417-250-5	151436-99-6	Eye Dam. 1 Skin Sens. 1	H318 H317

Appendix 4. REACH Registrations

Table 46: REACH Registrations

Substance		Tonnage (tonnes / annum)	
Name	EC/ list number	Full registration	Intermediate registration
Nickel	231-111-4	>100 000 (130 reg)	
Slags, ferronickel-manufg.	273-729-7	>100 000 (<5 reg)	
Matte, nickel	273-749-6	>100 000 (<5 reg)	10 000-100 000 (<5 reg)
Nickel monoxide	215-215-7	10 000-100 000 (51 reg)	10 000-100 000 (6 reg)
Nickel sulphate	232-104-9	10 000-100 000 (15 reg)	1000-10 000 (<5 reg)
Nickel dichloride	231-743-0	10 000-100 000 (8 reg)	
Nickel sulphide	240-841-2	10 000-100 000 (23 reg)	1000-10 000 (24 reg)
Trinickel disulphide	234-829-6	100-1000 (35 reg)	1000-10 000 (33 reg)
Residues, copper-iron-lead-nickel matte, sulfuric acid-insol.	310-050-8	100-1000 (<5 reg)	10 000-100 000 (<5 reg)
[carbonato(2-)]tetrahydroxy-trinickel	235-715-9	10 000-100 000 (12 reg)	1000-10 000 (<5 reg)
Reaction mass of cobalt sulphide and nickel sulphide and trinickel disulphide	910-663-6		10 000-100 000 (<5 reg)
Nickel dinitrate	236-068-5	10 000-100 000 (12 reg)	100-1000 (<5 reg)
Speiss, lead, nickel-contg.	308-765-5	1000-10 000 (<5 reg)	1000-10 000 (<5 reg)
Nickel dihydroxide	235-008-5	1000-10 000 (17 reg)	1000-10 000 (5 reg)
Antimony nickel titanium oxide yellow	232-353-3	1000-10 000 (5 reg)	

Substance		Tonnage (tonnes / annum)	
Name	EC/ list number	Full registration	Intermediate registration
Nickel oxalate	208-933-7		1000-10 000 (<5 reg)
Nickel iron chromite black spinel	275-738-1	1000-10 000 (13 reg)	
Nickel bis(dihydrogen phosphate)	242-522-3	1000-10 000 (6 reg)	
Reaction mass of nickel monoxide and silicon dioxide	910-417-8		1000-10 000 (<5 reg)
2-Butenedioic acid (2Z)-, reaction products with ammonium di-µ3-hydroxyhexacosa-µ-oxodo-decaoxododecatungstate(6-) (6:1), ammonium octa-µ-oxodi-µ3-oxo-µ4-oxododecaoxoheptamolybdate(6-) (6:1), nickel(2+) nitrate (1:2) and nickel(2+) sulfate (1:1)	800-777-3		1-1000 (<5 reg)
Reaction mass of diiron trioxide and divanadium pentaoxide and nickel monoxide	909-880-9		1-1000 (<5 reg)
Reaction product of soluble nickel salt, cobalt salt, manganese salt with alkalines	931-895-4		1-1000 (<5 reg)
Pentanickel octahydroxide carbonate	941-652-4	1-1000 (<5 reg)	
{5,5'-[(E)-diazenediyl]bis[6-(hydroxy-kO)pyrimidine-2,4(1H,3H)-dionato](2-)}nickel compound with melamine	939-379-0	1-1000 (<5 reg)	
cobalt lithium manganese nickel oxide	480-390-0	1-1000 (<5 reg)	
Nickel difluoride	233-071-3	1-1000 (5 reg)	
Nickel bis(sulphamidate)	237-396-1	100-1000 (7 reg)	
Dialuminium nickel tetraoxide	234-454-8	1-1000 (<5 reg)	100-1000 (5 reg)
Lithium Nickel Cobalt Aluminium Oxide	700-042-6	1-1000 (<5 reg)	

Substance		Tonnage (tonnes / annum)	
Name	EC/ list number	Full registration	Intermediate registration
Nickel di(acetate)	206-761-7	1-1000 (<5 reg)	
Nickel tungsten tetraoxide	238-032-4		100-1000 (<5 reg)
Nickel bis(2-ethylhexanoate)	224-699-9	1-1000 (<5 reg)	1000-10 000 (<5 reg)
Molybdenum nickel tetraoxide	238-034-5	1-1000 (<5 reg)	100-1000 (5 reg)
Nickel(2+) propionate	222-102-6		1-1000 (<5 reg)
Reaction mass of aluminium fluoride and aluminium oxide and chromium (III) oxide and nickel dichloride	909-803-9		1-1000 (<5 reg)
Reaction mass of aluminium fluoride and chromium trifluoride and nickel difluoride	914-309-1	1-1000 (<5 reg)	
Citric acid, nickel salt	245-119-0		1-1000 (<5 reg)
Trinickel dicitrate	227-873-2		1-100 (5 reg)
sodium μ-[5-{[7-(hydroxy-1κO)-2,6-disulfo-1-naphthyl]diazenyl-1κN}-1H-1,2,4-triazole-3-carboxylato(2-)-1κN1′:2κN2′]-μ-[5-{[7-(hydroxy-2κO)-2,6-disulfo-1-naphthyl]diazenyl-2κN}-1H-1,2,4-triazole-3-carboxylato(3-)-1κN2′:2κN1′]dinickelate(1-)	443-510-2	1-1000 (<5 reg)	
nickel(2+) bis(2-carboxyacetate)	931-258-0		1-1000 (<5 reg)
Nickel(2+) hydrogen citrate	242-533-3		1000-10 000 (6 reg)
Aluminium, compound with nickel (1:1)	234-439-6	1-1000 (<5 reg)	
Nickel hydroxide oxide (Ni (OH) O (1:1:1))	700-710-7	1-1000 (<5 reg)	

Substance		Tonnage (tonnes / annum)	
Name	EC/ list number	Full registration	Intermediate registration
bis(triphenylphosphine)nickel(II) chloride	238-154-8		1-1000 (<5 reg)
(3-carboxy-1,1'-(1,2-dicyanovinylenebis(nitrilomethylidyne)-2,2'-dinaphtholato)nickel(II)	403-550-3	1-1000 (<5 reg)	
Bis-DPP Nickel(II)chloride	467-300-5	1-1000 (<5 reg)	
[2,2'-[1,2-phenylenebis(nitrilomethylidyne)]-bis(phenolato)]-N,N',O,O'-nickel(II)	400-870-5	1-1000 (<5 reg)	
[2,3'-bis[[(2-hydroxyphenyl)methylene]amino]but-2-enedinitrilato(2-)-N2,N3,O2,O3]nickel	265-022-7	1-1000 (<5 reg)	
[1,3-dihydro-5,6-bis[[(2-hydroxy-1-naphthyl)methylene]amino]-2H-benzimidazol-2-onato(2-)-N5,N6,O5,O6]nickel	255-965-2	1-1000 (<5 reg)	

Appendix 5. Summary tables of cohort studies

Table 47: Summary of the most relevant cohort studies and nested case-control studies therein assessing the association between occupational exposure to nickel compounds and lung cancer. Standardised mortality ratios (SMR) and other risk estimates are expressed in decimal form, i.e. no increase of risk equals a value of 1.00.

Cohort (Reference)	Cohort description	Exposure assessment	Outcome	Exposure	N of cases	Relative risk (95 % CI)	Comments
Finnish nickel refinery (Harjavalta) Anttila 1998	1388 workers employed for ≥ 3 months between 1945-85 followed through 1995	Air measurements available beginning in 1966	Incidence	Refinery Overall Latency ≥ 20 years	 6 6	SIR 2.61 (0.96 – 5.67) 3.38 (1.24 – 7.36)	
				Smelter Overall Latency ≥ 20 years	 15 13	 1.39 (0.78 – 1.58) 2.00 (1.07 – 3.42)	
				All exposed Overall Latency ≥ 20 years	 21 20	 1.39 (0.86 – 2.13) 2.12 (1.29 – 3.27)	
Finnish nickel refinery (Harjavalta) Pavela 2017	1309 workers employed for ≥ 3 months between 1945-85 followed from 1967 to 2011	Air measurements available beginning in 1966	Incidence	Refinery	14	SIR 2.01 (1.10 – 3.36)	
				Maintenance	8	1.40 (0.60 – 2.75)	
				Smelter	25	1.41 (0.91 – 2.08)	
				All exposed	47	1.55 (1.01 – 2.27)	
Norwegian nickel refinery workers (Kristiansand) Andersen 1996	Cohorts of 379 workers with 1st employment 1916-40 and	Air measurements since 1973, but very few before that year	Incidence	Total	182	SIR (unadjusted) 3.2 (2.7 – 3.7)	

Cohort (Reference)	Cohort description	Exposure assessment	Outcome	Exposure	N of cases	Relative risk (95% CI)	Comments
	employed for ≥ 3 years and 4385 workers with 1st employment in 1946-83 and ≥ 1 year of employment			Exposure to soluble Ni (mg/m^3) 86 < 1 1-4 5-14 ≥ 15	 86 36 23 55	RR adjusted for smoking, age, exposure to nickel oxide 1.0 reference 1.2 (0.8 – 1.9) 1.6 (1.0 – 2.8) 3.1 (2.1 – 4.8)	p for trend < 0.001
				Exposure to nickel oxide (mg/m^3) < 1 1-4 5-14 ≥ 15	 53 49 53 45	RR adjusted for smoking, age, exposure to soluble Ni 1.0 reference 1.0 (0.6 – 1.5) 1.6 (1.0 – 2.5) 1.5 (1.0 – 2.2)	p for trend 0.05
				Unexpsed workers of the refinery	21	SIR 1.8 (1.1 -2.8)	
Norwegian nickel refinery workers (Kristiansand) Grimsrud 2002	Nested case-control study of 213 lung cancers and 525 controls matched by age, sex and year of birth	Work history from plant records, nickel exposure from 5900 measurements for total nickel between 1973-1994 and estimates of specific nickel species	Incidence	Median cumulative exposure (mg/m^3 year) by quintiles		RR adjusted for smoking	
				Soluble Ni Unexposed 0.05 0.28 0.63 1.60 4.93	 9 27 33 36 42 66	 1.0 reference 1.3 (0.5 – 3.5) 1.8 (0.7 – 4.5) 1.9 (0.8 – 4.6) 2.5 (1.0 – 6.0) 3.8 (1.6 – 9.0)	p for trend 0.002
				Sulfidic Ni Unexposed 0.02 0.06 0.16 0.41 1.43	 10 27 48 42 40 46	 1.0 reference 1.6 (0.6 – 4.2) 2.8 (1.1 – 6.9) 2.5 (1.0 – 6.3) 2.3 (0.9 – 5.5) 2.8 (1.1 – 6.7)	p for trend 0.119
				Oxidic Ni Unexposed	 9	 1.0 reference	p for trend 0.201

Cohort (Reference)	Cohort description	Exposure assessment	Outcome	Exposure	N of cases	Relative risk (95% CI)	Comments
				0.02 0.10 0.36 1.67 12.6	29 42 47 45 41	1.7 (0.7 – 4.2) 2.3 (0.9 – 5.8) 2.7 (1.1 – 6.6) 2.3 (1.0 – 5.7) 2.2 (0.9 – 5.4)	
				Metallic Ni Unexposed 0.01 0.03 0.13 0.35 2.32	 14 31 37 28 46 57	 1.0 reference 1.4 (0.6 – 3.3) 1.3 (0.6 – 3.0) 1.3 (0.6 – 3.3) 1.7 (0.8 – 3.8) 2.4 (1.1 – 5.3)	p for trend 0.126
						RR adjusted for smoking and exposure to soluble Ni	
				Sulfidic Ni Unexposed 0.02 0.06 0.16 0.41 1.43	 10 27 48 42 40 46	 1.0 reference 1.5 (0.6 – 3.9) 2.2 (0.9 – 5.5) 1.8 (0.7 – 4.5) 1.3 (0.5 – 3.3) 1.2 (0.5 – 3.3)	p for trend 0.344
				Oxidic Ni Unexposed 0.02 0.10 0.36 1.67 12.6	 9 29 42 47 45 41	 1.0 reference 1.5 (0.6 – 3.8) 1.8 (0.7 – 4.5) 1.4 (0.6 – 3.7) 1.5 (0.6 – 3.7) 0.9 (0.4 – 2.5)	p for trend 0.406
				Metallic Ni Unexposed 0.01 0.03 0.13 0.35 2.32	 14 31 37 28 46 57	 1.0 reference 1.2 (0.5 – 2.9) 1.0 (0.5 – 2.4) 1.0 (0.4 – 2.3) 1.0 (0.4 – 2.4) 0.9 (0.3 – 2.4)	p for trend 0.972
	Cohort of 5297 workers employed	Work history from plant records,	Incidence	Cumulative exposure (mg/m^3 year)		RR adjusted for age and smoking	

Cohort (Reference)	Cohort description	Exposure assessment	Outcome	Exposure	N of cases	Relative risk (95% CI)	Comments
Norwegian nickel refinery workers (Kristiansand) Grimsrud 2003	for ≥ 1 year between 1910-1989 and alive on 1 January 1953.	nickel exposure from 5900 measurements for total nickel between 1973-1994 and estimates of specific nickel species					
				Total Ni Unexposed 0.01- 0.41 0.42 – 1.99 ≥ 2.0	 11 37 72 147	 1.0 reference 1.2 (0.6 – 2.4) 2.1 (1.1 – 3.9) 2.4 (1.3 – 4.5)	
				Water-soluble Ni Unexposed 0.01- 0.34 0.35 – 1.99 ≥ 2.0	 13 68 94 92	 1.0 reference 1.3 (0.7 – 2.4) 1.8 (1.0 – 3.2) 3.1 (1.7 – 5.5)	
				Ni oxide Unexposed 0.01- 0.12 0.13 – 1.99 ≥ 2.0	 13 72 109 73	 1.0 reference 1.7 (1.0 – 3.1) 2.5 (1.4 – 4.4) 2.1 (1.2 – 3.8)	
				Year of first employment 1910-29 1930-55 1956-78 1979-89 Total	 17 170 75 5 267	SIR 4.8 (2.8 – 7.6) 2.7 (2.3 – 3.1) 2.2 (1.7 – 2.7) 3.7 (1.2 – 8.7) 2.6 (2.3 – 2.9)	
Welsh nickel refinery workers (Clydach)	Cohort of workers with ≥ 5 years of employment hired 1902-69 or between 1953-92 and followed through 1982 and 2000 respectively	Estimated based on process knowledge, subjective impressions of relative dustiness, and a few measurements	Mortality				
  Easton 1992 Easton 1992 Easton 1992 Easton 1992				Year of first employment 1902 – 1919 1920 – 1929 1930 – 1939 1940 – 1949	 83 88 20 14	SMR 6.2 (4.9 – 7.7) 3.1 (2.5 – 3.9) 1.4 (0.8 – 2.1 1.2 (0.6 – 2.0)	

Cohort (Reference)	Cohort description	Exposure assessment	Outcome	Exposure	N of cases	Relative risk (95% CI)	Comments
Sorahan 2005 Grimsrud 2006				1953 – 1992 1930 - 1992	28 62	1.4 (0.9 – 2.0) 1.3 (1.0 – 1.7)	
Canadian (Alberta) hydrometallurgical nickel refinery workers Egedahl 2001	Cohort of 1649 male workers with ≥ 12 months employment in 1954-78	Not estimated	Mortality	Total	7	SMR 0.7 (0.2 – 1.5)	
English nickel platers Pang 1996	Cohort of 284 male workers with ≥ 3 months employment in 1945-75	Not estimated	Mortality	Total	11	SMR 1.1 (0.5 – 1.9)	p for trend 0.5 by duration of employment
Oak Ridge Gaseous Diffusion Plant worker cohort ICNCM 1990	Cohort of 813 men exposed to metallic nickel	Estimated based on measurements done in 1948-63	Mortality	Total	9	SMR 0.5 (0.3 – 1.0)	
Canadian nickel refinery facilities (INCO Ontario) ICNCM 1990	Cohorts of workers from three facilities	Estimated based on dust measurements and process information	Mortality	Coniston sinter facility Ever ≥ 5 years Copper Cliff sinter facility Ever ≥ 5 years Port Colborne leaching, calcining and sintering facility Ever ≥ 5 years Port Colborne Electrolysis department and no other department Ever ≥ 10 years Sudbury non-sinter workers, mining Ever	 8 6 63 33 72 38 19 10 310	SMR 2.9 (1.3 – 5.8) 4.9 (1.8 – 11) 3.1 (2.4 – 4.0) 7.9 (5.4 – 11) 2.4 (1.9 – 3.0) 3.7 (2.6 – 5.0) 0.9 (0.5 – 1.4) 0.9 1.1 (1.0 – 1.2)	

Cohort (Reference)	Cohort description	Exposure assessment	Outcome	Exposure	N of cases	Relative risk (95% CI)	Comments
				≥ 5 years	231	1.1 (1.0 – 1.3)	
				Sudbury non-sinter workers, smelter			
				Ever	219	1.1 (0.9 – 1.2)	
				≥ 5 years	145	1.1 (0.9 – 1.3)	
				Sudbury non-sinter workers, all			
				Ever	493	1.1 (1.0 – 1.2)	
				≥ 5 years	416	1.1 (1.0 – 1.3)	
Canadian nickel refinery facilities (INCO, now Vale Canada, Ontario) Seilkop 2016	Various cohorts, the main ones listed here	Estimated based on dust measurements and process information	Mortality and incidence	Mortality (1950-2000)		SMR	
				Coniston sinter, ever	16	2.3 (1.3 - 3.7)	
				Copper Cliff sinter, ever	144	2.1 (1.8 – 2.5)	
				Port Colborne, leaching, calcining, sintering, ever	115	1.8 (1.5 – 2.2)	
				Port Colborne, electrolysis department, never sinter	68	1.2 (0.95 – 1.5)	
				Sudbury non-sinter workers, mining, never sinter	897	1.1 (1.1 – 1.2)	
				Sudbury non-sinter workers, smelter/refining, never sinter	808	1.1 (1.1 – 1.2)	
				Sudbury non-sinter workers, all, never sinter	1434	1.1 (1.0 – 1.2)	
				Inicidence (1969-2000)		**SIR**	
				Coniston sinter, ever	14	1.9 (1.0 – 3.2)	
				Copper Cliff sinter, ever	165	2.0 (1.7 – 2.3)	
				Port Colborne, leaching, calcining, sintering, ever	96	1.3 (1.1 – 1.6)	

Cohort (Reference)	Cohort description	Exposure assessment	Outcome	Exposure	N of cases	Relative risk (95% CI)	Comments
				Port Colborne, electrolysis department, never sinter	68	1.1 (0.83 – 1.4)	
				Sudbury non-sinter workers, mining, never sinter	1036	1.1 (1.1 -1.2)	
				Sudbury non-sinter workers, smelter/refining, never sinter	924	1.1 (1.0 - 1.2)	
				Sudbury non-sinter workers, all, never sinter	1619	1.1 (1.0 – 1.1)	
Alloy manufacturers Arena 1998	Cohort of 31 165 workers from 13 US nickel alloy production plants	Estimated based on measured data	Mortality			SMR	
				Comparison to US national rates			
				Total	955	1.13 (1.06 – 1.21)	
				White men	831	1.13 (1.05 – 1.21)	
				Non-white men	78	1.08 (0.85 – 1.34)	
				Women	46	1.33 (0.98 – 1.78)	
				Comparison to local rates			
				Total	955	1.01 (0.95 – 1.08)	
				White men	831	1.02 (0.96 – 1.10)	
				Non-white men	78	0.82 (0.66 – 1.03)	
				Women	46	1.26 (0.94 – 1.68)	

Table 48: Summary of the most relevant cohort studies and nested case-control studies therein assessing the association between occupational exposure to nickel compounds and nasal cancer. Standardised mortality ratios (SMR) and other risk estimates are expressed in decimal form, i.e. no increase of risk equals a value of 1.00.a value of 1.00.

Cohort (Reference)	Cohort description	Exposure assessment	Outcome	Exposure	N of cases	Relative risk (95 % CI)	Comments
Welsh nickel refinery workers Easton 1992	Cohort of workers with ≥ 5 years of employment hired 1902-69 or between 1953-92 and followed through 1982 and 2000 respectively	Estimated based on process knowledge, subjective impressions of relative dustiness, and a few measurements	Mortality				
				Year of first employment		SMR	
Easton 1992				1902 – 1919	55	376 (284 – 493)	
Easton 1992				1920 – 1929	12	72.6 (37.5 – 127)	
Easton 1992				1930 – 1939	1	14.3 (0.36 – 80.0	
Easton 1992				1940 – 1949	0	0.00	
Sorahan 2005				1953 – 1992	1	9.95 (0.25 – 55.4)	
Grimsrud 2006				1930 – 1992	2	8.70 (1.05 – 31.4)	
Norwegian nickel refinery workers Andersen 1996	Cohorts of 379 workers with 1st employment 1916-40 and employed for ≥ 3 years and 4385 workers with 1st employment in 1946-83 and ≥ 1 year of employment	Air measurements since 1973, but very few before that year	Incidence			SIR	
				Soluble nickel compounds Highest cumulative exposure category ≥ 15 mg/m³ year	15	81.7 (45.0– 135)	
				Nickel oxide Highest cumulative exposure category ≥ 15 mg/m³ year	13	36.6 (19.5 – 62.5)	
				All	32	18.0 (12.3 – 25.4)	
Finnish nickel refinery Anttila 1998	1388 workers employed for ≥ 3 months between 1945-85 followed through 1995	Air measurements available beginning in 1966	Incidence			SIR	
				Refinery			
				Overall	2	41.1 (4.97 – 148)	
				Latency ≥ 20 years	2	67.1 (8.12 – 242)	
				Smelter			
				Overall	0	0.00 (0.00 – 24.8)	

Cohort (Reference)	Cohort description	Exposure assessment	Outcome	Exposure	N of cases	Relative risk (95% CI)	Comments
				Latency ≥ 20 years	0	0.00 (0.00 – 46.1)	
				All exposed Overall Latency ≥ 20 years	 2 2	 8.79 (1.06 – 31.7) 15.9 (1.92 – 57.3)	
Finnish nickel refinery Pavela 2017	1309 workers employed for ≥ 3 months between 1945-85 followed from 1967 to 2011	Air measurements available beginning in 1966	Incidence	 Refinery	 3	SIR 26.7 (5.50 – 78.0)	
				Maintenance	1	13.3 (0.34 – 7.21)	
				Smelter	0	0.00 (0.00 – 18.3)	
				All exposed	4	9.52 (1.15 – 34.4)	
Canadian nickel refinery facilities (INCO Ontario) ICNCM 1990	Cohorts of workers from three facilities	Estimated based on dust measurements and process information	Mortality	Coniston sinter facility Ever ≥ 5 years Copper Cliff sinter facility Ever ≥ 5 years Port Colborne leaching, calcining and sintering facility Ever ≥ 5 years Port Colborne Electrolysis Ever ≥ 5 years Sudbury, non-sinter workers with no electrolysis work	 0 0 6 6 19 15 0 0 6	 0.00 0.00 36.2 (13.3 – 78.9) 131 (35.8 – 337) 77.8 (46.8 – 121) 188 (105 – 305) 0.00 0.00 1.5 (0.6 – 3.3)	

Cohort (Reference)	Cohort description	Exposure assessment	Outcome	Exposure	N of cases	Relative risk (95% CI)	Comments
Canadian nickel refinery facilities (INCO, now Vale Canada, Ontario) Seilkop 2016	Various cohorts, the main ones listed here	Estimated based on dust measurements and process information	Mortality and incidence	Mortality (1950-2000)		SMR	
				Coniston sinter, ever	0	0.00	
				Copper Cliff sinter, ever	10	30.3 (14.5 – 55.7)	
				Port Colborne, leaching, calcining, sintering, ever	24	61.7 (39.5 – 91.9)	
				Port Colborne, electrolysis department, never sinter	x	Not increased, but 210onfidential N of cases	
				Sudbury non-sinter workers, mining, never sinter	5	1.2 (0.4 – 2.8)	
				Sudbury non-sinter workers, smelter, never sinter	4	1.0 (0.3 – 2.7)	
				Sudbury non-sinter workers, all, never sinter	9	1.3 (0.6 – 2.4)	
				Incidence (1969-2000)		**SIR**	
				Coniston sinter, ever	0	0.00	
				Copper Cliff sinter, ever	18	19.2 (11.4 – 30.4)	
				Port Colborne, leaching, calcining, sintering, ever	17	20.0 (11.6 – 32.0)	
				Port Colborne, electrolysis department, never sinter	X	Not increased, but 210onfidential N of cases	
				Sudbury non-sinter workers, mining, never sinter	15	1.4 (0.8 – 2.3)	
				Sudbury non-sinter workers, smelter, never sinter	18	1.8 (1.1 – 2.9)	
				Sudbury non-sinter workers, all, never sinter	29	1.6 (1.1 – 2.3)	

Cohort (Reference)	Cohort description	Exposure assessment	Outcome	Exposure	N of cases	Relative risk (95% CI)	Comments
Oak Ridge Gaseous Diffusion Plant worker cohort (ICNCM 1990)	Cohort of 813 men exposed to metallic nickel	Estimated based on measurements done in 1948-63	Mortality	Total	0	SMR 0.0 (0.0 – 5.1)	

Table 49: Estimated average (or range) airborne exposure levels in some nickel exposed cohorts.

Cohort / depratment	Estimated expsoures (mg Ni / m³)					Reference
	Sulfidic	Oxidic	Soluble	Metallic	Total Ni	
Clydach, calciners						ICNMC 1990
1902 – 1930, linear calciner	6.8	18.8	0.8	5.3	30	
1930 – 1936, linear calciner	9.0	16.5	0.8	3.0	30	
1937 – 1949, rotary calciner	2.3	6.3	0.3	0.8	10	
1950 – 1954, rotary calciner	1.3	6.8	0.3	1.3	10	
1955 – 1959, rotary calciner	0.3	8.8	0.8	-	10	
1960 – 1971, rotary calciner	0.2	2.3	0.4	0.2	3	
1972 – 1979, Shed 4	0.2	2.3	0.4	0.2	3	
1902 – 1936, milling and grinding	6.8	18.8	0.8	5.3	30	
Copper Cliff sinter plant						ICNCM 1990
1948 – 1954	15 – 35	25 – 60	< 4	0	40 – 100	
1955 – 1963	3 – 15	5 – 25	< 2	0	8 – 40	
Coniston sinter plant	1 – 5	0.1 – 0.5	0	0	1 – 5	ICNCM 1990
Port Colborne leaching, calcining, sintering						ICNCM 1990
1926 – 1935	10 – 20	20 – 40	<3	0	30 – 80	
1936 – 1945	2 – 10	3 – 15	<3	0	5 – 25	
1946 – 1958	3 – 15	5 – 25	<3	0	8 – 40	
Port Colborne electrolysis department						ICNCM 1990
General	< 0.5	< 0.2	< 0.3	< 0.5	< 1	
Pumping anode slime, washing anode scrap	< 0.8	< 0.2	1-3	< 0.2	< 4	
Sudbury, non-sinter workers						ICNCM 1990
Mining	< 0.5	0	0	0	< 0.5	
Milling	< 0.25	0	0	0	< 0.25	
Smelter					< 1	
Iron ore recovery	< 0.2	< 1	<0 .2	< 0.1	< 1	
Copper refinery	0	< 0.5	< 0.1	< 0.1	< 0.5	
Kristiansand (old estimates)						

Cohort / depratment	Estimated expsoures (mg Ni / m^3)					Reference
Roasting, smelting and calcining						ICNCM 1990
1946-1967	<0.5	2 - 8	0	<0.5 – 2		
1969-1977	0 – 2	0.5 - 8	0	<0.5		
1978-1984	<0.5	<0.5	0	0		
Electrolysis						
1946-1967	0 – 2	<0.5 – 2	<0.5 – 8	<0.5 – 2		
1969-1977	0 – 2	<0.5 – 2	<0.5 – 8	<0.5 – 2		
1978-1984	0	<0.5	<0.5 – 2	<0.5		
Kristiansand (new estimates)						Grimsrud 2003
Old smelter building						
1910-1929	0.08	3.4	0.4	0.04	4.0	
1930-1950	0.08	3.1	0.4	0.32	4.0	
1951-1977	0.10 – 0.18	1.8 – 3.0	0.26 – 0.44	0.5 – 0.8	2.6 - 4.4	
Calcining, smelting department						
1951-1977	0.08 – 0.17	1.3 – 2.9	0.15 – 0.34	0.015 – 0.034	1.5 – 3.4	
1978-1994	0.007	0.4	0.06	0.005	0.5	
Roasting department						
1910-1977	0.29 – 0.80	1.4 – 3.8	0.19 – 0.53	0.06 – 0.16	1.9 – 5.3	
1978-1994	0.02	0.32	0.06	0.0	0.4	
Nickel electrolysis						
1910-1977	0.005 – 0.01	0.008 – 0.016	0.09 – 0.17	$\underline{\leq}$0.002	0.1 – 0.2	
1978-1994	0.001 – 0.004	0.003 – 0.011	0.02 – 0.08	$\underline{\leq}$0.002	0.03 –0.1	
Harjavalta						Anttila et al. 1998
Smelter	0.02 – 0.2	0	0	0		
Refinery	< 0.4	0	0.25	0		
Oak Ridge Gaseous Diffusion Plant	0	0	0	<0.1 – 1.8		ICNCM 1990