Nickel dinitrate

CAS-No.: 13138-45-9

EINECS-No.: 236-068-5

RISK ASSESSMENT

Final version
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Chapters 0, 1, 2, 4, 5, 6 & 7 – human health only

Danish Environmental Protection Agency

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Foreword to Draft Risk Assessment Reports

This risk assessment of the priority substance covered by this Draft Risk Assessment Report is carried out in accordance with Council Regulation (EEC) 793/93 (EEC, 1993) on the evaluation and control of the risks of "existing" substances. Regulation 793/93 provides a systematic framework for the evaluation of the risks to human health and the environment of these substances if they are produced or imported into the Community in volumes above 10 tonnes per year.

There are four overall stages in the Regulation for reducing the risks: data collection, priority setting, risk assessment and risk reduction. Data provided by Industry are used by Member States and the Commission services to determine the priority of the substances which need to be assessed. For each substance on a priority list, a Member State volunteers to act as "Rapporteur", undertaking the in-depth Risk Assessment and if necessary, recommending a strategy to limit the risks of exposure to the substance.

The methods for carrying out an in-depth Risk Assessment at Community level are laid down in Commission Regulation (EC) 1488/94 (EC, 1994a) which is supported by a technical guidance document (European Commission 1996, 1997). Normally, the "Rapporteur" and individual companies producing, importing and/or using the chemicals work closely together to develop a draft Risk Assessment Report, which is then presented to the Competent Group of Member State experts for endorsement. Observers from Industry, Consumer Organisations, Trade Unions, Environmental Organisations and certain International Organisations are also invited to attend the meetings. The Risk Assessment Report is then peer-reviewed by the Scientific Committee on Health and Environmental Risks (SCHER) which gives its opinion to the European Commission on the quality of the risk assessment.

This Draft Risk Assessment Report is currently under discussion in the Competent Group of Member State experts with the aim of reaching consensus. During the course of these discussions, the scientific interpretation of the underlying scientific information may change, more information may be included and even the conclusions reached in this draft may change. The Competent Group of Member State experts seek as wide a distribution of these drafts as possible, in order to assure as complete and accurate an information basis as possible. The information contained in this Draft Risk Assessment Report does not, therefore, necessarily provide a sufficient basis for decision making regarding the hazards, exposures or the risks associated with the priority substance under consideration herein.

This Draft Risk Assessment Report is the responsibility of the Member State rapporteur. In order to avoid possible misinterpretations or misuse of the findings in this draft, anyone wishing to cite or quote this report is advised to contact the Member State rapporteur beforehand.

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Not included in this report.

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0.2.1 OCCUPATIONAL ASSESSMENT

(X) i) There is need for further information and/or testing

(X) ii) There is at present no need for further information and/or testing or for risk reduction measures beyond those which are being applied

(X) iii) There is a need for limiting the risks: risk reduction measures which are already being applied shall be taken into account

Conclusion (i) (on hold) is reached because:

- There is a need for further studies to evaluate the possible effects of nickel nitrate on germ cells, but further testing is not considered practicable.

Conclusion iii) is reached because:

- The risk assessment has shown that following inhalational exposure and for the endpoints: acute toxicity, respiratory sensitisation, repeated dose toxicity, carcinogenicity, effects on fertility and development; concern is expressed for all inhalational exposure scenarios in relation to worst case exposure levels. For typical exposure levels concern is expressed to the majority of the end points/ exposure scenarios.

Conclusion ii) is reached because:

- The risk assessment has shown that following typical inhalational exposure for some scenarios effects on acute toxicity, fertility and development, and for all scenarios for dermal exposures for acute and repeated dose toxicity, irritation, sensitisation, carcinogenicity and reproductive toxicity, there is no need for limiting the risks taking into account the risk reduction measures that are already being applied.

0.2.2 CONSUMER ASSESSMENT

There is no known consumer exposure to nickel nitrate.

0.2.3 INDIRECT EXPOSURE VIA THE ENVIRONMENT

See the common MvE RAR for the nickel substances (nickel; nickel carbonate; nickel chloride; nickel dinitrate and nickel sulphate): "Humans exposed indirectly via the environment and combined exposure - exposure assessment and risk characterisation".

0.2.4 COMBINED EXPOSURE

See the common MvE RAR for the nickel substances (nickel; nickel carbonate; nickel chloride; nickel dinitrate and nickel sulphate): "Humans exposed indirectly via the environment and combined exposure - exposure assessment and risk characterisation".

0.2.5 PHYSICOCHEMICAL PROPERTIES

( ) i) There is need for further information and/or testing

(X) ii) There is at present no need for further information and/or testing or for risk reduction measures beyond those which are being applied

( ) iii) There is a need for limiting the risks: risk reduction measures which are already being applied shall be taken into account

Conclusion ii) is reached because:

- Nickel dinitrate is an oxidiser and there is concern for flammability. However, compliance with proper risk reduction measures should be adequate to meet the concerns. There is no concern for explosive properties of nickel dinitrate.

1. GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

Table 1.1.A: Substance Identification

CAS No.:	13138-45-9	14216-75-2
EINECS No.:	236-068-5	238-076-4
EINECS Name:	nickel dinitrate	nitric acid, nickel salt
Synonyms:	nickel (2+) nitrate; nickel bis(nitrate); nickel (II) nitrate; nickel bisnitrate; nickel nitrate; nickelous nitrate	
Molecular formula:	$Ni(NO_3)_2$	
Structural formula:		
Molecular weight:	182.71	

There are two entries for nickel nitrate in EINECS. Only one of these (236-068-5) is included in the fourth list of priority substances (EC, 2000b) under Council Regulation (EEC) 793/93 (EEC, 1993).

The second substance (238-076-4) is also a nickel(II) salt of nitric acid. This second substance is not included in the TSCA Inventory. The risk assessment is also considered to apply to this substance.

Nickel nitrate forms a number of hydrates. These are shown in the Table below.

Table 1.1.B: Hydrates of nickel nitrate (Hindenburg, 2001).

Species	**CAS-No**	**Molecular weight**	**Stability range**
$Ni(NO_3)_2$	13138-45-9	182.71	240 – 260 °C
$Ni(NO_3)_2 .2H_2O$		218.74	detected in solution: 85.4 – 119.8 °C
$Ni(NO_3)_2 .4H_2O$		254.77	detected in solution: 54 – 85.4 –°C
$Ni(NO_3)_2 .6H_2O$	13478-00-7	290.80	detected in solution: -34.1 – 54 °C
$Ni(NO_3)_2 .9H_2O$		344.85	detected in solution: -27.8 – -11.1 °C

Similar but not identical temperatures for the stability ranges for the different hydrates are given by Lascelles *et al*. (1991). Nickel nitrate hexahydrate looses water on heating and eventually decomposes forming nickel oxide. The loss of the individual waters of hydration upon heating the hexahydrate can be studied and the existence of the anhydrous covalent compound can be observed, before it decomposes, using differential thermal analysis and thermogravimetric analysis techniques (Antonsen, 1981, quoted from HSDB, 2003).

The EINECS number shown in Table 1.1.A applies to all the hydrates of nickel nitrate shown in Table 1.1.B. The criteria for reporting for the EINECS Inventory (CEC, 1982) states in Point 14:
"Hydrates of a substance or hydrated ions, formed by association of a substance with water should not be reported. The anhydrous form can be reported and will, by implication, represent all hydrated forms."

The EINECS inventory therefore lists the CAS number for the anhydrous form (13138-45-9) together with the EINECS number (236-068-5) associated with this CAS number. As the rule quoted above indicates, this EINECS number represents by implication all hydrated forms, whether or not they are shown with a CAS number in Table 1.1. B above.

Nickel nitrate with CAS No.: 13138-45-9 is included in the European Customs Inventory of Chemical Substances (ECIS, 1997) with the number 20750. The hexahydrate with CAS No.: 13478-00-7 is also included in ECIS with the number 39097.

Both substances are included in the European Community's Combined Nomenclature (eight digit CN code). The CN is based on the "Harmonized Commodity Description and Coding System" emanating from WCO, in use throughout the world. The substances can be registered under two CN numbers. The first number is 2834 29 10, the second 2834 29 20. Both relate to "other" carbonates. The 2834 29 10 CN number includes barium, beryllium, cadmium and cobalt nitrates. The 2834 29 20 CN number includes barium, beryllium, cadmium, cobalt and lead nitrates.

1.2 PURITY / IMPURITIES, ADDITIVES.

Nickel nitrate is available as the hexahydrate as a laboratory reagent of > 99% purity and as crystals and flakes (J.T. Baker, 1988, quoted in IARC, 1990).

Nickel ammonium nitrate ($H_3N.xHNO_3.xNi$, CAS No. 22026-79-5) is formed in the commercial methods where nickel nitrate is produced from nickel metal (Antonsen, 1996).

Nickel nitrate is commercially available as a solid or as a solution.

Table 1.2.A: Purity of a commercially available nickel nitrate hexahydrate (HEDSET, 2003a).

	CAS-No [1].	**Name**	**Value**
Purity:		nickel nitrate hexahydrate	> 95 %
Impurities:		sodium	< 2 %
		calcium	< 0.3 %
		sulphate	< 2 %

1: No CAS numbers are included for these metals, as the limit values shown here do not relate specifically to the metal but relate to the total amounts of metallic impurity.

Nickel nitrate solution is marketed at concentrations of about 18%.

Table 1.2.B: Purity of a commercially available nickel nitrate solution (PCF, 2004).

	CAS-No [1].	**Name**	**Value**
Purity:		nickel	13.8 – 14.2 %
Impurities:		chloride	≤ 100 ppm
		sulphate	≤ 200 ppm
		calcium	≤ 10 ppm
		chromium	≤ 10 ppm
		cobalt	≤ 200 ppm
		copper	≤ 50 ppm
		iron	≤ 100 ppm
		lead	≤ 20 ppm
		magnesium	≤ 10 ppm
		manganese	≤ 10 ppm
		potassium	≤ 10 ppm
		sodium	≤ 30 ppm
		zinc	≤ 10 ppm

1: No CAS numbers are included for these metals, as the limit values shown here do not relate specifically to the metal but relate to the total amounts of metallic impurity.

Nickel nitrate may contain nitric acid, either as an impurity from the production process or as an additive as an ingredient that acts with specific properties in the finished product.

Nitric acid may be present as an impurity from the production process in nickel nitrate solutions at concentrations from 0 – 4% (PCF, 2004). The maximum concentration of nitric acid in other products is lower. Königswarter & Ebell produce a nickel nitrate solution with pH from 3 – 4.5, and the concentration of nitric acid in the solution is < 1% (Königswarter & Ebell, 2004).

Nitric acid (EC No. 231-714-2) can also be present as an additive. Some nickel nitrate products contain nitric acid at a concentration of up to ca. 10% (IUCLID, 2003).

1.3 PHYSICO-CHEMICAL PROPERTIES

Table 1.3.A: Summary of the physico-chemical properties of nickel nitrate hexahydrate

	Value	Comment	Reference
Physical State:	solid	green deliquescent crystals	IARC (1990), NiPERA (1996), US ATSDR (1997).
Melting Point:	56.7 °C	dissolves in its own water of crystallisation	IARC (1990), Lascelles *et al.* (1991), NiPERA (1996), US ATSDR (1997). IUCLID (2003)
Boiling Point:	136.7 °C	decomposes	IARC (1990), NiPERA (1996), US ATSDR (1997), IUCLID (2003).
Density:	2.05 g/cm^3		NiPERA (1996), US ATSDR (1997), IUCLID (2003).
Vapour Pressure	no data		US ATSDR (1997), IUCLID (2001), IUCLID (2002, 2003), HEDSET (2002a)
	not applicable	crystalline solid	HEDSET (2002b)
LogK_{ow}	no data		US ATSDR (1997), IUCLID (2001), IUCLID (2002, 2003).
	not applicable		HEDSET (2002a)
		crystalline solid	HEDSET (2002b).
Water Solubility:	2385 g/l at 0°C	see also section 1.3.2 below.	IARC (1990), NiPERA (1996), TERA (1999), US ATSDR (1997).
Surface Tension	no data		IUCLID (2001), IUCLID (2002, 2003) HEDSET (2002b)
Flash Point	no data		US ATSDR (1997), IUCLID (2001), IUCLID (2002, 2003)
Autoflammability	no data		US ATSDR (1997), IUCLID (2001), IUCLID (2002, 2003).
Flammability	no data		US ATSDR (1997), IUCLID (2001), IUCLID (2002, 2003)
Explosive Properties	not explosive		Hindenburg (2001).
	no data		IUCLID (2003).
Oxidising Properties		Classified as oxidising. See section 1.3.3 below	Hindenburg (2001), HEDSET, (2002b)
		other: contact with combustible material may cause fire	IUCLID (2003)
Viscosity	no data		IUCLID (2001), IUCLID (2002)

	Value	Comment	Reference
	not applicable		Hindenburg (2002a)
		crystalline solid	HEDSET (2002b)

Table 1.3.B: Summary of the physico-chemical properties of nickel nitrate solution (PCF, 2004).

	Value	Comment
Physical State:	liquid	green
Odour		slightly acid
pH	0 – 6	
Boiling point	from 106°C	for a solution with 14.2 % nickel metal
Melting point	not applicable	
Crystallisation temperature.	from - 25°C	for a solution with 14 % nickel metal
Flash Point	no data	
Flammability	no data	
Autoflammability	no data	
Vapour pressure	no data	
Density	1.45 – 1.55 g/cm^3	
Water Solubility:	2280 g/l at 25 °C	
Viscosity	no data	
Oxidising Properties		14 % nickel nitrate solutions are not classified as oxidising.

1.3.1 Conversion factors:

(101 kPa, 20 °C): 1 ppm = [...] mg/m³; 1 mg/m³ = [...] ppm

1.3.2 Water solubility of nickel nitrate.

The available literature on the aqueous solubility of inorganic nickel compounds has been reviewed (Carlsen, 2001).

Nickel nitrate is reported to be virtually freely soluble in water. Thus, at 25°C a saturated solution of $Ni(NO_3)_2 \cdot 6H_2O$ is reported to contain 49.8 (CRC, 2000) or 50.0 (Linke, 1965) gr/100 g solution, respectively, corresponding to a concentration of 3.44 mol/L. The solubility increases slightly with temperature. Thus at 0°C and 50°C the solubilities were estimated to be 2.48 and 4.79 mol/L, respective. Within this temperature range the solid phase is $Ni(NO_3)_2 \cdot 6H_2O$. At higher temperatures the number of crystal water molecules is reduced to 4 (around 54°C) and to 2 around 90°C (see also Table 1.1.B) (Carlsen, 2001).

It appears that nickel nitrate in more concentrated solutions, i.e., >0.5 eq/L, is not fully dissociated. The degree of dissociation has been found to be 28, 44, 54 and 63% at concentrations equal to 4, 2, 1, and 0.5 eq/L, respectively (Gmelin, 1966a, quoted from Carlsen, 2001).

In the presence of excess of nitrate ions, the tetravalent hexanitrato nickelate ion may be formed. Thus, the potassium hexanitrato nickelate, $K_4Ni(NO_3)_6$, appears to be easily dissolved in water (Gmelin, 1966b). No further data on the hexanitrato nickelate ion has been retrieved (Carlsen, 2001).

1.3.3 Oxidising properties.

Nickel nitrate is classified in UN Transport class 5.1 (oxidising substances), packaging group III (see section 1.4.1.1. below).

The substance was first included in class 5.1 in the Transport Regulations in 1977. This classification predates the UN Transport Manual of Tests and Criteria. When the section of the Manual of Tests and Criteria on class 5.1 was developed, several substances were tested, including nickel nitrate, and examples of tests results were given in 34.4.1.5, with a warning that these were illustrative only since the tests results depend on several factors such as granulometry (Kervella, 2003).

The criteria for packaging group III given in the Manual of Tests and Criteria (UN, 1999) require that the mean burning time for a 4:1 or 1:1 sample-to-cellulose ratio (by mass) exhibits a mean burning time equal to or less than the mean burning time of a 3:7 mixture (by mass) of potassium bromate and cellulose (and the criteria for packaging groups I or II are not met).

The results shown in the Manual are given in the table below.

Table 1.3.B: Oxidising properties of nickel nitrate (UN, 1999).

	Mean burning times (s)	
	4:1 (1)	1:1 (1)
nickel nitrate	101	221
	2:3 (1)	3:7 (1)
potassium bromate	54	100

1: sample:cellulose ratio (by mass).

The test result given in the Manual for nickel nitrate is 101 s, which is just higher than the limit for classification in class 5.1 (100 s for a 3:7 potassium bromate sample). This result is reported as negative ("Not 5.1"), which implies that the substance as tested did not belong to class 5.1 (UN, 1999).

The manual includes a footnote, pointing out that the substance is currently classified in packaging group III (UN, 1999). When the new criteria were adopted, it was agreed that the classification of substances already listed would remain unchanged, unless a specific request for reclassification was made and accompanied with a comprehensive full data sheet on the substance. No specific request for a change in classification of nickel nitrate has subsequently been made. As a result, according to Transport Regulations, nickel nitrate must be classified as a substance in class 5.1, packaging group III, unless the producer can prove, on the basis of tests performed according to the UN Manual of Tests and Criteria, that the substance does not meet the class 5.1 criteria (Kervella, 2003).

In the absence of any additional data to provide further evidence that the substance is not oxidising, the Rapporteur accepts that the substance should be classified as a Category 3 oxidising solid according to the criteria of the Globally harmonised system of classification and labelling of chemicals (GHS) (UN, 2003).

1.3.4 Summary

The data on physico-chemical properties are based on information from reviews, data supplied by the producers and additional information from the UN ECE Transport Division.

Whilst information is available for the flash point, flammability and autoflammability of nickel sulphate and nickel chloride, no data is available for these properties for nickel nitrate. This information is regarded as "not applicable" in two HEDSET submissions (HEDSET 2000a, 2000b). The US Coastguard (1984-5) includes under Fire potential "Contact of solid with wood or paper may cause fires", Hawley's Condensed Chemical Dictionary (1987) includes: "Hexahydrate dangerous fire risk." (quoted from HSDB, 2003).

Additional information is required on the flammability / autoflammability of nickel nitrate. Otherwise, the data are considered sufficiently reliable to fulfil Annex VIIA requirements.

1.4 CLASSIFICATION

1.4.1 Current classification

1.4.1.1 UN Transport labelling.

Nickel nitrate is included as a specific entry in the UN Recommendations on the Transport of Dangerous Goods (UN, 2001) and ADR (UN ECE 2001b).

	UN Number	Class	Subsidiary risk	Packaging Group
Nickel nitrate (Nickel (II) nitrate, nickelous nitrate)	2725	5.1		III

Class 5.1 is for oxidising substances. These are substances which, while in themselves not necessarily combustible, may, generally by yielding oxygen, cause, or contribute to, the combustion of other material. Such substances may be contained in an article (UN, 2001).

The same classification applies for air transport (ICAO, IATA) (Hindenburg, 2001).
Nickel nitrate is not included in Annex B.2 – Appendix 4 of the ADN (UN ECE, 2001a).

Nickel nitrate solution is transported under UN No. 3264 (Corrosive liquid, acidic, inorganic, N.O.S) as class 8, label 8 and packaging group II (PCF, 2004).

1.4.1.2 Classification according to Directive 67/548/EEC.

Nickel nitrate is not currently included in Annex I to Directive 67/548/EEC (EEC, 1992a). For compounds not included in Annex I, Industry is required to evaluate the available data to evaluate the hazard, and to apply a provisional classification.

Several different provisional classifications are used by Industry.

Classification						Reference
	Carc. Cat. 1; R45	T; R23/24/25	C; R34			IUCLID, 2001
O; R8	Carc. Cat. 1; R45 (1)	Xn; R22		R43		HEDSET (2003a)
O; R8	Carc. Cat. 3; R40	Xn; R22	C; R34	R42/43		HEDSET (2002b)
O; R8	Carc. Cat. 3; R40	Xn; R22	C; R34	R43	N; R50/53	IUCLID (2003)
O; R8	Carc. Cat. 3; R40	Xn; R22		R42/43 (2)	N; R50/53	IUCLID (2003)
(3)	Carc. Cat. 3; R40	Xn; R22	Xi; R38/41	R43	(4)	PCF (2004)
O; R8		Xn; R22	Xi; R38/41			HEDSET (2003b)
O; R8		Xn; R22		R43		HEDSET (2002a)

1) The classification category is not shown. Category 1 is assumed on the basis of the IARC conclusion and the lack of any animal data.
2) R42 is applied when the nickel solution is used as an aerosol (IUCLID, 2003).
3) This provisional classification is for a nickel nitrate solution; the 14 % solution is not oxidising.
4) The safety data sheet states that no data is available.

These provisional classifications reflect differences in all the endpoints considered.

1.4.2 Proposed classification according to Directive 67/548/EEC.

The for nickel dinitrate (EC No. 236-068-5, CAS No. 13138-45-9) and nitric acid, nickel salt, (EC No. 238-076-4, CAS No. 14216-75-2) has been included for the first time in Annex I of Council Directive 67/548/EEC in the 30th. ATP is[1]:

Classification								
O; R8	Carc. Cat. 1; R49	Repr. Cat. 2; R61	Muta. Cat. 3; R68	T R48/23	Xn; 20/22	Xi; R38-41	R42/43	N; R50-53

Labelling	
Symbols	O, T, N
R Phrases	8-49-61-20/22-38-41-42/43-48/23-68-50/53
S-Phrases	53-45-60-61
Notas	E

Concentration limits according to Annex I of Council Directive 67/548/EEC:

C≥25%:	T, N; R49-61-20/22-38-41-42/43-48/23-68-50/53
20%≤C<25%:	T, N; R49-61-38-41-42/43-48/23-68-51/53
10%≤C<20%:	T, N; R49-61-41-42/43-48/23-68-51/53
5%≤C<10%	T, N; R49-61-36-42/43-48/23-68-51/53
2.5%≤C<.5%:	T, N; R49-61-42/43-48/23-68-51/53
1%≤C<2.5%:	T; R49-61-42/43-48/23-68-52/53
0.5%≤C<1%:	T; R49-61-43-48/20-52/53
0.25 %≤C<0.5 %:	T; R49-43-48/20-52/53
0.1 %≤C<0.25 %:	T; R49-43-48/20
0.01%≤C<0.1%:	Xi; R43

These limits are specific for R38 (20%), R43 (0.01%) and R48/23 (1%).

The entry for Annex I to Directive 67/548/EEC in the 30th ATP is given in Appendix 7.4.

[1] The 30th ATP was adopted by a Technical Progress Committee in February 2007, but has not yet been adopted by the Commission or published in the Official Journal. This classification is therefore not yet legally binding.

2. GENERAL INFORMATION ON EXPOSURE

Nickel nitrate belongs to the group of inorganic nickel compounds. A list of inorganic nickel compounds in EINECS and in the inventory maintained by the US EPA in support of TSCA regulation is shown as an Appendix in the Background Report on Nickel and Nickel compounds.

2.1 PRODUCTION

2.1.1 Production methods.

Nickel nitrate is produced in the EU from nickel metal or from secondary raw materials. A number of other methods are described in the literature (e.g. Antonsen (1981, quoted in IARC, 1990) but these methods do not appear to be used commercially in Europe.

2.1.1.1 Nickel nitrate production from metallic nickel.

Nickel nitrate hexahydrate is prepared on a commercial basis from metallic nickel by (1) slowly adding nickel powder to a stirred mixture of nitric acid and water or (2) a two-tank reactor system, one with solid nickel and one with nitric acid and water (Antonsen, 1981, quoted in IARC, 1990).

Nickel nitrate is made commercially by several methods. Nickel metal reacts vigorously with nitric acid and, if the reaction is not closely controlled, excess heating occurs and causes breakdown of the nitric acid. Nickel ammonium nitrate ($H_3N.xHNO_3.xNi$) (CAS No. 22026-79-5) also forms in the commercial methods that use nitric acid and metallic nickel because nickel absorbs the released hydrogen and catalytically reduces the nitrate anion to ammonia. The methods vary as to the amounts of ammonia formed and the relative concentrations of acid and metal control the ammonia formation. The use of solid nickel such as electrolytic nickel or nickel briquettes enhances ammonia formation. Nickel powder, added slowly to a stirred mixture of nitric acid and water, yields nickel nitrate containing the least ammonia. Adding nitric acid to nickel powder in water results in the formation of considerable quantities of ammonium nitrate (Antonsen, 1996).

The details of nickel nitrate production from nickel pellets at Königswarter & Ebell in Germany have been provided by Hindenburg (2001). The major production steps are feeding, dissolving, filtering, crystallisation, drying and packaging. Nickel pellets are transferred from the pellet production plant to a pellet feed hopper in the nickel nitrate plant. This feeding operation is batch and closed. Nickel pellets are treated with hot nitric acid in a closed vessel to produce a strong liquor (dissolution). The strong liquor is pumped to the crystallisers via filters to remove any suspended solids (filtration). Both dissolution and filtering steps are closed and continuous processes. The strong liquor is fed to the crystallisers, where the temperature of the contents is controlled by means of cooling water coils (crystallisation). The slurry is siphoned off at a controlled rate to the centrifugal separators. The nickel nitrate crystals are separated from the mother liquor in a centrifuge where they are washed by fine water sprays. The wet crystals are transported to a fluid bed dryer while the separated liquor flows to the mother liquor tank. It is recycled from this tank to the reactors. Crystallisation and separation are continuous and partially closed processes. Drying is carried out in a vibrating fluid bed dryer using hot and cold fluidising air. The fluid bed dryer is maintained under slightly negative pressure to prevent dust emission to the atmosphere. The exhaust air passes through a cyclone, exhaust fan and scrubber before discharge to the atmosphere. The packing is fully automated for the marketed product in a batch, closed process (Hindenburg, 2001).

Nickel metal pellets are used as starting material in other production processes. In one process, water is added by a pipe during production, nitric acid is pumped from a tank beside the reactor by a volumetric pump and the nickel grains added by hand. After the batch process, the produced raw material (nickel nitrate solution) is pumped via a stable pipe into a storage tank. The production reactor is not cleaned, i.e. the residues in the reactor are used as a “starter” of the next batch. (Henkel, 2003).

Nickel metal pellets and electrode sheet nickel are used for nickel nitrate production at Pharmacie Centrale de France (PCF, 2002). Nickel metal in the form of briquets, nickel sheets, broken cathodes etc. is dissolved in nitric acid as batch operations. The product is a solution of nickel dinitrate. To produce dry nickel nitrate, the solution is first concentrated and the nickel nitrate is crystallised (PCF, 2003). The production process at Floridienne Chimie SA is very similar (Floridienne Chimie, 2003b).

2.1.1.2 Nickel nitrate production from secondary raw materials.

Nickel nitrate solution is prepared from secondary raw materials at Siegfried Jacob Metallwerke, Ennepetal, Germany (Hindenburg, 2001). Metal hydroxides with used metal residues are dissolved and extracted with a mixture of different waste acids. The solution obtained is then refined by typical chemical separation steps. Nickel and zinc are separated by solvent extraction, whilst copper is produced by electrolysis (Meyer-Wulf 2001). This process is similar to the production of nickel sulphate described in chapter 2.1.1.3 of the nickel sulphate risk assessment report.

Secondary raw materials are used for nickel nitrate production at Pharmacie Centrale de France (PCF, 2002).

No details of the production process have been provided by Industry.

2.1.1.3 Other methods of nickel nitrate production.

A number of methods of nickel nitrate production are described in the literature. None of these methods appears to be in use in the EU at the present time.

A method to eliminate the ammonia formation seen in the reaction between nickel metal and nitric acid employs the addition of nitric acid to a mixture of black nickel oxide powder and hot water. The reaction is controlled using a cooling coil or cold water condenser because the reaction is highly exothermic (Antonsen, 1996). The dissolution of nickel oxide in nitric acid is easier to control than dissolving nickel metal. The hexahydrate is produced by crystallisation of the resulting solution (Lascelles *et al*., 1991). No further information is available about this method of production.

Nickel nitrate hexahydrate is prepared by reaction of dilute nitric acid and nickel carbonate (Antonsen, 1996). No further information is available about this method of production.

Nickel sulphate can also be used to produce nickel nitrate (Meyer-Wulf, 2002). No further information is available about this method of production.

2.1.1.4 Anhydrous nickel nitrate production.

Anhydrous nickel nitrate can be prepared by the reaction of fuming nitric acid and nickel nitrate hexahydrate (Antonsen, 1981, quoted in IARC, 1990). The anhydrous covalent compound ($Ni(NO_3)_2$) is prepared by the addition of methyl glyme to nickel nitrate hexahydrate followed by vacuum distillation and drying (Antonsen, 1996). It is difficult to prepare the pale green anhydrous nickel(II) nitrate by dehydration of the hexahydrate. It can be obtained by dehydration with dinitrogen pentoxide in fuming nitric acid, or from nickel tetracarbonyl and dinitrogen tetroxide (Lascelles *et al*., 1991). Anhydrous nickel nitrate does not appear to be produced use in the EU at the present time. No further information is available about this method of production.

2.1.2 Production volumes

The realistic worst-case figures for nickel nitrate production are shown below.

Table 2.1.2.A: Realistic worst-case production of nickel nitrate in Europe (t / year).

	2001	**2002**
calculated as nickel nitrate hexahydrate		
calculated as $Ni(NO_3)_2$	3300	3300
calculated as Ni		

n.a.: not available.

No specific information on the export of nickel nitrate from the EU is available as customs statistics do not distinguish nickel nitrate from a number of other metal nitrate salts (ECIS, 1997). The gross weight of all nickel salts exported from the EU in 2000 was 7901 t (Laine, 2003). Only limited information on the export of nickel nitrate from the EU is available. The export of nickel nitrate is believed to be limited.

No information has been provided by Industry about the amounts of nickel nitrate produced outside the EU.

No information has been provided by Industry about imports of nickel nitrate to the EU.
No specific information on the import of nickel nitrate to the EU is available as customs statistics do not distinguish between nickel nitrate and a number of other metal nitrate salts (ECIS, 1997). The gross weight of all nickel salts imported to the EU in 2000 was 3980 t (Laine, 2003).

2.1.3 Production sites

In 1988, nickel nitrate was produced by four companies in the UK, two companies each in Germany, France, Italy and Spain, and one company in Belgium (Chemical Information Services Ltd. 1988, quoted in IARC, 1990).

The companies currently producing nickel nitrate in the EU/EEA are shown in the Table below (Hindenburg, 2001). The table also shows some of the different raw materials and products produced.

Table 2.1.3.A: Nickel nitrate producing companies in Europe (Hindenburg, 2001, IUCLID, 2002).

Company	Location	Raw materials	Products
Pharmacie Centrale de France	La Voulte sur Rhone, France	metallic nickel pellets, sheets	nickel nitrate hexahydrate
		secondary raw materials	nickel nitrate solution
Königswarter & Ebell	Hagen, Germany	metallic nickel pellets	nickel nitrate hexahydrate
Siegfried Jacob Metallwerke GmbH	Ennepetal, Germany	secondary raw materials	nickel nitrate solution
Floridienne Chimie S.A.	Belgium	metallic nickel	nickel nitrate hexahydrate
			nickel nitrate solution
Henkel	Caleppio di Settala (MI), Italy	metallic nickel pellets	nickel nitrate solution

Floridienne Chimie has not produced nickel nitrate in recent years (Floridienne Chimie, 2003a).

The information provided by Hindenburg (2001) included BASF, Ludwigshafen, Germany as a producer of nickel nitrate. BASF have subsequently informed the Rapporteur (BASF, 2002) that as their process does not result in any isolated nickel nitrate they are not producers of nickel nitrate. BASF have provided information for IUCLID on nickel nitrate (IUCLID, 2001). IUCLID data for nickel nitrate has also been supplied by MG Chemiehandel, Frankfurt am Main, Germany (IUCLID, 2002).

Nickel nitrate is also produced outside the EU at sites in the US, Brazil, Japan, India, Argentina, Australia, Mexico and Switzerland. (Chemical Information Services Ltd. 1988, quoted in IARC, 1990).

2.2 USE PATTERN

2.2.1 Current Use Pattern

Nickel nitrate is used for:

- Production of catalysts
- Production of nickel-cadmium batteries
- Chemical pre-treatment of metals prior to plating and in cold-forming.

Other uses of nickel nitrate may include the synthesis of other nickel containing compounds.

The main use of nickel nitrate is in the production of catalysts, especially sulphur sensitive catalysts, and as an intermediate in the production of nickel-cadmium batteries (Antonsen, 1981, quoted in IARC, 1990; Lascelles *et al*. 1991, Hindenburg, 2001). Information from ECMA (2002) suggests that a substantial proportion of the estimated 3300 t nickel nitrate used annually in the EU is used in catalyst production.

Some production processes for nickel catalyst and nickel battery production may use nickel nitrate as a non-isolated intermediate. However, the nickel nitrate produced and subsequently used in these processes will not appear in the production or use figures for nickel nitrate.

Nickel nitrate is also to make products used in the pre-treatment of metals prior to painting and prior to cold-forming processes. The concentration of nickel in these products is low (< 5%) (Eurométaux, 2001).

The Merck Index (1996) and Hawley's Condensed Chemicals Dictionary (1997) lists the main uses as nickel plating and the manufacture of brown ceramic colours (quoted from HSDB, 2003). Hawley's Condensed Chemicals Dictionary (1997) also lists preparation of catalysts (quoted from HSDB, 2003).

Information from the Danish Product Registry (2001) shows that nickel nitrate containing products with concentrations < 5% are used for "sales, maintenance and repair of motor vehicles and motor cycles" and for "research and development".

The annual 1994 worldwide usage of nickel nitrate hexahydrate is 8000 tonnes. The price was $3.50/kg (Antonsen, 1996).

No information is available from Industry about the total amounts of nickel nitrate used in the EU. In the absence of any information on import or export of the chemical, the whole of the estimated EU production is assumed to be used in the EU.

2.2.1.1 Nickel nitrate used in the production of catalysts.

The production of catalysts has been described in detail in chapter 2.2.1.5.2 of the risk assessment report on nickel metal.

ECMA (2002) has provided information on catalyst manufacturing feedstocks used by different nickel catalyst producers. Nickel nitrate is an important feedstock as a source of the nickel used in catalyst production. Nickel nitrate also occurs as an intermediate in some processes when nickel metal used as the prime raw material.

From the information supplied by Industry, the production process is similar to that for nickel sulphate, described in section 2.2.1.3 of the risk assessment report for nickel sulphate.

2.2.1.2 Nickel nitrate used in the production of nickel-cadmium batteries.

The production of nickel-cadmium batteries have been described in chapter 2.2.1.4.1.1 of the nickel metal risk assessment report.

Nickel nitrate crystals or solution are used as a feedstock for NiCd battery production (NiPERA, 1996).

Nickel nitrate is an intermediate in loading active mass in nickel-cadmium batteries of the sintered-plate type. Typically, hot nickel nitrate syrup is impregnated in the porous sintered-nickel positive plates. Subsequently, the pores are soaked in potassium hydroxide solution whereupon nickel hydroxide precipitates within the pores of the plate (Antonsen, 1981, quoted in IARC, 1990).

No specific information on the use of nickel nitrate in NiCd battery production has been provided by Industry.

2.2.1.3 Nickel nitrate used in chemical pre-treatment of metals.

Nickel nitrate solution and nickel nitrate hexahydrate are used as components of products used in the pre-treatment of metals prior to painting and prior to cold-forming processes such as tube or wire drawing, cold heading etc..

The main ingredients in the acid phosphating solution are zinc, manganese, nickel, phosphate and nitrate ions. Additionally an accelerator can be used.

The main reactions which occur in the phosphating solution are :

a) etching of the metal by the acid solution
b) depolarisation of the hydrogen atoms developed during etching by the accelerator to prevent the formation of hydrogen gas
c) Deposition of an inorganic crystalline zinc-phosphate layer on the metal.

Nickel nitrate in the phosphating solution results in nickel-phosphate on the metallic surface. This phosphate has the general formula: $ZnMe(P0_4)_2\ nH_2O$, where Me can be Zn, Fe, Mn, Ca and Ni and n is 2 when the metal is Ca, or 4 in all other cases.

About 40-50% of the nickel is going into the zinc/nickel/manganese phosphate layer (which is also called conversion coating). About 20-30% of the introduced nickel goes into the zinc phosphating sludge, that contains mainly iron-phosphate and some zinc phosphate. About 30% is carried out of the treatment bath with the metal parts (e.g. car bodies) that are pretreated before subsequent painting.

This process is also described in the risk assessment report for zinc phosphate prepared by the Netherlands Rapporteur.

Whilst the numbers of companies producing such products is fairly limited, use of the products for metals pre-treatment is widespread, and can take place at up to an estimated five thousand sites across the EU (Eurométaux, 2001). This could be an over-estimate. Information from Chemetall in Germany, a leading supplier of these products, suggests that there are 2000 – 2500 sites in the EU (Chemetall. 2003)

2.2.1.4 Other uses of nickel: Chemicals production.

Black nickel oxide, a finely divided, pure nickel monoxide, is produced by calcining nickel nitrate at 600 °C (Antonsen, 1981, quoted from IARC, 1990). No information has been supplied by Industry about this method of production. Nickel oxide is also used to produce nickel nitrate (see chapter 2.1.1.2 above). According to Antonsen (1996), in 1994 the price of nickel oxide was slightly higher ($4.00/kg) than that of nickel nitrate ($3.50/kg).

2.2.2 Recycling

The major uses of nickel nitrate described above result in the production of catalysts and batteries. NiCd batteries and catalysts and are recycled, and the recycling of these products is described in Chapters 2.2.3.3.3.2 and 2.2.3.3.3.3 of the Risk Assessment report for metallic nickel. The recycling process is intended to recover nickel rather than nickel nitrate specifically.

2.2.3 Discontinued Uses of the Substance

There is no information on any discontinued uses of nickel nitrate that the Rapporteur considers should be considered separately in this risk assessment.

2.2.4 Industrial and use categories for nickel nitrate

Only very limited information on production, import, export or use of nickel nitrate in the EU has been provided by Industry.

No information on EU production, import, export or use have been provided by Industry.

Table 2.2.4.A: Tonnes / year calculated as $Ni(NO_3)_2$. Data for 2001 and 2002.

	2001		2002	
	Tonnes / year	%	Tonnes / year	%
Production	3300		3300	
Import	n.a.		n.a.	
Export	small.		small.	
Used in the EU	3300		3300	

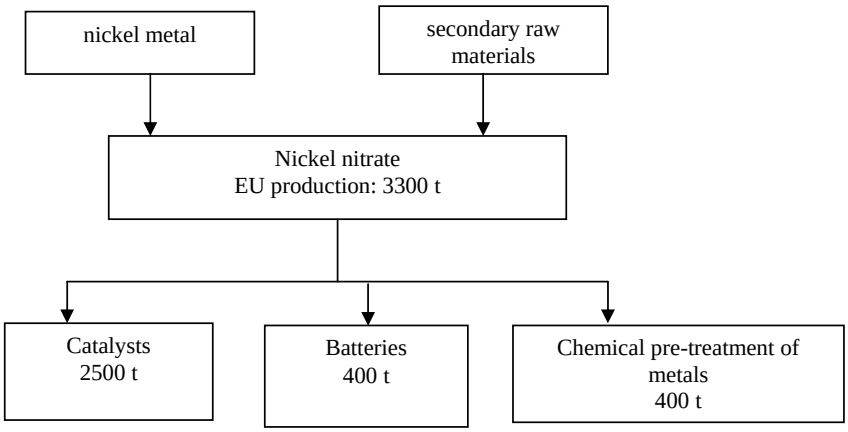
n.a.: not available.

Table 2.2.4.B: Industrial and use categories.

Scenario	Lifecycle Stage	Industry category	Use category	Main category	Tonnes / year	%

Scenario	Lifecycle Stage	Industry category	Use category	Main category	Tonnes / year	%
A1	Production	IC8 (Metal extraction, refining and processing)	UC55 (Others)	MC 1c	3300	
B1	Processing	IC3 (Basic chemical used in synthesis)	UC 33 (Intermediates, other salts, catalysts)	MC3	2500	76.
B2		IC4 (Electrical / electronic industry)	UC 12 (Conductive agents)	MC 3	400	12
B3		IC8 (Metal extraction, refining and processing)	UC 17 (Electroplating agents)	MC3	400	12

Figure 2.2.4.A. Nickel Nitrate. Primary production and first use.



2.3 TRENDS

The use of nickel nitrate in the production of nickel-cadmium batteries is declining (Hindenburg, 2001). No other information has been supplied by industry on which it is possible to evaluate trends in nickel nitrate production or use.

2.4 LEGISLATIVE CONTROLS

The following section follows the description of risk reduction measures described in the Nordic Risk Reduction report (NMR, 2002) and the TGD for risk reduction (European Commission, 1998).

2.4.1 General Measures.

2.4.1.1 Directive 67/548/EEC on dangerous substances.

Nickel nitrate is not included in Annex I to the Directive with a harmonised classification. The substance must therefore be evaluated and, if necessary, be given a provisional classification by the manufacturers and producers (EEC, 1992a). Details of the different provisional classifications used by Industry are shown in Chapter 1.4.1.2. A harmonised Annex I entry for this substance is included in the 30th ATP.

Professional users of users have to be provided with a Safety data sheet by the manufacturer or supplier. The format for Safety data sheets is described in a separate Directive, EC (2001c).

Nickel nitrate is included in EINECS. As described in Chapter 1, the EINECS number shown in Table 1.1.A applies to all hydrates of nickel nitrate.

2.4.1.2 Directive 1999/45/EC on dangerous preparations.

This Directive (EC, 1999) should have been implemented into national law by the Member States by 30th. July 2002 and replaces Directive 88/379/EEC (EEC, 1988).

Classification of hazards of preparations containing nickel nitrate is based on the general rules set out in the Directive. However, specific concentration limits for R38 (skin irritation), R43 (skin sensitisation) and R48/23 (serious effects after repeated exposure) are included in the harmonised Annex I entry in the 30th ATP.

2.4.1.3 National Initiatives.

Nickel nitrate, like other nickel compounds, (see background report on nickel and nickel compounds) is included in the Danish list of undesirable substances (Danish EPA, 2000).

2.4.2 Protection of workers.

The occupational use of nickel nitrate is covered by the provisions of Directive 98/24/EC on the protection of the health and safety of workers from the risks related to chemical agents at work (EC, 1998).

The Directive (Article 3) provides a framework for setting occupational exposure limit values and biological limit values. The Directive requires that risks arising from chemical agents are identified by employers through risk assessment (Article 4) and reduced by application of a set of general principles (Articles 5 and 6), which include substitution, prevention, protection and control. In those instances where a national OEL is exceeded, the employer is to remedy the situation through preventative and protective measures. The figures in Table 2.4.A show the OEL values for nickel nitrate in force in various countries.

Table 2.4.A: Occupational Exposure Limits (OEL) for nickel nitrate in force in various countries (NIPERA, 1996 with updates).

Country/Body	**mg/m^3 as nickel** [(1)]	**Comments**
Austria	0.05	nickel compounds as inhalable droplets
Belgium	0.1	soluble nickel compounds
Denmark	0.01	soluble nickel compounds, Arbejdstilsynet (2000)
France	0.1	soluble nickel compounds, VME (Valeur Moyenne d'exposition)
Finland	0.1	soluble nickel compounds
Germany	0.05	nickel compounds as inhalable droplets. TRK (Technische Richtkonzentrationen) [(2)] (TRGS 900, 2000)
Greece	no information	no information
Ireland	0.1	soluble nickel compounds
Italy	0.1	soluble nickel compounds
Luxembourg	0.1	soluble nickel compounds
The Netherlands	0.1	soluble nickel compounds
Portugal	0.1	soluble nickel compounds
Spain	0.1	soluble nickel compounds
Sweden	0.1	soluble nickel compounds
United Kingdom	0.1	soluble nickel compounds, MEL (Maximum Exposure Limit) based on 'total inhalable' aerosol as measured with the seven-hole sampler. UK HSE (2000).
EU (proposed)	[0.1]	soluble nickel compounds, NiPERA (1996) proposal under discussion in SCOEL.
Norway		nickel and nickel compounds

USA (OSHA)	1.0	PEL (Permissible exposure limit)

1: 8-hour TWA (Time-Weighted Average) unless otherwise noted.
2): In Germany, nickel compounds are classified by MAK as Carc. Cat. 1 if they occur as respirable droplets, and therefore MAK values cannot be fixed for these substances. The MAK list also notes the risk of sensitisation of the skin and respiratory tract (BAuA, 2003).
3) According to German national regulations, soluble nickel salts are classified as Carc. Cat. 1 (TRGS 905, 2002, in connection with EU Regulations) (BAuA, 2003)

ACGIH (1998) has an inhalable Threshold limit Value (TMV) of 0.1 mg Ni /m^3 for soluble nickel compounds.

Nickel nitrate is not currently classified in Annex I to Directive 67/548/EEC. However, some companies have given this substance a provisional classification as a Category 1 carcinogen. The substance is covered by the provisions of Directive 90/394/EEC on the protection of workers from the risks related to exposure to carcinogens at work (EEC, 1990) only for those companies that have provisionally classified the substance as a carcinogen. The same qualification applies to the provisions of Directive 92/85/EEC on the introduction of measures to encourage improvements in the safety and health at work of pregnant workers and workers who have recently given birth and are breastfeeding (EEC, 1992b). For workers exposed to chemicals classified as a carcinogen, mutagen or as toxic for reproduction, this Directive requires that the employer shall assess the nature, degree and duration of exposure in the undertaking and/or establishment concerned, of pregnant workers, workers who have recently given birth and workers who are breast feeding in all activities liable to involve a specific risk of exposure to the agents. Changes to the classification included in Annex I to Directive 67/548/EEC in the 30th ATP will bring the substance within the scope of these Directives when these changes come into force.

The possibility for young people to work with nickel nitrate and nickel nitrate-containing preparations classified as harmful under Directive 88/379/EEC is covered by the provisions of Directive 94/33/EC (EC, 1994b) on the protection of young people at work. This Directive prohibits the employment of young people for work involving exposure to such harmful agents.

The use of personal protective equipment at the workplace is regulated by Directive 89/656/EEC (EEC, 1989). The safety advice given by industry includes labelling with S24-37 (Avoid contact with skin; wear suitable gloves) (Hindenburg, 2001). Other labelling is more comprehensive, and includes the use of S45 (In case of accident ….. seek medical advice…;), S26 (in case of contact with the eyes, rinse immediately with plenty of water and seek medical advice), S36/37/39 (wear suitable protective clothing, gloves and eye/face protection), S23 (do not breathe gas/fumes/vapour/spray (*appropriate wording to be specified by the manufacturer*) (IUCLID 2001). HEDSET (2002) uses S17 (keep away from combustible material), S26 (in case of contact with the eyes, rinse immediately with plenty of water and seek medical advice) and S37/39 (wear suitable gloves and eye/face protection).

2.4.3 Protection of consumers.

There is no specific legislation related to consumer protection for nickel nitrate.

2.4.4 Emissions to water

Legislation related to emissions to water normally addresses concerns related to the nickel ion, rather than to specific nickel compounds.

2.4.4.1 Directive 96/61/EC concerning integrated pollution prevention and control (IPPC)

The Directive (EC, 1996) re is no specific legislation related to consumer protection for nickel nitrate.

Emission limit values shall be based on best available techniques. The Commission has published eight IPPC BAT Reference Documents (BREFs) on Best Available techniques in a number of industries (EC, 2002a).

2.4.4.2 Directive 76/464/EEC on pollution of the aquatic environment by certain dangerous substances.

Nickel is included in List II of families and groups of substances covered by the Directive (EEC, 1976). For further details, see Background report on nickel and nickel compounds.

2.4.4.3 Directive 2000/60/EC establishing a framework for Community action in the field of water policy.

Nickel and nickel compounds are specifically listed in the Decision (EC, 2001d) establishing the list of priority substances in the field of water policy and amending Directive 2000/60/EC (EC, 2000a). For further details, see Background report on nickel and nickel compounds.

2.4.4.4 Directive 80/68/EEC on the protection of groundwater against pollution caused by certain dangerous substances

Nickel is included in List II of families and groups of substances covered by the Directive (EEC, 1980). According to the Water Policy Framework Directive (2000/60/EC, see section 2.4.4.3) the Groundwater Directive will be repealed with effect from 13 years after the data of entry into force of the Directive, that is 22.12.2013. For further details, see Background report on nickel and nickel compounds.

2.4.4.5 Directive 2000/76/EC on the incineration of waste.

Nickel and its compounds are included in Annex III of the Directive (EC, 2000c) which sets emission limit values of 0.5 mg/l (expressed as nickel, Ni) for discharges of waste water from the cleaning of exhaust gases. For further details, see Background report on nickel and nickel compounds.

2.4.4.6 National Legislation.

In Finland, the IPPC Directive is implemented by the Environmental Protection Act (2000/86) (Finland, 2000). In addition to installations listed in Annex I of the IPPC Directive, several other activity categories and activities not exceeding capacity thresholds set in the IPPC Directive require a permit according to the Finnish Act. Concerning nickel emissions, the most important difference is that all surface treatment installations using electrolytic or chemical process require a permit regardless of the capacity. So far permit conditions for nickel have been included in permits issued for the following sectors: mines, smelters, metal refiners, primary and secondary steel production, electrolytic and chemical metal plating (including aluminium anodising) and waste handling (Heiskanen, 2003).

In the Netherlands there is a general prohibition on discharge of nickel to surface water (Netherlands, 1974).

2.4.5 Emissions to air

Legislation related to emissions to air normally addresses concerns related to the nickel ion, rather than to specific nickel compounds.

2.4.5.1 Directive 96/61/EC concerning integrated pollution prevention and control (IPPC)

See section 2.4.4.1 above.

2.4.5.2 Directive 2000/76/EC on the incineration of waste.

The Directive (EC, 2000c) sets air emission limit values for nickel and its compounds. For further details, see Background report on nickel and nickel compounds.

2.4.5.3 National Legislation.

In Finland, the IPPC Directive is implemented by the Environmental Protection Act (2000/86) (Finland, 2000). See Chapter 2.4.4.6 above.

Nickel nitrate emissions are regulated in Germany by TA Luft (2002) under section 5.2.2 (inorganic dusts) in hazard class II, with emission limits expressed as nickel of 2.5 g/h or 0.5 mg/m^3. Nickel nitrate is included in section 5.2.7.1.1. (Carcinogens) with emission limits expressed as nickel of 1.5 g/h or 0.5 mg/m^3.

The Netherlands Emissions Guidelines for air (NeR) regard nickel and nickel compounds as category C.2 carcinogens. C2 carcinogens are carcinogens without a threshold value and compulsory minimisation of emissions is required. Specifically, in the case of an untreated mass flow of 5.0 grams per hour or more, an emission standard of 1.0 mg/m_o^3 (calculated as nickel) applies (Netherlands, 2001). From 1. April, 2003, nickel and nickel compounds are regarded as Class C carcinogens for which compulsory minimisation applies. For an

untreated mass flow of 0.15 g/hr, an emission standard of 0.05 mg/m^3 applies. An immission assessment must be carried out once every five years. (InfoMil, 2003)

2.4.6 Emissions to Soil

2.4.6.1 National Legislation.

In the Netherlands, there is a general prohibition against discharge of liquids containing nickel into soil, although exceptions are possible (Netherlands, 1997).

2.4.7 Waste management.

2.4.7.1 Directive 96/61/EC concerning integrated pollution prevention and control

See section 2.4.4.1 above.

2.4.7.2 Council Directive 91/689/EEC of 12 December 1991 on hazardous waste

Annex II of the Directive (EEC, 1991) includes C5 nickel compounds as constituents of wastes in Annex IB which render them hazardous when they have the properties described in Annex III of the Directive. For further details, see Background report on nickel and nickel compounds.

Lists of hazardous wastes of hazardous wastes have been published as two Commission Decisions (EC, 2001a, 2001b). Decision 2001/118/EC (EC, 2001a) divides wastes into different chapters. These include a number of chapters related to processes relevant to nickel nitrate production and use, such as:
06 Wastes from inorganic chemical processes
11 Wastes from chemical surface treatment and coating of metals and other materials; non-ferrous hydro-metallurgy

Spent catalysts and NiCd batteries are included in Chapter 16: Wastes not otherwise specified in the list.

In general, wastes are classified as hazardous if they fulfil the same classification criteria for dangerous substances and preparations given in Directives 67/548/EEC and 88/379/EEC.

3. ENVIRONMENT

Please consult separate document.

4. HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

4.1.1.1 General

The human population may be exposed to nickel dinitrate:

- at the workplace and
- indirectly via the environment.

Humans may be exposed to nickel dinitrate by different routes:

- by skin exposure,
- by respiratory exposure, and/or
- by oral exposure

4.1.1.1.1 Skin exposure.

Skin exposure to nickel is due to occupational contact with nickel dinitrate, either as a solid or in solution.

4.1.1.1.2 Respiratory exposure.

Respiratory exposure to nickel dinitrate occurs only in an occupational exposure context, by inhalation of aerosols containing nickel dinitrate.

4.1.1.1.3 Oral exposure.

Oral exposure to nickel from nickel dinitrate occurs either by ingestion of nickel aerosols at the workplace, or by indirect exposure to nickel dinitrate released during production or processing. This latter exposure is a contribution to the total nickel intake in food and drinking water, and forms only part of the indirect nickel intake via the environment.

4.1.1.2 Occupational exposure

4.1.1.2.1 General

Occupational exposure to nickel dinitrate may occur by skin contact or by inhalation of aerosols containing nickel dinitrate. Nickel-containing aerosols may also be ingested by nickel workers. By definition an aerosol is an assemblage of small particles, solid or liquid, suspended in air, while dust is an assemblage of small solid particles. Occupational exposure to aerosols may often involve many different substances (metals and non-metals) acting in concert, and nickel-bearing aerosols may contain various chemical species of nickel. Occasionally exposure may be to just one species of nickel, but usually exposure is mixed and involves several nickel compounds and other contaminants. Such mixed exposures complicate the interpretation of health effects related to specific nickel components of the air contaminants. Previous epidemiological studies have based estimates of exposure to different nickel species on knowledge of the metallurgical process, but recent speciation results indicate that this can lead to serious misjudgements (Andersen *et al*, 1998). For the present assessment an emphasis was made to estimate exposure to different nickel species from speciation results. For scenarios involving just one species of nickel exposure to other nickel species was considered unlikely.

Data used for the occupational exposure assessment are:

- Data available from the literature
- Exposure data from the HEDSET
- Data regarding the production processes and use pattern of the products
- Measured data for nickel compounds
- When available monitoring data of the workers
- Physico-chemical data and physical appearance
- Results from exposure models (EASE-model).

EASE is a general-purpose predictive model for workplace exposure assessments. It is an electronic, knowledge based, expert system which is used where measured data are limited or not available. The model is in widespread use across the European Union for the occupational exposure assessment of new and existing substances. All models are based upon assumptions. Their outputs are at best approximate and may be wrong. EASE is only intended to give generalized exposure data and works best in an exposure assessment when the relevance of the modelled data can be compared with and evaluated against measured data.

It is noted that published data and results provided by industry may have a natural bias towards high levels since it is not practice to carry out extensive air sampling surveys where the levels are known or suspected to be very low. Another natural bias is introduced if historical and current data are included for the assessment. Symanski *et al.* (2000) evaluated temporal changes in exposure to nickel aerosols in the nickel-producing and nickel-using industries, and provided evidence of largely downward trends in exposure to nickel aerosols in industries involved with the primary production of nickel and in the manufacture of nickel alloys. However, the decline in nickel aerosols appeared greater for exposures first evaluated during the 1970s compared with data collected in the 1980s and onwards. For the period 1973-1995 Symanski *et al*. (2001) reported statistically significant trends towards lower levels of exposure in the smelting (-6%/year) and refining (-8%/year) sectors of the nickel industry. To minimize bias from trends in exposure the assessment has focus on current data. The exposure is assessed using the available information on the products, processes and work tasks. More detailed information on these parameters may lead to a more accurate exposure assessment.

In this part of the assessment, external exposure is assessed using the available information on substance, processes and work tasks. Internal dose depends on external exposure and the percentage of the substance that is absorbed (through the respiratory system, the gastro-intestinal system, and through the skin). According to the Technical Guidance Document, exposure by inhalation is defined as the concentration of substance in the breathing zone and is usually expressed as a time average concentration over a reference period. By convention this reference period may be either 8 hours to represent long-term exposure or 15 minutes to represent short-term exposure. In general it is difficult to estimate personal exposure from data obtained by area (static) sampling (Leidel *et al*., 1977), and for this assessment priority is given to personal sampling.

The exposure is assessed without taking account of the possible influence of personal protective equipment (PPE). If the assessment as based on potential exposure indicate that risks are to be expected, the use of PPE may be one of the methods to decrease exposure, although other approaches (technical and organizational) are to be preferred. In fact this is obligatory following harmonized European legislation. The efficiency of PPE is largely dependent on site-specific aspects of management, procedures and training of workers. Thus no default factors for reduction of exposure as a result of the use of PPE are used in this part of the assessment.

4.1.1.2.1.1 Scenarios for the occupational exposure assessment.

The production and use of nickel dinitrate involve several industrial sectors as outlined in section 2. The scenarios considered for the occupational exposure assessment are tabulated below (Table 4.1.1.2.1.A).

Table 4.1.1.2.1.A: Scenarios for the risk assessment

Scenario	**Lifecycle stage**	**Industry category** [A]	**Use category** [B]	**Additional**
A1	Production	8	55	Nickel nitrate production from metallic nickel
A2		8	55	Nickel nitrate production from secondary raw materials.
B1	Use of nickel nitrate	3	33	Nickel nitrate used in the production of catalysts
B2		4	12	Nickel nitrate used in the production of nickel-cadmium batteries
B3		8	55	Nickel nitrate used in chemical pre-treatment of metals
B4		15	55	Other uses of nickel: chemicals production

A: 3=Chemical industry: 4=Electrical/electronic engineering industry, 8=Metal extraction industry, refining and processing industry. 15=Others.
B: 12=Conductive agents (sub-category: electrode materials), 33=Intermediates, 55=Others.

The following parameters of exposure are assessed for each scenario:

- full shift reasonable worst-case inhalation exposure level: the exposure level considered representative for a high percentile (90 percentile) of the distribution of full shift exposure levels. If limited data sets are available (e.g. only measurements from one site or only small numbers of measurements or data with little detail on tasks, working conditions, etc.) often the highest measured value is used or the upper range of the results of modelling are preferred;
- full shift typical inhalation exposure level: the exposure level considered representative for a median percentile (50 percentile) of the distribution of full shift exposure levels;
- short term inhalation exposure level: the exposure level considered representative for a high percentile (90 percentile) of the distribution of short term exposure levels; short term exposure is considered to be exposure for less than one hour, with typical duration of approximately 15 minutes;
- dermal exposure level: the exposure level considered representative for a high percentile (90 percentile) of the full shift dermal exposure levels.

4.1.1.2.1.2 Measurement techniques

Over the years, a number of aerosol sampling (and subsequent analytical) procedures have been applied in worker exposure assessment and this may compromise comparison of results. Traditionally sampling was based on the concept of so-called 'total' aerosol with implication that the sample taken was uniformly representative of all the particles present in workplace air. At this point, it should be noted that the term 'total' aerosol does not actually represent all the particles that are airborne. In reality, it has only been defined by whatever sampling instrument has been chosen to measure it. However, in the workplace or the ambient atmosphere health-related sampling of aerosols should be based on biologically relevant fractions. Three aerosol fractions are defined; the inhalable, thoracic, and respirable fractions (CEN, 1993; ISO, 1992). The inhalable fraction is the mass fraction of airborne particles which is inhaled through the nose and mouth. The thoracic fraction is the mass fraction of inhalable aerosols penetrating beyond the larynx, and the respirable fraction is the mass fraction of inhalable aerosols penetrating to the unciliated airways. When the data are expressed in terms of a health-related aerosol fraction, this raises some interesting issues about how such exposure information might be related to health effects. For example, if the health effect of interest in a given study were lung cancer, then it might be argued that the aerosol fraction most relevant to the health-related dose is the thoracic fraction. For nickel, lung cancer is certainly one of the endpoints of interest.

A new generation of sampling instruments has been developed to match the criteria for health-related sampling, and perhaps the IOM sampler is the most common for personal sampling of the inhalable fraction. Comprehensive data on the sampling characteristics of the IOM sampler are available (Mark *et al*., 1986; Vincent *et al*., 1990; Mark *et al*., 1994). For comparison of results it is important to establish conversion factors to translate traditional data of 'total' aerosol into inhalable aerosol. Such conversion factors should take into account the design of the 'total' aerosol sampler and the size distribution of the aerosol under consideration. Thus there is no simple relationship from concentrations given as ’total’ aerosols to concentrations given as inhalable aerosols. However, it has to be noted that a concentration in terms of inhalable aerosols often is high compared to the concentration of ’total’ aerosols due to an insufficient sampling efficiency of a ’total’ aerosol sampler.

Kenny *et al*. (1997) have summarized technical characteristics of common (statutory or recommended) instruments within Europe for personal sampling of aerosols. The sampling efficiency of the instruments were compared in the laboratory at well defined ambient air velocities (wind tunnel experiments) and the obtained correction factors to obtain satisfactory performance in sampling inhalable aerosols are tabulated in Table 4.1.1.2.1.1.A. It is noted that the sampling efficiency for many sampler types decreased as wind speed increased. In typical workplaces wind speeds range from 0.04 to 2.02 m/s and have an arithmetic mean value of 0.3 m/s. Therefore, the current inhalable convention, which is based on tests conducted at higher wind speeds (0.5-4.0 m/s) may not fully reflect human inhalability at lower wind speeds (Li *et al*., 2000). In low air movement environments (wind speed less than 0.1 m/s) Aitken *et al*. (1999) found that human inhalability is significantly greater than the current inhalable convention.

Table 4.1.1.2.1.1.A: Correction factors to obtain aerosol concentrations in terms of inhalable aerosols (Kenny et al., 1997)

Sampler type	**Manufacturer**	**Correction factor 0.5 m/s** [1]	**Correction factor 1.0 m/s** [1]
IOM	SKC	0.9	1.0

Seven-hole	Casella, SKC, JS Holdings	1.0	1.2
GSP	Ströhlein	1.0	1.0
PAS-6	University of Wageningen	1.0	1.25
PERSPEC	Lavoro e Ambiente	1.0 [2]	NA [3]
CIP10-I	Arelco	1.15	1.15
37-mm open face	Millipore	1.15	1.15
37-mm closed face	Millipore	1.0	1.2

1) Ambient air velocity; 2) Inlet losses recovered and included in sample; 3) Not available.

It is difficult to simulate workplace conditions in the laboratory. Thus the correction factors tabulated in Table 4.1.1.2.1.1.A may not be valid to convert 'total' aerosol concentrations into 'inhalable' aerosols. Some workplace comparisons of sampler types have been carried out most extensively for the IOM and 37-mm closed face samplers, the IOM and 37-mm open-face samplers, and the IOM and seven-hole samplers. Limited data are also available comparing the CIP10-I and the IOM samplers. As reviewed by Kenny *et al*. (1997) the field comparisons of IOM and 37-mm samplers (both closed and open face) generally show the IOM samplers collecting 2-3 times as much as the 37-mm sampler in contrast to the factor of 1.2 as tabulated in Table 4.1.1.2.1.1.A. The comparisons of IOM and seven-hole samplers showed a median IOM/seven-hole ratio of 1.17, and the comparisons of IOM and CIP10-I showed a median IOM/CIP10-I ratio of 1.5. Both of these latter results are reasonably consistent with the data tabulated in Table 4.1.1.2.1.1.A but are based on a relatively small number of field tests. Personal sampling data from comprehensive field studies in the nickel-producing and -using industries has been published (Tsai *et al*., 1995; Tsai *et al*., 1996a; Tsai *et al*, 1996b) in which the closed-face 37-mm filter holder was compared with inhalable aerosol as measured using the IOM sampler. Data were also obtained by an approach of static sampling using mannequins to simulate personal sampling (Tsai & Vincent, 2001). The statistical analysis of the personal sampling results has been summarized (NIPERA, 1996) and the regression results are tabulated in Table 4.1.1.2.1.1.B for each sampled industry sector. The static sampling results were in good agreement with the personal sampling results for most of the work sites. As already mentioned priority is given to personal sampling and the static sampling results are not further discussed.

Table 4.1.1.2.1.1.B: Comparison between the IOM and the 37-mm samplers. Regression results from each sampled facility process.

Industry sector	**Regression results**					
	Total aerosol			**Total nickel**		
Mining	3.64±0.50	N=30	R^2=0.88	3.20±0.48	N=32	R^2=0.86
Milling	2.61±0.46	N=20	R^2=0.88	2.72±0.67	N=21	R^2=0.78
Smelting	1.97±0.23	N=39	R^2=0.89	1.65±0.17	N=35	R^2=0.92
Smelting	2.43±0.69	N=23	R^2=0.71	2.84±0.73	N=23	R^2=0.75
Refining	2.50±0.34	N=37	R^2=0.86	2.12±0.45	N=36	R^2=0.72
Nickel alloy production	1.94±0.45	N=45	R^2=0.86	2.29±0.39	N=46	R^2=0.76
Electroplating	2.77±0.44	N=25	R^2=0.87	2.02±0.53	N=21	R^2=0.76
Electroplating	3.29±0.70	N=26	R^2=0.79	3.01±0.93	N=21	R^2=0.70

The values in the table correspond to 'S±standard error' in the relationship $E_{IOM}=S\times E_{37}$; N corresponds to the number of samples analysed; R^2 corresponds to the regression coefficient.

The nickel data (Table 4.1.1.2.1.1.B) show the levels of 'total' aerosol exposure to be markedly lower than those of inhalable aerosol, with the bias ranging from about 1.7 to 3.2 depending on the industry sector and workplace in question. Consistent with what would be expected from aerosol sampling theory, the observed biases tended to be greater for workplaces where aerosols are coarser.

In this part of the assessment exposure levels measured with the 37-mm closed-face cassette are converted to inhalable aerosols taking into account the conversion factors tabulated in Table 4.1.1.2.1.1.B. Perhaps droplets are the predominant aerosol in the nickel nitrate production scenarios. For such cases the two conversion factors

for electroplating are considered useful for the assessment, and the upper factor (=3.0) for total nickel is taken forward for the assessment. Aerosols as measured with the seven-hole sampler is converted to inhalable aerosols by a factor of 1.17 while aerosols collected with the CIP10-I sampler is converted to 'inhalable' taking into account a conversion factor of 1.5. Aerosols collected with the GSP sampler is considered inhalable. It is recognized that the factor used for the 37-mm closed face cassette is derived from rather solid data (work place sampling in the nickel industry). In contrast the factors used for other types of samplers were derived from work place sampling in other industries or from experiments in the laboratory.

During the production and use of nickel dinitrate a number of nickel species may occur in the workroom air to which workers are exposed. The International Committee on Nickel Carcinogenesis in Man (Doll, 1990) identified four classes of nickel compounds as having different intrinsic activity or biological availability as cancer causing agents. The specific categories identified were sulfidic, oxidic, metallic and water-soluble nickel. Few methodologies are currently available for chemical speciation of nickel in workroom air. However, for speciation of aerosols originating from sulfide ore processing, a sequential leaching scheme has been developed by Zatka *et al*. (1992) for the determination of the four mentioned nickel fractions. It is noted that the scheme does not identify individual nickel species and the soluble fraction includes all nickel salts (e.g. sulphate and chloride). On the basis of the Zatka-scheme Andersen *et al.* (1998) introduced a simplified procedure allowing analysis for only two groups (soluble/insoluble) of nickel species. Based mainly on the Zatka-scheme Bolt *et al*. (2000) introduced a flow-injection analytical system to reduce the time required for the analysis in the laboratory. For the assessment exposure to nickel is given in terms of 'total' mass of nickel (nickel species left alone). If possible exposure is also given by nickel species. It is noted that exposure by nickel species is given in terms of mass of nickel.

4.1.1.2.2 Production of nickel nitrate.

4.1.1.2.2.1 *Scenario A1 – Nickel nitrate production from metallic nickel*

As already mentioned (section 2.1.1.1) nickel nitrate is prepared from metallic nickel by (1) slowly adding nickel powder to a stirred mixture of nitric acid and water or (2) a two-tank reactor system, one with solid nickel and one with nitric acid and water. The major production steps are feeding, dissolving, filtering, crystallisation, drying and packaging. The production may involve generation of aerosols and to minimise exposure by inhalation it is possible to run all the steps as closed or partially closed processes. From the tabulated steps involved in the production of nickel nitrate it has to be expected that workers within the overall scenario may not have similar tasks. As an effort to identify tasks with high risk of exposure the available data on exposure were tabulated, if possible, by sub-groups (sub-scenarios) of workers with similar tasks. Such listing was kept within a given set of data and no attempt was made to join similar tasks cross data sets. The reason not to join similar tasks cross data sets was that prior to the collapse of similar tasks a statistical analysis is required for identity between data sets in terms of type of statistical distribution, mean and variance. The data for the assessment were not available in details to allow such statistical analysis.

4.1.1.2.2.1.1 Exposure by inhalation – nickel species

For the scenario no data are available on nickel species in workroom air. Feeding metallic nickel at the front end of the production may cause risk of exposure by inhalation of aerosols high in content of metallic nickel while aerosols at the last stage of production (packaging) is expected to be high in content of nickel nitrate. For the assessment measured exposure levels in terms of 'total' nickel are considered being all nickel nitrate (worst-case).

4.1.1.2.2.1.2 Exposure by inhalation – measured exposure levels

Data sets on current exposure were obtained from industry and literature (Table 4.1.1.2.2.1.A). If possible data are listed using the format of the specific company data submission scheme, i.e. year(s) of measurement(s), number of samples, range, median and 95th percentile value. It is noted that the vast majority of the data sets were given in terms of full-shift time weighted averages. Thus the listed data are considered full-shift exposure. The information available on the sampling technique and aerosol fraction is included in the listed data. Note that all data sets were obtained by an approach of personal sampling. Exposure measured in terms of the 'total' aerosol fraction was converted to the inhalable fraction by a factor of 3.0 (37-mm or 25-mm closed face filter cassettes). It appears that the current exposure to 'total' nickel ('total' aerosol fraction) ranged from a median or mean level of less than 0.001 mg/m^3 to 0.14 mg/m^3. The low exposure level was reported for a small data set (3 observations) of workers involved in the formulation of products, while the high exposure level was for a small data set (1 observation) of workers involved in the production of nickel nitrate. In terms of the inhalable aerosol fraction current 'total' nickel exposure ranged from a median or mean level of less than 0.003 mg/m^3 to 0.52

mg/m^3. The median of the median or mean levels was ~0.2 mg/m^3 of inhalable 'total' nickel (typical exposure level).

By definition the reasonable worst-case exposure is the exposure experienced in a reasonable unfavourable but not unrealistic situation and the prediction should also consider upper estimates of the extreme use. In the Risk Assessment Report on Zinc Oxide (Netherlands Rapporteur, 2003) the reasonable worst-case exposure was estimated at the 90th percentile value of the available data. A similar approach was used for the present exposure assessment. Detailed data sets are required to allow an estimate of the true 90th percentile value. Data were not available at such details and a rough estimate of the 90th percentile was derived using the following three-step procedure. Simple calculations are used for the first two steps while the third step involves 'professional judgement' taking into account the quality of the data sets with an emphasis on the size of the data sets, the medians and the year of sampling. A given data set includes the range of observations. The upper limit of the range was used for ranking the data sets, and all data sets (sub-scenarios) at or above the 90th percentile were considered important for the estimation of the reasonable worst-case exposure. The 90th percentile of the available data sets (N=3; 14 observations) was ~1.6 mg/m^3 inhalable 'total' nickel. Such upper limit of exposure was reported for a sub-group of workers (6 observations) with the task 'production of nickel acetate/nitrate'. The other two data sets reported an upper limit of exposure at levels of 0.07 mg/m^3 (5 observations) and less than 0.003 mg/m^3 (3 observations). Thus it seems prudent to estimate the reasonable worst-case exposure at a level of 1.6 mg/m^3. Data on short-term exposure to nickel seem unavailable, and it is difficult (if not impossible) to derive an estimate on short-term exposure from data characterizing full shift exposure. For the risk assessment of nickel metal (RAR, 2002) no data were available on short-term exposure and an estimate was derived as twice the reasonable worst-case exposure level. A similar approach ('expert judgement') was taken for the present risk assessment. Thus the estimated short-term exposure is 2×1.6 mg/m^3~ 3.2 mg/m^3.

Table 4.1.1.2.2.1.A: Scenario A1: Nickel nitrate production from metallic nickel – current exposure by inhalation of 'total' nickel.

Ref.	Process	N	Year	Type of Sampler	Aerosol Fraction	Exposure to 'total' nickel mg/m^3					
						'Total' aerosol fraction			Inhalable aerosol fraction		
						Range	Median	95th perc.	Range	Median	95th perc.
Donaldson *et al.*, 1978*	Production of nickel acetate/nitrate from nickel or nickel oxide	6	1978	Personal [1]	'Total'	0.038-0.53	0.099 [4]	NA [3]	0.12-1.6	0.3[4]	NA
HSE-40*	Packaging of nickel nitrate	5 [A]	1985	Personal [2]	'Total'	0.017-0.022	0.019 [5]	NA	0.05-0.07	0.06 [5]	NA
HEDSET Comp. #3	Production of nickel nitrate	1	2002	Personal [2]	'Total'		0.14			0.52	
	Product formulation	3	2001	Personal [2]	'Total'	<0.001	<0.001	<0.001	<0.003	<0.003	<0.003

*: As quoted by NIPERA (1996). A: The number of observations was estimated from the arithmetic mean and the range using an approach given by Vincent & Werner (2003).
1: 37-mm closed face filter cassette. 2: 25-mm closed face filter cassette. 3: Not available. 4: Geometric mean. 5: Arithmetic mean.

4.1.1.2.2.1.3 Exposure by inhalation - modelled data (EASE 2.0)

No detailed information was available on specific tasks in the production of nickel nitrate. For the assessment packaging of the chemical was considered a common task. Thus the typical and the reasonable worst-case exposure was modelled for this task. Any manipulation of a dry material enters the EASE model by the term 'dry manipulation'. To model the exposure EASE requires input on the tendency of a material to aggregate. No data are available on the tendency of nickel nitrate to aggregate, and the chemical was considered non-sticky (aggregate is false).

Estimation of the typical exposure level
If sufficient care is exercised to reduce potential exposure the task enter the EASE model as 'low dust technique', and for the modelling this description was considered to be true. For the modelling the control of exposure by local exhaust ventilation was considered present.
Model input:
The name of the substance is nickel nitrate
The temperature of the process is 20
The physical-state is solid
Dust-inhalation is true
Mobile-solid is true
Solid-vp is false
The exposure-type is dust
The particle-size is inhalable
The operations is low dust techniques
The dust-type is non-fibrous
Aggregates is false
The pattern-of-control is local exhaust ventilation present
Model output:
Conclusion: The predicted dust exposure to nickel nitrate is 0-1 mg/m^3

Estimation of the reasonable worst-case exposure level
Model input:
Except for the type of operation and the pattern-of-control model input was kept identical to the input for estimation of the typical exposure level. The type of operation was specified as dry manipulation (includes any manipulation, also dry brushing) and the pattern-of-control was specified as no local exhaust ventilation.
Model output:
Conclusion: The predicted dust exposure to nickel nitrate is 5-50 mg/m^3.

The predicted typical exposure level is rather similar to the measured exposure levels as tabulated in Table 4.1.1.2.2.1.A. By contrast to the measured data the predicted reasonable worst-case exposure level was high. However, the lower limit of the predicted interval for the reasonable worst-case exposure was rather similar to the estimated level. Thus it appears prudent to accept the estimated exposure level for the assessment. The estimated exposure by inhalation of nickel nitrate is estimated as tabulated below (Table 4.1.1.2.2.1.B).

Table 4.1.1.2.2.1.B. Estimated exposure by inhalation of nickel nitrate in the production of nickel nitrate.

Nickel Species (1)	Typical exposure			Reasonable worst-case exposure			Short-term exposure (mg/m^3)
	Nickel species as % of 'total' nickel	Exposure to inhalable 'total' nickel (mg/m^3)	Exposure to inhalable nickel nitrate (mg/m^3)	Nickel species as % of 'total' nickel	Exposure to inhalable 'total' nickel (mg/m^3)	Exposure to inhalable nickel species (mg/m^3)	
SO	100	0.2	0.2	100	1.6	1.6	3.2

1: Soluble nickel considered being all nickel nitrate (worst-case).

4.1.1.2.2.1.4 Dermal exposure – measured exposure levels

Nickel nitrate is sold in the crystalline form that is packed in a fully automated, enclosed system and therefore is likely to have minimal dermal exposure. Hughson (2004) did a comprehensive study on occupational dermal

exposure to nickel in a chemical plant of a refinery where nickel hydroxycarbonate and nickel sulphate are produced from leaching of nickel matte using nickel sulphate. The study focused on dermal exposure during packing of the final products. The tasks in nickel nitrate packing are expected to be similar to the tasks in packing nickel sulphate. Thus the data reported by Hughson (2004) are considered useful for an assessment of dermal exposure in the production of nickel nitrate from metallic nickel.

The chemical plant used nickel sulphate solution to produce nickel hydroxycarbonate and nickel sulphate hexahydrate. The chemical reactions and transfer of compounds to the packing area was entirely automatic and completely enclosed. The packing area was highly automated with modern robotic packing and bag handling equipment. The nickel compounds (nickel sulphate hexahydrate and nickel hydroxycarbonate) were packed into 25-kg sacks using this equipment and there was no manual involvement with the bag filling operation whatsoever. The 25-kg sacks were automatically stacked onto pallets by robotic arms and the pallets were automatically shrink-wrapped before being conveyed through to the warehouse area. The workers were required to supervise the machinery and correct any faults that developed. There were four workers on one-day shift, involved with supervising the process. All of these workers were monitored.

One of the workers had some involvement in machine repair work, involving replacement of a pneumatic cylinder and considerable time was spent preparing the machine for production. Otherwise, the remaining packing lines were relatively trouble free and the workers had only incidental contact with the packing equipment and final products.

Nickel hydroxycarbonate in powder, paste or granular form was also packed into containers (‘big bag’) at a number of fill points. One operator was involved with this work. The main involvement comprised removing the spout of the container from the filling nozzle and tying this up with the cord provided. The empty bag was attached to the filling nozzle and the full bag transferred to the warehouse area by forklift truck. The forklift truck had an enclosed cab. During the bag replacement task, there was some noticeable spillage of powder onto the surface of the bag, but this was a minor amount.

All workers in the chemical plant wore air assisted filtering visors, cotton overalls and rigger type gloves. The workers returned to the main control room area when they were not required to directly observe the process. There were hygiene procedures in place for entering the control room, involving removal of work footwear and outer clothing, with hand washing prior to accessing the clean areas.

The measured dermal exposure to nickel is tabulated below (Table 4.1.1.2.2.1.C). The measurement method was repeated wiping of the skin using a commercial moist wipe (Jeyes ‘Sticky Fingers’ Wet Ones) and an acetate template with an open aperture of 25 cm^2 pressed onto the relevant anatomical area at the time of sampling. Wipe samples were collected from the palm and back of each hand and from both forearms. This was done before rest breaks so that contamination was not lost from the skin prior to washing. Samples of skin contamination were collected at three different intervals over the working day in order to assess contamination while at work. Additional samples were collected from the side of the neck, face and chest. The neck and face samples were used to provide an estimate of exposure for the head and also help make informed estimates about the potential for ingestion exposure. The sample from the chest was used to assess the degree of contamination under work clothes. The face, neck and chest samples were collected once, near the end of the shift i.e., before the afternoon break or before showering. The sampling efficiency of the method was tested in the laboratory by applying pre-weighted quantities of nickel powder onto the surface of a section of chamois leather. This leather was intended to act as a surrogate for human skin. The procedure was repeated using a solution of nickel sulphate hexahydrate in solution, applied to the surrogate skin surface using a pipette. The method showed an acceptable level of recovery (≈92%) for solid nickel particles, although there was poor recovery (≈16%) for water-soluble salts in solution. Using a different cured soft leather product as a surrogate skin improved the recovery of water-soluble salts to a level of ≈97%. All wipe samples were analysed to determine the soluble and insoluble nickel content using a variation of a published method (Zatka *et al.*, 1992). The modification of the method used only the first step in the Zatka method to differentiate between the soluble nickel salts (e.g. nickel sulphate hexahydrate, nickel chloride hexahydrate) and the other nickel substances that less readily dissolve or corrode (e.g. nickel subsulphide, nickel metal, nickel oxide). Therefore, the soluble nickel fraction is predominantly representative of the nickel salts, while the insoluble fraction contains the more refractory nickel substances (i.e. the "intermediate, sparingly, or insoluble" nickel substances).

For hands and arms of nickel compound packing operators the median dermal exposure to total nickel was 0.6 $\mu g/cm^2$. This median is considered an estimate of the typical exposure level, while the 90^{th} percentile (1.0 $\mu g/cm^2$) is considered to be an estimate of the reasonable worst-case exposure level. For soluble nickel the

median is 0.4 μg/cm^2 (the typical exposure level), while the 90th percentile is 0.7 μg/cm^2 (the reasonable worst-case exposure level). For insoluble nickel the median is 0.2 μg/cm^2 (the typical exposure level), while the 90th percentile is 0.4 μg/cm^2 (the reasonable worst-case exposure level). Both nickel hydroxycarbonate and nickel sulphate are packed in the same area, with workers rotating between packing of the two substances so dermal exposure data for the operations reflects exposure to both substances.

Table 4.1.1.2.2.1.C: Measured dermal nickel exposure (μg/cm^2) for nickel compound packing operators (Hughson, 2004).

Anatomical area	N[1]	Soluble nickel [A]		Insoluble nickel [A]		Total nickel	
Nickel compound packing operators							
		Median (range)	90th %	Median (range)	90th %	Median (range)	90th %
Average Hands	8 [2]	0.6 (0.2-0.9)	0.8	0.3 (<0.1-0.7)	0.5	0.9 (0.2-1.4)	1.4
Average forearms	8 [2]	0.3 (<0.1-0.9)	0.7	0.1 (<0.1-0.4)	0.3	0.4 (<0.1-1.3)	0.9
Hands & Arms	8 [3]	0.4 (0.1-0.9)	0.7	0.2 (<0.1-0.4)	0.4	0.6 (0.1-1.3)	1.0
Neck	8 [4]	0.5 (0.1-1.0)	0.8	0.2 (<0.1-0.6)	0.3	0.7 (0.1-1.5)	1.1
Face (perioral region)	8 [4]	0.5 (<0.1-1.5)	1.3	0.2 (<0.1-0.6)	0.5	0.8 (<0.1-2.0)	1.8
Chest	8 [4]	0.2 (<0.1-0.9)	0.6	<0.1 (<0.1-0.3)	0.2	0.2 (<0.1-1.1)	0.7
Control group (non-occupationally exposed volunteers)							
Average Hands	10	NA	NA	NA	NA	0.03 (0.01-0.09)	0.05
Average forearms	10	NA	NA	NA	NA	0.01 (0.01-0.06)	0.03
Hands & Arms	10	NA	NA	NA	NA	0.02 (0.01-0.07)	0.04

1: number of subjects. The exposure of the packing operators (N=4) was measured two times (day No. 1 and day No. 2). 2: per subject dermal exposure was measured three times during a shift (first break; mid-shift break; end of shift); every time one sample was collected from palms of both hands and another was taken from back of both hands. 3: exposure is given as an area weighted average of the measured data for the hands (area 840 cm^2) and forearms (area 1140 cm^2). 4: at end of shift one sample was collected per person.

A: The soluble and insoluble nickel content was analysed using a variation of a published method (Zatka et. al, 1992).

4.1.1.2.2.1.5 Dermal exposure - modelled data (EASE 2.0)

Hughson (2004) did a comprehensive study on occupational dermal exposure to nickel in a chemical plant that used nickel sulphate solution to produce nickel sulphate hexahydrate and nickel hydroxycarbonate. Hughson (2004) included a description of the workplace conditions in terms of the EASE model. The tasks covered by the study were assigned EASE exposure criteria of non-dispersive use with intermittent direct contact. Thus this scenario is modelled.

Estimation of dermal exposure for nickel compound packing operators
Model input:
The name of the substance is nickel
The temperature of the process is 20
The physical-state is solid
Dust-inhalation is false
Solid-vp is false
The exposure-type is dermal
The use-pattern is non-dispersive use
The pattern-of-control is direct handling
The contact-level is intermittent
Model output:
The predicted dermal exposure to nickel is 0.1-1 mg/cm^2/day.

The level of dermal exposure in the nickel nitrate production from metallic nickel was estimated by two approaches, (i) by analogy to measured data for operators packing nickel sulphate and (ii) by modelling. The measured dermal exposures were much less than predicted values generated by the EASE model. In addition, the measured dermal nickel levels were lower than levels of exposure previously obtained from the zinc industry (Hughson and Cherrie, 2001). This might be due to the higher levels of engineering controls applied to the nickel

sulphate production, combined with specific hygiene measures such as the consistent use of personal protective equipment (Hughson, 2004). The measured data were obtained at conditions typical of normal production, so the measured exposures can be considered representative of normal production conditions (Hughson, 2004). Based on expected similarities in tasks of packing operators it appears prudent to consider the Hughson-data useful for an assessment of dermal exposure in the production of nickel nitrate from metallic nickel. It is noted that the solubility (in water) of nickel nitrate is rather similar to the solubility of nickel sulphate. In terms of the content (as a percentage) of soluble nickel the mass of contaminants deposited on the skin of nickel sulphate packing operators is expected to be similar to the contaminants experienced by nickel nitrate packing operators. Thus the Hughson-data are taken forward to the risk characterization. The estimated typical and reasonable worst-case exposure levels for hands and forearms are summarized below. It is noted that the measured data (Table 4.1.1.2.2.1.C) indicate that there is potential for inadvertent ingestion of nickel, either through hand to mouth contact or from deposition into or around the perioral region.

Nickel species	Typical exposure		Reasonable worst-case exposure	
	μg/cm^2/day	mg/day [1]	μg/cm^2/day	mg/day [1]
Total nickel	0.6	1.2	1.0	2.0
Soluble nickel	0.4	0.8	0.7	1.4
Insoluble nickel	0.2	0.4	0.4	0.8

1: The area is 1980 cm^2 (hands: 840 cm^2; forearms: 1140 cm^2)

4.1.1.2.2.1.6 Discussion and conclusions

Rather few data were available for the assessment of exposure by inhalation of 'total' nickel in the production of nickel nitrate from metallic nickel. An emphasis was made to assess exposure in terms of inhalable aerosols, and data were tabulated for sub-groups of workers with similar tasks as an effort to identify groups of workers at high risk of exposure by inhalation of dust. However the information was sparse on tasks characterized by the measured data and a very detailed classification of sub-groups was not possible. The typical exposure to inhalable nickel was estimated at a level of 0.2 mg/m^3; such exposure might be expected for a sub-group of workers with the task 'production of nickel acetate/nitrate from nickel or nickel oxide'. The reasonable worst-case exposure level was estimated to be 1.6 mg/m^3; such exposure might be expected for a sub-group of workers with the task 'production of nickel acetate/nitrate from nickel or nickel oxide'. No data on nickel species in workroom air were available and, as an alternative, the content of 'total' nickel in air was considered being all nickel nitrate (worst-case).

No data were available on dermal exposure to nickel nitrate, and the exposure was estimated by two approaches, (i) by analogy to measured dermal exposure in nickel sulphate production from nickel matte and (ii) by modelling. The measured data focused on nickel compound packing operations. The predicted exposure level (EASE) was much higher than the levels estimated by analogy to measured data. However, the predicted exposure levels produced by EASE are intended to be estimates of potential exposure and do not therefore take into account the attenuating effect of gloves and other protective clothing. For the production of nickel nitrate the highest exposure to nickel nitrate is expected to be during packing of the crystallized chemical. Based on expected similarities in tasks in packing nickel nitrate and packing nickel sulphate it appears prudent to take the exposure estimated by analogy forward to the risk characterization. In conclusion the estimated levels of exposure to groups of nickel species are summarized below. In conclusion the estimated levels of exposure to nickel nitrate are summarized below. These levels can be used in risk characterization comparison with acute toxicity data.

Nickel species [1]	**Exposure by inhalation (mg/m^3)**			**Dermal exposure (mg/day)**	
	Typical	**Reasonable worst-case**	**Short term**	**Typical**	**Reasonable worst-case**
T	0.2	1.6	3.2		
SO				0.8	1.4
U				0.4	0.8

1: T = Total nickel considered to be all nickel nitrate (worst-case); SO = Soluble nickel salts considered to be all nickel nitrate (worst-case); U = Other nickel species than soluble nickel salts.

4.1.1.2.2.2 Scenario A2 – Nickel nitrate production from secondary raw materials

4.1.1.2.2.2.1 Exposure by inhalation – measured and modelled levels

In the production of nickel nitrate from secondary raw materials, metal hydroxides with the used metal residues are dissolved and extracted with a mixture of different waste acids. The solution obtained is then refined by chemical separation steps. Nickel and zinc are separated by solvent extraction, whilst copper is produced by electrolysis. This process is very similar to the production of nickel sulphate described in chapter 2.1.1.3 (Scenario A3) of the nickel sulphate risk assessment report.

Few data on personal exposure to nickel nitrate were available for the assessment. From industry a small data set (3 observations) on exposure by inhalation of 'total' nickel ranged from 0.009 mg/m^3 to 0.017 mg/m^3 (inhalable fraction). The median was 0.01 mg/m^3. As already mentioned the process in nickel nitrate production is very similar to the production of nickel sulphate. Thus it appears prudent to consider the data on exposure to nickel in nickel sulphate production as valid for a rough estimate of the exposure to nickel in the production of nickel nitrate. The estimated exposure is tabulated below and further details are given in the risk assessment report on nickel sulphate (Scenario A3). It has to be emphasized that the validity of the estimated exposure remains unknown but the estimated exposure levels appear rather similar to the small data set provided by industry.

Nickel species (1)	**Exposure by inhalation (mg/m^3)**		
	Typical	**Worst-case**	**Short term**
SO	0.07	1.0	2.0
U	0.05	~0	~0

1: SO = Soluble nickel salts considered to be all nickel nitrate (worst-case); U = Other nickel species than soluble nickel salts.

4.1.1.2.2.2.2 Dermal exposure – measured and modelled exposure levels

Hughson (2004) did a comprehensive study on occupational dermal exposure to nickel in the chemical plant of a refinery. The chemical plant used nickel sulphate solution to produce nickel sulphate hexahydrate and nickel hydroxycarbonate. The dermal exposure was measured during packing of the final product. The tasks in the packing of nickel sulphate and nickel carbonate are expected to be similar to the tasks in packing nickel nitrate. Thus it appears prudent to estimate dermal exposure in the nickel nitrate production by analogy to measured exposure for operators involved in the packing of nickel sulphate and nickel carbonate. It is noted that the solubility (in water) of nickel nitrate is rather similar to the solubility of nickel sulphate. In terms of the content (as a percentage) of soluble nickel the mass of contaminants deposited on the skin of nickel sulphate packing operators is expected to be similar to the contaminants experienced by nickel nitrate packing operators. Thus it appears prudent to consider the Hughson-data useful for an assessment of dermal exposure in the production of nickel nitrate from secondary raw materials. The estimated typical and reasonable worst-case exposure levels for hands and forearms are summarized below. Further details of the estimated data are given above (section 4.1.1.2.2.1.4 and 4.1.1.2.2.1.5).

Nickel species	Typical exposure		Reasonable worst-case exposure	
	µg/cm^2/day	mg/day [1]	µg/cm^2/day	mg/day [1]
Total nickel	0.6	1.2	1.0	2.0
Soluble nickel	0.4	0.8	0.7	1.4
Insoluble nickel	0.2	0.4	0.4	0.8

1: The area is 1980 cm^2 (hands: 840 cm^2; forearms: 1140 cm^2)

4.1.1.2.2.2.3 Discussion and conclusions

Rather few data were available for the assessment of exposure by inhalation of 'total' nickel in the production of nickel nitrate from secondary raw materials. Tasks in the production of nickel sulphate by leaching are very similar to the tasks in nickel nitrate production from secondary raw materials. Thus it appeared prudent to estimate the exposure by inhalation by analogy to measured data for nickel sulphate production (scenario A2 of the nickel sulphate risk assessment report). It has to be emphasized that the validity of the estimated exposure

remains unknown but the estimated exposure level appears rather similar to the small data set provided by industry.

No data were available on dermal exposure to nickel nitrate, and the exposure was estimated by two approaches, (i) by analogy to measured dermal exposure in nickel sulphate production from nickel matte and (ii) by modelling. The measured data focused on nickel compound packing operations. The predicted exposure level (EASE) was much higher than the levels estimated by analogy to measured data. However, the predicted exposure levels produced by EASE are intended to be estimates of potential exposure and do not therefore take into account the attenuating effect of gloves and other protective clothing. For the production of nickel nitrate the highest exposure to nickel nitrate is expected to be during packing of the crystallized chemical. Based on expected similarities in tasks in packing nickel nitrate and packing nickel sulphate it appears prudent to take the exposure estimated by analogy forward to the risk characterization. In conclusion the estimated levels of exposure to groups of nickel species are summarized below.

Nickel species (1)	Exposure by inhalation (mg/m^3)			Dermal exposure (mg/day)	
	Typical	Worst-case	Short term	Typical	Worst-case
SO	0.07	1.0	2.0	0.8	1.4
U	0.05	~0	~0	0.4	0.8

1: SO = Soluble nickel salts considered to be all nickel nitrate (worst-case); U = Other nickel species than soluble nickel salts

4.1.1.2.3 Use of nickel nitrate.

4.1.1.2.3.1 Scenario B1 – Nickel nitrate used in the production of catalysts

Nickel is an important hydrogenation catalyst because of its ability to chemisorb hydrogen. The feedstock and unit operations of the processes for making catalysts are as various as the different catalyst products themselves. Commonly, however, catalyst production utilizes feedstock such as nickel metal, finely divided Raney nickel, nickel nitrate crystals or solutions, nickel carbonate pastes or solutions, and nickel oxide. Production processes are described in chapter 2.2.1.1. More detailed descriptions are given in chapter 2.2.1.5.2 and with additional information shown in Appendix 7.7. of the risk assessment report for nickel metal.

Personal exposure to catalyst aerosols may occur at different operations including catalyst manufacturing, on-site catalyst handling operations including charging/discharging operations, and treatment of spent catalyst. Thus workers within the overall scenario may not have similar tasks. As an effort to identify tasks with high risk of exposure the available data on exposure were tabulated, if possible, by sub-groups (sub-scenarios) of workers with similar tasks. Such listing was kept within a given set of data and no attempt was made to join similar tasks cross data sets. The reason not to join similar tasks cross data sets was that prior to the collapse of similar tasks a statistical analysis is required for identity between data sets in terms of type of statistical distribution, mean and variance. The data for the assessment were not available in details to allow such statistical analysis.

4.1.1.2.3.1.1 Exposure by inhalation – nickel species

Data on airborne nickel species are sparse for the production of catalysts and for nickel nitrate no data were available for the risk assessment. In the early 1980s Warner (1984) reported comprehensive data on occupational exposure to airborne nickel in producing and using primary nickel products. The data included information on exposure by inhalation of ‘total’ and soluble nickel in the catalyst production from nickel sulphate. The measured concentrations are tabulated below (Table 4.1.1.2.3.1.A). As a percentage of exposure to ‘total’ nickel the data indicate that exposure to soluble nickel ranged from 1 % to ~6 %. By analogy the data reported by Warner (1984) were considered useful as a rough estimate of exposure by inhalation of soluble nickel in the catalyst production from nickel nitrate. For the assessment soluble nickel was considered being all nickel nitrate (worst-case). For the assessment the median (3.5 %) of the data (Table 4.1.1.2.3.1.A) was considered typical while the upper limit of the range (~6 %) was considered a worst-case. It has to be emphasized that the validity of the analogy of catalyst production from nickel nitrate to the production from nickel sulphate remains unknown.

Table 4.1.1.2.3.1.A: Nickel speciation data for aerosols collected in catalyst production from nickel sulphate (Warner, 1984). By analogy the data are considered valid as a rough estimate for the catalyst production from nickel nitrate.

Type of sampler	N	Exposure level (µg/m^3)				Nickel speciation (%)	
		Soluble nickel (SO)		Insoluble nickel (U)		Soluble Nickel [1,3]	Insoluble nickel [2]
		Range	Average	Range	Average		
Personal [A]	NA [B]	2-9	3	12-160	52	5.8	94.2
Static [A]	NA [B]	1-7	3	13-1200	290	1.0	99.0

A: type of dust sampler not specified. B: not available.
1: Estimated as SO/(SO+U). 2: Estimated as U/(SO+U). 3: For the present assessment soluble nickel is considered being all nickel nitrate (worst-case).

It has to be noted that the European Catalyst Manufactures Association (ECMA) has provided comprehensive data on occupational exposure by inhalation of nickel during catalyst production (Delabarre, 1989). In general data were given in terms of 'total' nickel but Delabarre (1989) did compare workers exposed to soluble nickel compounds to workers exposed to insoluble nickel compounds (Table 4.1.1.2.3.1.B). Unfortunately the two groups of data were not collected from similar environments so the soluble nickel fraction cannot be estimated as a percentage of 'total' nickel.

Table 4.1.1.2.3.1.B: Exposure by inhalation of soluble and insoluble nickel in catalyst production (Delabarre, 1989)

	N	Year	Type of sampler	Exposure to nickel (µg/m^3)	
				Range	Mean [2]
Workers exposed to soluble nickel	34	1986-87	Personal [1]	<10-1560	20
Workers not exposed to soluble nickel	49	1986-87	Personal [1]	<10-1740	250

1: the seven-hole sampler. 2: geometric mean.

4.1.1.2.3.1.2 Exposure by inhalation – measured exposure levels

Current data on occupational exposure in catalyst production from nickel nitrate were obtained from industry and tabulated by sub-groups of workers with similar tasks (Table 4.1.1.2.3.1.C). The risk assessment report for nickel metal has a section for a scenario on the production of catalysts from metallic nickel. Some data from that section might include exposure to nickel nitrate and data considered useful for the present scenario were extracted from the risk assessment report on nickel metal and tabulated (Table 4.1.1.2.3.1.C) by sub-groups of workers with similar tasks. If possible data are listed using the format of the specific company data submission scheme, i.e. year(s) of measurement(s), number of samples, range, median and 95th percentile value. It is noted that the vast majority of the data sets were given in terms of full-shift time weighted averages. Thus the listed data are considered full-shift exposure. The information available on the sampling technique and aerosol fraction is included in the listed data. Exposure measured in terms of the 'total' aerosol fraction was converted to the inhalable fraction by a factor of 2.5 (37-mm/25-mm open or closed face cassettes) as recommended for dust by Werner *et al.* (1996). A factor of 1.17 was used for the seven hole sampler. The powders used in catalyst manufacturing are likely to be 'fine'. As mentioned above (section 4.1.1.2.1.1) the smaller the particles, the smaller the conversion needed to convert 'total' dust to inhalable dust. The factor 2.5 is close to the factors tabulated above (Table 4.1.1.2.1.1.B) for mining, milling, smelting, refining, nickel alloy production, and electroplating. No specific conversion factor is available for catalyst manufacturing and the factor of 2.5 recommended for dust by Werner *et al*. (1996) is used as a rough estimate. It is recognized that such an approach may bias the estimated exposure to inhalable dust towards high levels.

As observed from Table 4.1.1.2.3.1.C some sets of data have little information on the tasks of the sub-groups of workers characterized by the data. Other sets of data have rather detailed information on sub-groups of workers with similar tasks, but the strategy in collecting the data included an approach of static sampling. It is noted that data collected by static samplers may not be valid as estimates of personal exposure. Including data obtained by an approach of personal or personal/static sampling it appears that current exposure to 'total' nickel ('total' aerosol fraction) ranged from a median or mean level of 0.004 mg/m^3 to 12 mg/m^3. The high median exposure of 12 mg/m^3 was observed for a sub-group of workers with the task of reactor off loading. It has to be noted that

this data set was small (2 observations) and that the aerosols were collected by an approach of personal/static sampling. The type of dust sampler was not specified for all sets of data, including some small data sets reporting high exposure to 'total' nickel. Some of the small data sets used an approach of static sampling and the reported concentrations may not be valid as estimates of personal exposure.

In terms of the inhalable aerosol fraction current exposure as obtained by personal sampling ranged from a median or mean level of less than 0.005 mg/m^3 to 0.5 mg/m^3. The median of the median or mean levels was within the range from 0.046 mg/m^3 to 0.05 mg/m^3 and the median (≈0.05 mg/m^3) of this range was taken as an estimate of the typical exposure level. A median exposure of 0.046 mg/m^3 was seen for a sub-group of workers with the task of routine operations, while a median exposure of 0.05 mg/m^3 was seen for a sub-group of workers with the task of catalyst production. Data sets with no specified type of dust sampler did not enter the estimation of the typical exposure level. It is recognised that the estimate perhaps is biased towards a low level by such an approach.

By definition the reasonable worst-case exposure is the exposure experienced in a reasonable unfavourable but not unrealistic situation and the prediction should also consider upper estimates of the extreme use. In the Risk Assessment Report on Zinc Oxide (Netherlands Rapporteur, 2003) the reasonable worst-case exposure was estimated at the 90th percentile value of the available data. A similar approach was used for the present exposure assessment. Detailed data sets are required to allow an estimate of the true 90th percentile value. Data were not available at such details and a rough estimate of the 90th percentile was derived using the following three-step procedure. Simple calculations are used for the first two steps while the third step involves 'professional judgement' taking into account the quality of the data sets with an emphasis on the size of the data sets, the medians and the year of sampling. The upper limit of the range of measured exposure was used for ranking the data sets, and all data sets (sub-scenarios) at or above the 90th percentile were considered important for the estimation of the reasonable worst-case exposure. Note that rather many data sets did not specify the range of measured exposure and such data sets did not enter the estimation of the reasonable worst-case exposure level. The 90th percentile of the available data sets (N=6; 297 observations) was 4.4 mg/m^3. An upper limit of exposure at such level was seen for a large data set (127 observations) for a sub-group of workers with the rather non-specific task of catalyst production. The median of the data set was low (0.07 mg/m^3). It is noted that an upper limit of 'total' aerosol exposure at a level of 22 mg/m^3 was reported for the task of reactor off loading. The data for this task were obtained by personal/static sampling and the data set was small (2 observations). A high median exposure level (0.46 mg/m^3) was seen for a small (4 observations) data set (HEDSET Comp. #7). Thus it seems prudent to consider the level of 4.4 mg/m^3 as an estimate of the reasonable worst-case exposure. Data on short-term exposure to nickel seem unavailable, and it is difficult (if not impossible) to derive an estimate on short-term exposure from data characterizing full shift exposure. For the risk assessment of nickel metal (RAR, 2002) no data were available on short-term exposure and an estimate was derived as twice the reasonable worst-case exposure level. A similar approach ('expert judgement') was taken for the present risk assessment. Thus the short-term exposure was estimated at a level of 2×4.4=8.8 mg/m^3. For the scenario no data were available on the size distribution of aerosols in the workroom air.

Table 4.1.1.2.3.1.C: Catalyst production – current exposure by inhalation of 'total' nickel.

Ref.	Process	N	Year	Type of Sampler	Aerosol Fraction	Exposure to 'total' nickel mg/m^3					
						'Total' aerosol fraction			Inhalable aerosol fraction		
						Range	Median	95th perc.	Range	Median	95th perc.
HEDSET Comp. #1	Routine plant operation	47	2000	Personal/ Static [2+]	'Total'	<0.01-0.38	0.048 [5]	0.22	<0.012-0.45	0.058 [5]	0.26
		59	2001	Personal/ Static [2+]	'Total'	<0.01-0.24	0.038	0.16	<0.012-0.29	0.046	0.19
HEDSET Comp. #2	Catalyst production, tabletting, packaging and cleaning	12	2002-2003	Personal [3]	'Total'	0.004-0.26	0.02	0.11	0.01-0.65	0.05	0.28
		27	2002-2003	Static [3]	'Total'	0.002-0.05	0.004	0.04	0.005-0.12	0.01	0.1
HEDSET Comp. #3	Catalyst production, extrusion and packing	NA[**]	2000-2001 [+]	Personal [2+]	'Total'	NA	<0.004	NA	NA	<0.005	NA
	Catalyst production, extrusion and packing	NA	2000-2001 [+]	Static [2+]	'Total'	NA	<0.007	NA	NA	<0.008	NA
HEDSET Comp. #4	Catalyst production	NA	2000-2001 [+]	Personal [1+]	'Total'	NA	0.12	NA	NA	0.12	NA
	Catalyst production	NA	2000-2001 [+]	Static [1+]	'Total'	NA	0.09	NA	NA	0.09	NA
	Packaging station	NA	2000-2001 [+]	Personal [1+]	'Total'	NA	0.05	NA	NA	0.05	NA
	Impregnation of carrier	NA	2000-2001[+]	Personal [1+]	'Total'	NA	0.03	NA	NA	0.03	NA
	Preparation of solutions	NA	2000-2001 [+]	Personal [1+]	'Total'	NA	0.1	NA	NA	0.1	NA
HEDSET Comp. #6	Catalyst production, impregnation	NA	2000-2001 [+]	Personal [2+]	'Total'	NA	<0.01	NA	NA	<0.012	NA
	Catalyst production, impregnation	NA	2000-2001[+]	Static [2+]	'Total'	NA	<0.01	NA	NA	<0.012	NA
	Catalyst production, reduction process	NA	2000-2001 [+]	Personal [2+]	'Total'	NA	<0.01	NA	NA	<0.012	NA
	Catalyst production, reduction process	NA	2000-2001 [+]	Static [2+]	'Total'	NA	0.02	NA	NA	0.023	NA
Hedset Comp. #7	Catalyst production	4	2001	Personal/Static [1+]	'Total'	<0.001-1.0	0.46 [9]	0.5	<0.001-1.0	0.46 [9]	0.5

HEDSET Comp. #8	Filling/discharging of Ni-catalysers	39	1995-2001	Personal [1,+]	'Total'	NA	0.0052	0.01	NA	0.005	0.1
Delabarre, 1989	Catalyst production	127	1985-1986	Personal [2]	'Total'	<0.01-38	0.06 [6]	NA	<0.012-4.4	0.07 [6]	NA
	Catalyst production	48	1986-1987	Personal [2]	'Total'	<0.01-1.7	0.08 [6]	NA	<0.012-2.0	0.09 [6]	NA
Almaguer, 1987	Catalyst prod, for petroleum industry	11	1986	Static [3]	'Total'	0.004-0.29	0.048 [5]	NA	0.01-0.73	0.12 [5]	NA
EIS-02, 1993*	Misc, duties in catalyst prod.	34	1990-1993	Personal/ Static [4]	'Total'	<0.001-0.26	0.27 [7,8]	NA	-	-	-
	Misc duties	1	1990-1993	Personal /Static [4]	'Total'	NA	0.68 [5]	NA	-	-	-
	Reactor off loading	2	1990-1993	Personal /Static [4]	'Total'	0.87-22	11.6 [7]	NA	-	-	-
EIS-11, 1993*	Granulating	4	1990-1992	Static [4]	'Total'	1.7-26	8.9 [5]	NA	-	-	-
	Compacting	2	1984-1987	Static [4]	'Total'	4.4-7.3	5.8 [5]	NA	-	-	-
	Milling	2	1987	Static [4]	'Total'	1.1-1.4	1.3 [5]	NA	-	-	-
	Mixing	2	1987-1989	Static [4]	'Total'	0.48-0.9	0.69 [5]	NA	-	-	-
	Tabletting	5	1987-1992	Static [4]	'Total'	0.09-1.6	0.69 [5]	NA	-	-	-
	Others	6	1987-1992	Static [4]	'Total'	0.037-3.7	1.1 [5]	NA	-	-	-
EIS-14, 1993*	Production (all aspects)	170	1985	Personal /Static [4]	'Total'	0.001-0.024	0.004 [5]	NA	-	-	-
	Operator/supervisor/maintenance	19	1985	Personal /Static [4]	'Total'	0.001-0.026	0.005 [5]	NA	-	-	-

*: Data tabulated by NIPERA (1996). **: Not available. +: presumably

1: GSP filter cassette. 2: the seven-hole sampler. 3: 37-mm or 25-mm closed face filter cassette. 4: type of sampler not specified. 5: arithmetic mean. 6: geometric mean. 7: weighted average. 8: Note that the average is high by contrast to the upper limit of the range. 9: The mean (arithmetic) was estimated from the range and the number of observations by an approach given by Vincent and Werner (2003).

4.1.1.2.3.1.3 Exposure by inhalation – modelled data (EASE 2.0)

No detailed information was available on specific tasks in the production of catalysts. For the assessment packaging of catalysts was considered a common task. Thus the typical and the reasonable worst-case exposures were modelled for this task. Any manipulation of a dry material enters the EASE model by the term 'dry manipulation'. To model the exposure EASE requires input on the tendency of a material to aggregate. No data are available on the tendency of a catalyst to aggregate, and a catalyst was considered non-sticky (aggregate is false).

Estimation of the typical exposure level

If sufficient care is exercised to reduce potential exposure the task enter the EASE model as 'low dust technique', and for the modelling this description was considered to be true. For the modelling the control of exposure by local exhaust ventilation was considered present.

Model input:

The name of the substance is catalyst dust
The temperature of the process is 20
The physical-state is solid
Dust-inhalation is true
Mobile-solid is true
Solid-vp is false
The exposure-type is dust
The particle-size is inhalable
The operations is low dust techniques
The dust-type is non-fibrous
Aggregates is false
The pattern-of-control is local exhaust ventilation present

Model output:

Conclusion: The predicted dust exposure to catalyst dust is 0-1 mg/m^3

Estimation of the reasonable worst-case exposure level

Model input:

Except for the type of operation and the pattern-of-control model input was kept identical to the input for estimation of the typical exposure level. The type of operation was specified as dry manipulation (includes any manipulation, also dry brushing) and the pattern-of-control was specified as no local exhaust ventilation.

Model output:

Conclusion: The predicted dust exposure to catalyst dust is 5-50 mg/m^3.

The predicted exposure level is rather close to the measured data as tabulated in Table 4.1.1.2.3.1.C. The measured data provide more detailed information than the EASE model, and the measured data are used for the assessment. Considering the assessed data on nickel species in workroom air (Table 4.1.1.2.3.1.A) current exposure to groups of nickel species is estimated as tabulated below (Table 4.1.1.2.3.1.D).

Table 4.1.1.2.3.1.D: Estimated exposure by inhalation of groups of nickel species in catalyst production.

Nickel Species (1)	**Typical exposure**			**Worst-case exposure**			**Short-term exposure (mg/m^3)**
	Nickel species as % of 'total' nickel	**Exposure to inhalable 'total' nickel (mg/m^3)**	**Exposure to inhalable nickel species (mg/m^3)**	**Nickel species as % of 'total' nickel**	**Exposure to inhalable 'total' nickel (mg/m^3)**	**Exposure to inhalable nickel species (mg/m^3)**	
SO	3.5	0.05	0.002	6.0	4.4	0.26≈0.3	0.6
U	96.5	0.05	0.048≈0.05	94	4.4	4.1	8.2

1: SO = Soluble nickel salts considered being all nickel nitrate (worst-case); U = Insoluble nickel species.

4.1.1.2.3.1.4 Dermal exposure – measured and modelled exposure levels

No measured data for dermal exposure to nickel seem available for the assessment. Hughson (2004) did a study on dermal exposure in the packing of nickel sulphate hexahydrate and nickel hydroxycarbonate at a chemical plant producing nickel sulphate and nickel hydroxycarbonate. The tasks in packing nickel nitrate are expected to be similar to the tasks in packing nickel sulphate. Thus it appears prudent to estimate the exposure in packing nickel nitrate by analogy to the measured data from packing of nickel sulphate. It is noted that the solubility (in water) of nickel nitrate is rather similar to the solubility of nickel sulphate. In terms of the content (as a percentage) of soluble nickel the mass of contaminants deposited on the skin of nickel sulphate packing operators is expected to be similar to the contaminants experienced by nickel nitrate packing operators. Since nickel nitrate crystals or solutions are used as feedstock for catalyst production, nickel nitrate packing data would provide the worst-case exposure data for this scenario until measured data is available. Thus the dermal exposure is estimated at the levels tabulated below. Further details of the estimated data are given above (section 4.1.1.2.2.1.4 and 4.1.1.2.2.1.5).

Nickel species	Typical exposure		Reasonable worst-case exposure	
	μg/cm^2/day	mg/day [1]	μg/cm^2/day	mg/day [1]
Total nickel	0.6	1.2	1.0	2.0
Soluble nickel	0.4	0.8	0.7	1.4
Insoluble nickel	0.2	0.4	0.4	0.8

1: The area is 1980 cm^2 (hands: 840 cm^2; forearms: 1140 cm^2)

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4.1.1.2.3.1.5 Discussion and conclusions

Rather few data were available for the assessment of exposure by inhalation of 'total' nickel in the production of nickel catalysts. An emphasis was made to assess exposure in terms of inhalable aerosols, and data were tabulated by sub-groups of workers with similar tasks as an effort to identify groups of workers at high risk of exposure. However the information was sparse on tasks characterized by the measured date and a very detailed classification of sub-groups was not possible. The estimated typical exposure level (0.07 mg/m^3) was seen for a sub-group of workers with the rather non-specific task of catalyst production. The estimated reasonably worst-case exposure level (4.4 mg/m^3) was also seen for this sub-group of workers. No data on nickel species in workroom air were available. By analogy data on airborne soluble nickel species (as a percentage of 'total' nickel) in the catalyst production from nickel sulphate were considered valid for airborne nickel species in the catalyst production from nickel nitrate. It is recognized that the validity of such analogy remains unknown.

No data were available on dermal exposure to nickel nitrate, and the exposure was estimated by two approaches, (i) by analogy to measured dermal exposure in nickel sulphate production from nickel matte and (ii) by modelling. The measured data focused on nickel compound packing operations. The predicted exposure level (EASE) was much higher than the levels estimated by analogy to measured data. However, the predicted exposure levels produced by EASE are intended to be estimates of potential exposure and do not therefore take into account the attenuating effect of gloves and other protective clothing. For the production of nickel nitrate the highest exposure to nickel nitrate is expected to be during packing of the crystallized chemical. Based on expected similarities in tasks in packing nickel nitrate and packing nickel sulphate it appears prudent to take the exposure estimated by analogy forward to the risk characterization. It is noted that the handling of nickel nitrate is expected to be more intensive than in the production of catalysts. Thus the estimated exposure is considered biased towards high levels. In conclusion the estimated levels of exposure to groups of nickel species are summarized below.

Nickel species [1]	**Exposure by inhalation (mg/m^3)**			**Dermal exposure (mg/day)**	
	Typical	**Reasonable worst-case**	**Short term**	**Typical**	**Reasonable worst-case**
SO	0.002	0.3	0.6	0.8	1.4
U	0.07	4.1	8.2	0.4	0.8

1: SO = Soluble nickel salts considered being all nickel nitrate (worst-case); U = Insoluble nickel species.

4.1.1.2.3.2 Scenario B2 – Nickel nitrate used in the production of nickel-cadmium batteries

The sector is characterized by certain commonalties such as the use of nickel and cadmium compounds in liquid and powder form to produce, respectively, anodic and cathodic materials. However, there are many variations in

the individual processes concerned. Feedstock for electrode manufacture includes nickel metal powder, black nickel oxide powder, nickel hydroxide particles, nickel nitrate crystals or solution, and nickel or stainless steel strips which, in some cases, are perforated. In addition to the chemical and powder handling processes, most battery production involves some metallurgical stages including spot welding, rolling, and cutting of metal components. Nickel nitrate is an intermediate in loading active mass in nickel-cadmium batteries of the sintered-plate type. Typically, hot nickel nitrate syrup is impregnated in the porous sintered-nickel positive plates. Subsequently, the pores are soaked in potassium hydroxide solution whereupon nickel hydroxide precipitates within the pores of the plate. The tabulated steps in the production of batteries indicate that workers within the overall scenario may not have similar tasks. As an effort to identify tasks with high risk of exposure the available data on exposure were tabulated, if possible, by sub-groups (sub-scenarios) of workers with similar tasks. Such listing was kept within a given set of data and no attempt was made to join similar tasks cross data sets. The reason not to join similar tasks cross data sets was that prior to the collapse of similar tasks a statistical analysis is required for identity between tasks in terms of type of statistical distribution, mean and variance. The data for the assessment were not available in details to allow such statistical analysis.

4.1.1.2.3.2.1 Exposure by inhalation – nickel species

No data on airborne nickel species seem available for the assessment and measured concentrations of 'total' nickel are considered being all nickel nitrate (worst-case).

4.1.1.2.3.2.2 Exposure by inhalation – measured exposure levels

The risk assessment report for nickel metal includes two scenarios for the production of batteries, (i) processes including primary nickel powder as feedstock and (ii) processes that do not include primary nickel powder as feedstock. Data on processes involving primary nickel powder as feedstock were excluded from the present risk assessment, while data less specific in terms of feedstock (nickel species) were considered useful for the assessment. Data on occupational exposure in the battery production were obtained from literature, industry, and the current version of UK HSE's NEDB (National Exposure Database). The data available are tabulated in Table 4.1.1.2.3.2.A by sub-groups of workers with similar tasks. If possible data are listed using the format of the specific company data submission scheme, i.e. year(s) of measurement(s), number of samples, range, median and 95th percentile value. It is noted that the vast majority of the data sets were given in terms of full-shift time weighted averages. Thus the listed data are considered full-shift exposure. The information available on the sampling technique and aerosol fraction is included in the listed data. Exposure measured in terms of the 'total' aerosol fraction was converted to the inhalable fraction by a factor of 1.29 (37-mm/25-mm closed face cassette). This factor was reported for lead air levels in lead battery manufacturing (Werner *et al*., 1996). In terms of aerodynamic diameter the particle size distribution in nickel-cadmium battery production was guessed to be similar to the size distribution in lead battery manufacturing. Therefore the factor of 1.29 was considered useful for the assessment.

In terms of 'total' nickel median exposure ranged from 0.002 mg/m^3 to 0.33 mg/m^3 as measured by an approach of personal sampling. The upper limit of the range was reported for a sub-group of workers with the task of 'leading hand', but it is noted that the median for this sub-group of workers was above the upper limit of the given range of exposure. Thus the data set is inconsistent and the data set is excluded from the following processing of data. In terms of 'total' inhalable nickel the median or mean exposure ranged from 0.002 mg/m^3 to 0.31 mg/m^3. The median of the median or mean exposure levels was 0.015 mg/m^3 inhalable nickel (the typical exposure level). Such an exposure was seen for sub-groups of workers with the task of sizing.

By definition the reasonable worst-case exposure is the exposure experienced in a reasonable unfavourable but not unrealistic situation and the prediction should also consider upper estimates of the extreme use. In the Risk Assessment Report on Zinc Oxide (Netherlands Rapporteur, 2003) the reasonable worst-case exposure was estimated at the 90th percentile value of the available data. A similar approach was used for the present exposure assessment. Detailed data sets are required to allow an estimate of the true 90th percentile value. Data were not available at such details and a rough estimate of the 90th percentile was derived using the following three-step procedure. Simple calculations are used for the first two steps while the third step involves 'professional judgement' taking into account the quality of the data sets with an emphasis on the size of the data sets, the medians and the year of sampling. A given data set includes the range of observations. The upper limit of the range was used for ranking the data sets, and all data sets (sub-scenarios) at or above the 90th percentile were considered important for the estimation of the reasonable worst-case exposure. The 90th percentile of the available data sets (N=27; 395 observations) was ≈0.29 mg/m^3. Three data sets had an upper limit at or above this level. An upper limit of exposure at 0.29 mg/m^3 was observed for a sub-group of workers with the task of slitting and blanking. The data set for this group of workers was rather large (27 observations). The median of the data set was low (0.05 mg/m^3). An upper limit of 0.37 mg/m^3 was given for a small data set (3 observations)

for the tasks of sorting and stacking (median exposure level 0.04 mg/m^3). An upper limit of exposure at a level of 0.81 mg/m^3 was reported for a large data set (42 observations). The median of this data set was rather low (0.097 mg/m^3). Thus it appears prudent to consider 0.29 mg/m^3≈0.3 mg/m^3 as an estimate of the reasonable worst-case exposure level. Data on short-term exposure to 'total' airborne nickel seem unavailable, and it is difficult (if not impossible) to derive an estimate on short-term exposure from data characterizing full shift exposure. For the risk assessment of nickel metal (RAR, 2002) no data were available on short-term exposure and an estimate was derived as twice the reasonable worst-case exposure level. A similar approach ('expert judgement') was taken for the present risk assessment. Thus the estimated short-term exposure is 2×0.3 mg/m^3~ 0.6 mg/m^3.

Data are sparse on the size distribution of nickel-bearing aerosols in battery production. Hassler *et al*. (1983) did a comprehensive study at an alkaline battery factory in Sweden and reported cadmium aerosols to consist mainly of respirable particles whereas the nickel particles were coarser. The fraction of respirable nickel was estimated to be 45% of the 'total' aerosol fraction of nickel.

Table 4.1.1.2.3.2.A: Battery production - current exposure to 'total' nickel. Feedstock (nickel powder) for the production was not specified

Ref.	Process	N	Year	Type of Sampler	Aerosol Fraction	Exposure to 'total' nickel mg/m^3					
						'Total' aerosol fraction			Inhalable aerosol fraction		
						Range	Median	95th perc.	Range	Median	95th perc.
HSE-30, 1985*	Neg. cell line operator	10	1985	Personal [1]	Total	0.003-0.050	0.009 [3]	NA [4]	0.004-0.065	0.012 [3]	NA
	Pos. cell line operator	12	1985	Personal [1]	Total	0.006-0.041	0.016 [3]	NA	0.008-0.053	0.021 [3]	NA
	Powder dispenser	1	1985	Personal [1]	Total	NA	0.24 [3]	NA	NA	0.31 [3]	NA
	Leading hand	6	1985	Personal [1]	Total	0.01-0.04	0.09-0.33 [5,9]	NA	0.01-0.052	0.12-0.43 [3,9]	NA
	Other	3	1985	Personal [1]	Total	NA	<0.009-0.24 [5]	NA	NA	<0.012-0.31 [3]	NA
Hammel *et al*., 1990*	Ni plating	12	1988	Personal [2]	Total	0.007-0.038	0.013 [3]	NA	0.009-0.049	0.017 [3]	NA
	Sizing	4	1988	Personal [2]	Total	0.011-0.027	0.012 [3]	NA	0.014-0.035	0.015 [3]	NA
	Spiralling	5	1988	Personal [2]	Total	0.010-0.067	0.055 [3]	NA	0.013-0.086	0.071 [3]	NA
	Impregnation (nitrate solution)	22	1988	Personal [2]	Total	0.004-0.056	0.016 [3]	NA	0.005-0.072	0.021 [3]	NA
	Despiralling	6	1988	Personal [2]	Total	0.008-0.069	0.028 [3]	NA	0.010-0.089	0.036 [3]	NA
	Electrochemical cleaning	14	1988	Personal [2]	Total	0.006-0.079	0.024 [3]	NA	0.008-0.10	0.031 [3]	NA
	Maintenance jobs	40	1988	Personal [2]	Total	0.003-0.092	0.008 [3]	NA	0.004-0.12	0.010 [3]	NA
	Preparation of paste	14	1988	Personal [2]	Total	0.001-0.17	0.008 [3]	NA	0.001-0.22	0.010 [3]	NA
	Tab welding	3	1988	Personal [2]	Total	0.011-0.012	0.011 [3]	NA	0.014-0.015	0.014 [3]	NA
	Paste operation machine	56	1988	Personal [2]	Total	0.000-0.004	0.002 [3]	NA	0-0.005	0.0026 [3]	NA
	Tab staking	18	1988	Personal [2]	Total	0.001-0.003	0.003 [3]	NA	0.001-0.0039	0.0039 [3]	NA
	Slitting	2	1988	Personal [2]	Total	0.012-0.031	0.022 [3]	NA	0.015-0.040	0.028 [3]	NA
	Setting up machines	3	1988	Personal [2]	Total	0.003-0.003	0.003	NA	0.004-0.004	0.004	NA
	Maintenance jobs	15	1988	Personal [2]	Total	0.001-0.011	0.003	NA	0.001-0.012	0.004	NA
	Rovers (job to job)	4	1988	Personal [2]	Total	0.003-0.024	0.003	NA	0.004-0.029	0.004	NA

	Leaders (crew chiefs)	5	1988	Personal [2]	Total	0.001-0.004	0.003	NA	0.001-0.005	0.004	NA
	Rework/reclaim/shaker	16	1988	Personal [2]	Total	0.001-0.014	0.006	NA	0.001-0.017	0.007	NA
	Slitting and blanking	27	1988	Personal [2]	Total	0.008-0.24	0.042	NA	0.010-0.29	0.050	NA
	Sorting and stacking	18	1988	Personal [2]	Total	0.006-0.11	0.033	NA	0.007-0.13	0.040	NA
	Materials handling	3	1988	Personal [2]	Total	0.009-0.31	0.034	NA	0.011-0.37	0.041	NA
	Rework	6	1988	Personal [2]	Total	0.017-0.048	0.028	NA	0.020-0.058	0.034	NA
	Winding cells	17	1988	Personal [2]	Total	0.001-0.11	0.008	NA	0.001-0.13	0.010	NA
	Closing cells	15	1988	Personal [2]	Total	0.001-0.035	0.002	NA	0.001-0.042	0.002	NA
Boiano *et al*., 1983	NA	42	1981	Personal [2]	Total	0.006-0.63	0.075 [6]	NA	0.008-0.81	0.097 [6]	NA
HEDSET, HSE[A]	Plate preparation	7	1987	Personal [8]	Total	0.001-0.33	0.019 [7]	0.33	-	-	-
	Pasting/plating	4	1987	Personal [8]	Total	0.01-0.12	0.018 [7]	0.12	-	-	-
	Other	3	1987	Personal [8]	Total	0.002-0.03	0.0056 [7]	0.03			

*: Data tabulated by NIPERA (1996). A: Current version of UK HSE's NEDB (National Exposure Database). 1: 25-mm closed face filter cassette. 2: 37-mm closed face filter cassette. 3: arithmetic mean. 4: not available. 5: range of mean exposure concentrations. 6: weighted average. 7; geometric mean. 8: unknown type of sampler. 9: The data may not be valid because the median is above the upper limit of the range of observations.

4.1.1.2.3.2.3 Exposure by inhalation - modelled data (EASE 2.0)

The most appropriate EASE scenario for the battery production was considered the task of materials handling such as handling a powder of nickel nitrate. Thus the typical and the reasonable worst-case exposures were modelled for this task. Any manipulation of a dry material enters the EASE model by the term 'dry manipulation'. To model the exposure EASE requires input on the tendency of a material to aggregate. No data are available on the tendency of nickel nitrate to aggregate, and nickel nitrate was considered non-sticky (aggregate is false).

Estimation of the typical exposure level
If sufficient care is exercised to reduce potential exposure the task enter the EASE model as 'low dust technique', and for the modelling this description was considered to be true. For the modelling the control of exposure by local exhaust ventilation was considered present.
Model input:
The name of the substance is nickel nitrate
The temperature of the process is 20
The physical-state is solid
Dust-inhalation is true
Mobile-solid is true
Solid-vp is false
The exposure-type is dust
The particle-size is inhalable
The operations is low dust techniques
The dust-type is non-fibrous
Aggregates is false
The pattern-of-control is local exhaust ventilation present
Model output:
Conclusion: The predicted dust exposure to nickel nitrate is 0-1 mg/m^3

Estimation of the reasonable worst-case exposure level
Model input:
Except for the type of operation and the pattern-of-control model input was kept identical to the input for estimation of the typical exposure level. The type of operation was specified as dry manipulation (includes dry brushing) and the pattern-of-control was specified as no local exhaust ventilation.
Model output:
Conclusion: The predicted dust exposure to nickel nitrate is 5-50 mg/m^3.

The predicted typical exposure level was rather similar to the level as estimated from measured data while the predicted reasonable worst-case exposure level was high. The EASE model is only intended to give generalized exposure data while the measured data (Table 4.1.1.2.3.2.A) were specific for battery production. Thus the exposures as estimated from measured data are taken forward for the risk characterization. Exposure to nickel species by inhalation is estimated as summarized below (Table 4.1.1.2.3.2.B).

Table 4.1.1.2.3.2.B: Estimated exposure by inhalation of nickel species in battery production

Nickel Species (1)	**Typical exposure**			**Worst-case exposure**			**Short-term exposure (mg/m^3)**
	Nickel species as % of 'total' nickel	**Exposure to inhalable 'total' nickel (mg/m^3)**	**Exposure to inhalable nickel species (mg/m^3)**	**Nickel species as % of 'total' nickel**	**Exposure to inhalable 'total' nickel (mg/m^3)**	**Exposure to inhalable nickel species (mg/m^3)**	
SO	100	0.015	0.015	100	0.3	0.3	0.6

1: SO: Nickel species may include metallic nickel, soluble nickel salts, and oxidic nickel. As a worst-case all airborne nickel is considered being soluble (nickel nitrate).

4.1.1.2.3.2.4 Dermal exposure - measured and modelled exposure levels

No measured data for dermal exposure to nickel seem available for the assessment. Hughson (2004) did a study on dermal exposure in the packing of nickel sulphate hexahydrate and nickel hydroxycarbonate at a chemical plant producing nickel sulphate and nickel hydroxycarbonate. The tasks in packing nickel nitrate are expected to

be similar to the tasks in packing nickel sulphate. Thus it appears prudent to estimate the exposure in packing nickel chloride by analogy to the measured data from packing of nickel sulphate. It is noted that the solubility (in water) of nickel chloride is very similar to the solubility of nickel sulphate. In terms of the content (as a percentage) of soluble nickel the mass of contaminants deposited on the skin of nickel sulphate packing operators is expected to be similar to the contaminants experienced by nickel chloride packing operators. Since nickel nitrate crystals or solutions are used as feedstock for the battery production, nickel nitrate packing data would provide the worst-case exposure data for this scenario until measured data is available. The dermal exposure is estimated at the levels tabulated below. Further details of the estimated data are given above (section 4.1.1.2.2.1.4 and 4.1.1.2.2.1.5).

Nickel species	Typical exposure		Reasonable worst-case exposure	
	μg/cm^2/day	mg/day [1]	μg/cm^2/day	mg/day [1]
Total nickel	0.6	1.2	1.0	2.0
Soluble nickel	0.4	0.8	0.7	1.4
Insoluble nickel	0.2	0.4	0.4	0.8

1: The area is 1980 cm^2 (hands: 840 cm^2; forearms: 1140 cm^2)

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4.1.1.2.3.2.5 Discussion and conclusions

Rather comprehensive data on exposure by inhalation of 'total' nickel were available for the scenario. Data were tabulated by sub-groups of workers with similar tasks as an effort to identify groups of workers at high risk of exposure. An emphasis was made to assess exposure in terms of inhalable aerosols. The typical exposure was estimated at a level of 0.015 mg/m^3. Such an exposure was seen for sub-groups of workers with the task of 'sizing'. The reasonable worst-case level was estimated at a level of 0.3 mg/m^3. Such exposure was observed for sub-groups of workers with the task of slitting and blanking. No data were available on groups of nickel species in workroom air, and for the assessment the predominant nickel species of 'total' nickel was considered being all nickel nitrate (worst-case). It is emphasized that more detailed information on groups of nickel species in work room air may lead to a more accurate exposure assessment.

No data were available on dermal exposure to nickel nitrate, and the exposure was estimated by two approaches, (i) by analogy to measured dermal exposure in nickel sulphate production from nickel matte and (ii) by modelling. The measured data focused on nickel compound packing operations. The predicted exposure level (EASE) was much higher than the levels estimated by analogy to measured data. However, the predicted exposure levels produced by EASE are intended to be estimates of potential exposure and do not therefore take into account the attenuating effect of gloves and other protective clothing. For the production of nickel nitrate the highest exposure to nickel nitrate is expected to be during packing of the crystallized chemical. Based on expected similarities in tasks in packing nickel nitrate and packing nickel sulphate it appears prudent to estimate the exposure in nickel nitrate packing operations by analogy to measured data for operations in packing nickel sulphate. Since nickel nitrate crystals or solutions are used as feedstock for the battery production, nickel nitrate packing data would provide the worst-case exposure data for this scenario until measured data is available. In conclusion the estimated levels of exposure to groups of nickel species are summarized below.

Nickel species [(1)]	**Exposure by inhalation (mg/m^3)**			**Dermal exposure (mg/day)**	
	Typical	**Reasonable worst-case**	**Short term**	**Typical**	**Reasonable worst-case**
T	0.015	0.3	0.6		
SO				0.8	1.4
U				0.4	0.8

1: T = Total nickel species - as a worst-case all nickel is considered soluble (nickel nitrate). SO = Soluble nickel considered to be nickel nitrate (worst-case); U = Other nickel species than soluble nickel.

4.1.1.2.3.3 Scenario B3 – Nickel nitrate used in chemical pre-treatment of metals

Nickel nitrate solution and nickel nitrate hexahydrate are used as components of products used in the pre-treatment of metals prior to painting and prior to cold-forming processes such as tube or wire drawing, cold

heading etc.. The nickel concentration in these products is low (<5%). Whilst the numbers of companies producing such products is fairly limited, use of the products for metals pre-treatment is widespread (see section 2.2.1.3). Workers within the overall scenario cannot be expected to have similar tasks. As an effort to identify tasks with high risk of exposure the available data on exposure were tabulated, if possible, for sub-groups (sub-scenarios) of workers with similar tasks. Such listing was kept within a given set of data and no attempt was made to join similar tasks cross data sets. The reason not to join similar tasks cross data sets was that prior to the collapse of similar tasks a statistical analysis is required for identity between data sets in terms of type of statistical distribution, mean and variance. The data for the assessment were not available in details to allow such statistical analysis.

4.1.1.2.3.3.1 Exposure by inhalation – nickel species

No data on airborne nickel species seem available for the assessment and measured concentrations of 'total' nickel are considered being all nickel nitrate (worst-case).

4.1.1.2.3.3.2 Exposure by inhalation – measured exposure levels

Current data (Table 4.1.1.2.3.3.A) on occupational exposure were obtained from industry; no data seem available from literature. If possible data are listed using the format of the specific company data submission scheme, i.e. year(s) of measurement(s), number of samples, range, median and 95th percentile value. It is noted that the vast majority of the data sets were given in terms of full-shift time weighted averages. Thus the listed data are considered full-shift exposure. The information available on the sampling technique and aerosol fraction is included in the listed data. Presumably the GSP sampler (see section 4.1.1.2.1.1) was used for the dust sampling and for the assessment all data are considered personal exposure to inhalable nickel. As tabulated in Table 4.1.1.2.3.3.A all data on exposure by inhalation of 'total' nickel were at or below a concentration of 0.05 mg/m^3 (limit of detection). The typical exposure level was estimated at guessed level of 50% (~0.025 mg/m^3) of the limit of detection, while the reasonable worst-case exposure was estimated (guessed) at the level of the limit of detection (~0.05 mg/m^3). Data on short-term exposure to 'total' airborne nickel seem unavailable, and it is difficult (if not impossible) to derive an estimate on short-term exposure from data characterizing full shift exposure. For the risk assessment of nickel metal (RAR, 2002) no data were available on short-term exposure and an estimate was derived as twice the worst-case exposure level. A similar approach ('expert judgement') was taken for the present risk assessment. Thus the estimated short-term exposure is 2×0.05 mg/m^3~ 0.1 mg/m^3.

Table 4.1.1.2.3.3.A: Nickel nitrate used in chemical pre-treatment of metals – current exposure by inhalation of 'total' nickel.

Ref.	Process	N	Year	Type of Sampler	Aerosol Fraction	Exposure to 'total' nickel mg/m^3					
						'Total' aerosol fraction			Inhalable aerosol fraction		
						Range	Median	95th perc.	Range	Median	95th perc.
HEDSET Comp. #1	Production of nickel nitrate: mixing reactors (equipped with exhaust)	NA*	NA	Personal [1]	'Total'	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
	Use of nickel nitrate (diluted form) in spray tunnels	NA	NA	Personal [2]	'Total'	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
	Use of nickel nitrate (diluted form) in open tanks or in enclosed installations	NA	NA	Personal [1]	'Total'	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05

*: Not available. 1: GSP filter cassette (presumably).

4.1.1.2.3.3.3 Exposure by inhalation - modelled data (EASE 2.0)

Preparation of solutions was considered the most appropriate EASE scenario nickel nitrate used in chemical pre-treatment of metals. Thus the typical and the reasonable worst-case exposures were modelled for this task. Any manipulation of a dry material enters the EASE model by the term 'dry manipulation'. To model the exposure EASE requires input on the tendency of a material to aggregate. No data are available on the tendency of nickel nitrate to aggregate, and nickel nitrate was considered non-sticky (aggregate is false).

Estimation of the typical exposure level
If sufficient care is exercised to reduce potential exposure the task enter the EASE model as 'low dust technique', and for the modelling this description was considered to be true. For the modelling the control of exposure by local exhaust ventilation was considered present.
Model input:
The name of the substance is nickel nitrate
The temperature of the process is 20
The physical-state is solid
Dust-inhalation is true
Mobile-solid is true
Solid-vp is false
The exposure-type is dust
The particle-size is inhalable
The operations is low dust techniques
The dust-type is non-fibrous
Aggregates is false
The pattern-of-control is local exhaust ventilation present
Model output:
Conclusion: The predicted dust exposure to nickel nitrate is 0-1 mg/m^3

Estimation of the reasonable worst-case exposure level
Model input:
Except for the type of operation and the pattern-of-control model input was kept identical to the input for estimation of the typical exposure level. The type of operation was specified as dry manipulation (includes any manipulation, also dry brushing) and the pattern-of-control was specified as no local exhaust ventilation.
Model output:
Conclusion: The predicted dust exposure to nickel nitrate is 5-50 mg/m^3.

As estimated from measured data the typical exposure level was rather similar to the level predicted from EASE. By contrast to the worst-case exposure level estimated from measured date the level was high as predicted by EASE. The EASE model is only intended to give generalized exposure data while the measured data (Table 4.1.1.2.3.3.A) were specific for nickel nitrate used in chemical pre-treatment of metals. Thus the exposures as estimated from measured data are taken forward for the risk characterization. Exposure to nickel species by inhalation is estimated as summarized below (Table 4.1.1.2.3.3.B).

Table 4.1.1.2.3.3.B: Estimated exposure by inhalation of nickel in chemical pre-treatment of metals

Nickel Species (1)	**Typical exposure**			**Worst-case exposure**			**Short-term exposure (mg/m^3)**
	Nickel species as % of 'total' nickel	**Exposure to inhalable 'total' nickel (mg/m^3)**	**Exposure to inhalable nickel species (mg/m^3)**	**Nickel species as % of 'total' nickel**	**Exposure to inhalable 'total' nickel (mg/m^3)**	**Exposure to inhalable nickel species (mg/m^3)**	
SO	100	0.025	0.025	100	0.05	0.05	0.1

1: SO: As a worst-case all airborne nickel is considered being soluble (nickel nitrate).

4.1.1.2.3.3.4 Dermal exposure - measured exposure levels

Dermal exposure during metal treatments is likely to occur when bath solutions are made up and added to the treatment bath. The nickel nitrate enters the process as a liquid. There is also the possibility of dermal exposure from handling of treated articles and splashes from drag-out. For the scenario no data seem available on dermal exposure to nickel nitrate. Bavazzano *et al*. (1994) performed a study on hand and facial contamination in 41

male subjects employed in electroplating operations in 25 small factories in Italy. Male subjects (N=15) non-professionally exposed to nickel served as control subjects. In most cases the sub-group of electroplating workers performed manual dipping operations (no automation) and local exhaust systems were operated on the electroplating tanks. Unfortunately no information was given on the use of personal protective equipment (gloves). Samples were taken by wiping worker's hands and face with a paper filter (10×10 cm^2) moistened with benzalconium chloride 1:750 and alcohol 20%. Nickel nitrate (diluted form) can be used in open tanks for chemical pre-treatment of metals. In terms of dermal exposure such a process might be rather similar to electroplating operations, and the data (Table 4.1.1.2.3.3.C) provided by Bavazzano *et al*. (1994) are considered a rough estimate for the dermal exposure to nickel chemicals in the pre-treatment of metals by an approach of open tanks. It is emphasized that the validity of such analogy remains unknown. For the scenario nickel deposited on the skin was considered being all nickel nitrate (worst-case).

Table 4.1.1.2.3.3.C: Measured dermal exposure to nickel in electroplating operations (Bavazzano et al., 1994).*

Percentiles	**Electroplaters (N=41)**		**Control subjects (N=15)**	
	Facial contamination (µg/day)	**Contamination of the hands (µg/day)**	**Facial contamination (µg/day)**	**Contamination of the hands (µg/day)**
5	1.1	5.6	-	-
50	9.0	39	0.79	0.30
95	60	370	-	-
Range	1.0-86	1.9-550	0.01-5.3	0.01-2.4

* Sampling was performed at the end of the work shift. The surface area measured in the study was quite high since the exposure of both hands and fingers were included.

4.1.1.2.3.3.5 Dermal exposure - modelled data (EASE 2.0)

The dermal exposure is modelled for chemical pre-treatment of metals by an approach of open tanks and the modelling is focused on drag-out of the treated articles from the bath. Thus the typical and the reasonable worst-case exposures were modelled for this task. The drag-out is carried out by a sub-group of workers with the knowledge of the process. For input to the EASE model such practice is characterized as non-dispersive use. For the modelling it is assumed that the workers handles all materials directly. For input to the EASE model such method of production is characterized as direct handling.

Estimation of the typical exposure level
The level of process activity may be low and 2-10 events per day was assumed. For input to the EASE such level of activity is characterized as intermittent level of contact.
Model input:
The name of the substance is nickel nitrate
The temperature of the process is 20
The physical-state is solid
Dust-inhalation is false
Solid-vp is false
The exposure-type is dermal
The use-pattern is non-dispersive use
The pattern-of-control is direct handling
The contact-level is intermittent
Model output:
Conclusion: The predicted dermal exposure to nickel nitrate is 0.1-1 mg/cm^2/day

Estimation of the reasonable worst-case exposure level
Except for the type contact level model input was kept identical to the input for estimation of the typical exposure level. The drag-out of articles from the baths was assumed being an extensive process (more than 10 events per day). For input to the EASE such level of activity is characterized as an extensive level of contact.
Model input:
The contact-level is extensive
Model output:
Conclusion: The predicted dermal exposure to nickel nitrate is 1-5 mg/cm^2/day

On condition that the palms of both hands are exposed (420 cm^2) the estimated typical exposure level ranged from 42 mg/day to 420 mg/day, while the reasonable worst-case exposure level ranged from 420 mg/day to 2100 mg/day.

Compared to the measured data (Table 4.1.1.2.3.3.C) the predicted exposure level is high by several orders of magnitude. The measured data were obtained by an approach of wipe sampling. Such a method is well known in characterizing the contamination of surfaces including the skin. It has to be noted than skin wipes may not collect all of the contaminant deposited on the worker's skin during exposure. As pointed out by McArthur (1992) the mass of material that has penetrated into the epidermis during exposure may not be recovered and for such cases the quantity of contaminant remaining on the skin is excluded from the exposure estimates. The sampling efficiency in wiping settled dust from a range of non-specified types of solid surfaces was as a rough estimate reported at a level of 50%, but the degree of precision was considered low (Lichtenwalner, 1992). By contrast to wipe sampling from solid surfaces it appears prudent to assume a low efficiency in sampling from the skin, but no data are available to estimate the bias of dermal exposure as estimated from wiping. Thus the dermal exposure data reported by Bavazzano *et al*. (1994) should be considered biased towards low levels. As already mentioned the Bavazzano-study has no details on the use of gloves. Thus the data might characterize a sub-group of workers at low risk of exposure by the use of gloves. It is emphasized that no information is available for testing the validity of such hypothesis. The EASE model is only intended to give generalized exposure data while the measured data provided by Bavazzano *et al*. (1994) were specific for electroplating. Although the bias of the Bavazzano-study remains unknown the reported data are taken forward to the risk characterization. It has to be emphasized that the validity of the analogy from exposure in electroplating to exposure in chemical pre-treatment of metals remains unknown. On condition the contaminants deposited on the skin has a content of nickel species similar to the airborne dust (≈all nickel nitrate) the typical (50^{th} percentile) and worst-case (95^{th} percentile) dermal exposure of the hands to nickel nitrate is estimated as given below. These levels can be used in risk characterization comparison with acute toxicity data.

Nickel species [1]	**Typical exposure**			**Worst-case exposure**		
	Nickel species as % of 'total' nickel	**Exposure to 'total' nickel (µg/day)**	**Exposure to nickel species (µg/day)**	**Nickel species as % of 'total' nickel**	**Exposure to 'total' nickel (µg/day)**	**Exposure to nickel species (µg/day)**
SO	100	39	39	100	370	370

1: SO = All nickel is considered being nickel nitrate (worst-case).

4.1.1.2.3.3.6 Discussion and conclusions

Rather few data were available for the assessment of exposure by inhalation of 'total' nickel in the chemical pre-treatment of metals. Data were tabulated by sub-groups of workers with similar tasks as an effort to identify groups of workers at high risk of exposure. An emphasis was made to assess exposure in terms of inhalable aerosols. All data sets reported the exposure by inhalation at levels below 0.05 mg/m^3 (limit of detection) and the typical exposure level was estimated (guessed) at 50% of the limit of detection. The reasonable worst-case level was estimated (guessed) at the limit of detection. It is noted that the reasonable worst-case exposure is biased towards a high level. No data were available on groups of nickel species in workroom air, and for the assessment the predominant nickel species of 'total' nickel was considered to be nickel nitrate (worst-case). It is emphasized that more detailed information on exposure by inhalation of groups of nickel species in work room air may lead to a more accurate exposure assessment.

No measured data on dermal exposure were available for the scenario. Measured data on dermal exposure were available for electroplaters and by analogy these data were considered useful for workers using nickel nitrate in open tanks for chemical pre-treatment of metals. It has to be noted that, (i) the validity of such analogy remains unknown and (ii) the sampling efficiency of the method used for measuring the dermal exposure in electroplating was less than 100%. The estimated typical exposure level was orders of magnitude low by contrast to the typical exposure level as predicted by the EASE model. A similar tendency in difference of magnitude was observed for the reasonable worst-case exposure level. The EASE model is only intended to give generalized exposure data, while the measured data were collected for the tasks of electroplaters. Although the validity of the exposure as estimated from the measured data remains unknown it appears prudent to take the estimated exposure levels forward to the risk characterization. As a first approximation nickel speciation of contaminants deposited on the skin was assumed being all nickel nitrate (worst-case). Personal protective equipment is a common approach to reduce dermal exposure in the chemical pre-treatment of metals. However, contamination

of the protective gear is almost impossible to avoid; thus an additional risk of exposure caused by contaminated personal protective equipment cannot be excluded. In conclusion the estimated levels of exposure to nickel nitrate are summarized below.

Nickel species (1)	Exposure by inhalation (mg/m³)			Dermal exposure (µg/day)	
	Typical	Worst-case	Short term	Typical	Worst-case
SO	0.025	0.05	0.1	20	370

1: SO = Soluble nickel salts considered being all nickel nitrate (worst-case).

4.1.1.2.3.4 Scenario B4 – Other uses of nickel: chemicals production

4.1.1.2.3.4.1 Exposure by inhalation – nickel species

Nickel nitrate is used as an intermediate in the manufacture of other nickel chemicals. No data seem available on airborne nickel species in the production of such chemicals. Hughson (2004) reported speciated inhalation exposure data measured in a facility producing nickel sulphate and nickel carbonate from nickel matte. The production of nickel sulphate involves exposure to soluble nickel during the production process. The use of nickel nitrate as an intermediate in the production of chemicals involves exposure to soluble nickel, and by analogy the data reported by Hughson (2004) were considered useful for the exposure assessment. It is noted that the validity of such analogy remains unknown. The data are summarized below. As a percentage of total nickel the dust had a content of soluble nickel ranging from 29% to 73%. The median of the data (≈60%) is considered a typical content while a content of 100% is considered a worst-case situation. It is noted that the data by Hughson (2004) is combined exposure to nickel sulphate and nickel carbonate. Thus the data are not considered useful for an estimate of the worst-case content of soluble nickel. For the exposure assessment soluble nickel is considered being all nickel nitrate (worst-case).

Process[1]	N	Exposure			Content of total Ni as % of dust	Content of soluble Ni as % of total Ni
		Dust (mg/m³)	Soluble Ni (µg/m³)	Insoluble Ni (µg/m³)		
Packing of Ni sulphate	4	0.5[2] (0.2-0.7)[3]	4 (2-11)	2 (2-4)	2 (0.7-5)	60 (50-73)
Packing of Ni carbonate	4	0.4 (0.3-5.9)	6 (1-41)	3 (1-20)	1 (0.5-4.7)	60 (50-71)

1: The two different processes noted are the specific jobs of the workers but the jobs occur in the same work area and workers rotate between these processes so exposures are a combination of both processes. 2: Median. 3: Range

4.1.1.2.3.4.2 Exposure by inhalation – measured and modelled exposure levels

Industry has not supplied information about this method of production. Hughson (2004) measured exposure by inhalation of soluble and insoluble nickel at a chemical plant that used nickel sulphate solution to produce nickel sulphate hexahydrate and nickel hydroxycarbonate. The chemical reactions and transfer of compounds to the packing area was entirely automatic and completely enclosed. The study focused on workers operating the packing equipment. By analogy the reported data (Table 4.1.1.2.3.4.A) are considered useful for the present scenario.

Table 4.1.1.2.3.4.A. Scenario B4: Production of chemicals – current exposure to soluble and insoluble nickel (Hughson, 2004).

Ref	Process[2]	N	Year	Type of sampler	Aerosol fraction	Exposure to nickel µg/m³					
						Inhalable aerosol fraction					
						Range		Median		90th percentile	
Hughson,	Packing Ni	4	2003-	Personal	Inhalable	1-41	SO[1]	6	SO	41	SO

2004	Carbonate		2004			1-20	U	3	U	20	U
	Packing Ni Sulphate	4	2003-2004	Personal	Inhalable	2-11	SO	4	SO	11	SO
						2-4	U	3	U	4	U

1: SO = Soluble nickel considered to be all nickel nitrate (worst case). U = Other nickel species than soluble nickel.
2: The two different processes noted are the specific job of the workers but the jobs occur in the same work area and workers rotate between these processes so exposures are a combination of both processes.

The RAR on nickel metal has a scenario (C5) for nickel metal in the production of other nickel-containing chemicals. That scenario covers an enormous range of processes and the typical exposure to total nickel was estimated at levels ranging from 6 μg/m^3 to 450 μg/m^3, while the worst-case exposure was estimated to be 7000 μg/m^3. The data reported by Hughson (2004) indicate an exposure rather similar to the lower limit of the typical exposures estimated for scenario C5 in the RAR on nickel metal. The data set reported by Hughson (2004) is rather small and the data may not reflect exposure to nickel throughout the enormous range of processes covered by the scenario. Thus it appears prudent to estimate the exposure by analogy to scenario C5 in the RAR for nickel metal.

4.1.1.2.3.4.3 Exposure by inhalation – modelled data (EASE 2.0)

For the assessment packaging of nickel chemicals was considered a common task. Thus the typical and the reasonable worst-case exposures were modelled for this task. Any manipulation of a dry material enters the EASE model by the term 'dry manipulation'. To model the exposure EASE requires input on the tendency of a material to aggregate. No data are available on the tendency of a nickel chemical to aggregate, and a chemical was considered non-sticky (aggregate is false).

Estimation of the typical exposure level
If sufficient care is exercised to reduce potential exposure the task enter the EASE model as 'low dust technique', and for the modelling this description was considered to be true. For the modelling the control of exposure by local exhaust ventilation was considered present.

Model input:
The name of the substance is nickel nitrate
The temperature of the process is 20
The physical-state is solid
Dust-inhalation is true
Solid-vp is false
The exposure-type is dust
The particle-size is inhalable
The operations is low dust techniques
The dust-type is non-fibrous
Aggregates is false
The pattern-of-control is local exhaust ventilation present
Model output:
Conclusion: The predicted dust exposure to nickel nitrate is 0-1 mg/m^3

Estimation of the reasonable worst-case exposure level
Model input:
Except for the type of operation and the pattern-of-control model input was kept identical to the input for estimation of the typical exposure level. The type of operation was specified as dry manipulation (includes any manipulation, also dry brushing) and the pattern-of-control was specified as no local exhaust ventilation.
Model output:
Conclusion: The predicted dust exposure to nickel nitrate is 5-50 mg/m^3.

The predicted typical exposure levels are rather similar to the exposure levels estimated by analogy to scenario C5 in the RAR on nickel metal. The measured data of scenario C5 provide more detailed information than the EASE model, and the data from scenario C5 are used for the assessment. Current exposure to groups of nickel species is estimated as listed below (Table 4.1.1.2.3.4.B).

Table 4.1.1.2.3.4.B: Estimated exposure by inhalation of nickel in the production of chemicals.

Nickel	Typical exposure	Worst-case exposure	Short-term

Species [1]	Nickel species as % of 'total' nickel	Exposure to inhalable 'total' nickel (mg/m^3)	Exposure to nickel species (mg/m^3)	Nickel species as % of 'total' nickel	Exposure to inhalable 'total' nickel (mg/m^3)	Exposure to nickel species (mg/m^3)	exposure (mg/m^3)
SO	60	0.006-0.45	0.004-0.27	100	7.0	7.0	14
U	40	0.006-0.45	0.002-0.18	≈0	7.0	≈0	≈0

1: SO = Soluble nickel considered to be all nickel nitrate (worst case). U = Other nickel species than soluble nickel.

4.1.1.2.3.4.4 Dermal exposure –measured and modelled exposure levels

No measured data for dermal exposure to nickel seem available for the assessment. Hughson (2004) did a study on dermal exposure in the packing of nickel sulphate hexahydrate or nickel hydroxycarbonate at a chemical plant producing nickel sulphate and nickel hydroxycarbonate. The tasks in packing nickel nitrate are expected to be similar to the tasks in packing nickel sulphate. Thus it appears prudent to estimate the exposure in packing nickel nitrate by analogy to the measured data from packing of nickel sulphate. Since nickel nitrate crystals or solutions are used, as feedstock for the production of chemicals, nickel nitrate packing data would provide the worst-case exposure data for this scenario until measured data is available. It is noted that the solubility (in water) of nickel nitrate is rather similar to the solubility of nickel sulphate. In terms of the content (as a percentage) of soluble nickel the mass of contaminants deposited on the skin of nickel sulphate packing operators is expected to be similar to the contaminants experienced by nickel nitrate packing operators. Thus the dermal exposure is estimated at the levels tabulated below. Further details of the estimated data are given above (section 4.1.1.2.2.1.4 and 4.1.1.2.2.1.5).

Nickel species	Typical exposure		Reasonable worst-case exposure	
	$\mu g/cm^2/day$	mg/day [1]	$\mu g/cm^2/day$	mg/day [1]
Total nickel	0.6	1.2	1.0	2.0
Soluble nickel	0.4	0.8	0.7	1.4
Insoluble nickel	0.2	0.4	0.4	0.8

1: The area is 1980 cm^2 (hands: 840 cm^2; forearms: 1140 cm^2)

4.1.1.2.3.4.5 Discussion and conclusions

No data were available for the assessment of exposure by inhalation of 'total' nickel in the production of nickel containing chemicals. The exposure was estimated by analogy to measured data for exposure to nickel metal in the production of nickel-containing chemicals. Soluble nickel as a percentage of 'total' nickel was estimated by analogy to speciated data collected at the packing of nickel sulphate and nickel carbonate For the assessment soluble nickel was considered all nickel nitrate (worst case). It has to be emphasized that the validity of the estimated exposure remains unknown.

No data were available on dermal exposure to nickel nitrate, and the exposure was estimated by two approaches, (i) by analogy to measured dermal exposure in nickel sulphate production from nickel matte and (ii) by modelling. The measured data focused on nickel compound packing operations. The predicted exposure level (EASE) was much higher than the levels estimated by analogy to measured data. However, the predicted exposure levels produced by EASE are intended to be estimates of potential exposure and do not therefore take into account the attenuating effect of gloves and other protective clothing. For the production of nickel nitrate the highest exposure to nickel nitrate is expected to be during packing of the crystallized chemical. Based on expected similarities in tasks in packing nickel nitrate and packing nickel sulphate it appears prudent to estimate the exposure in nickel nitrate packing operations by analogy to measured data for operations in packing nickel sulphate. Since nickel nitrate crystals or solutions are used as feedstock for the production of chemicals, nickel nitrate packing data would provide the worst-case exposure data for this scenario until measured data is available. In conclusion the estimated levels of exposure to groups of nickel species are summarized below.

Nickel species [1]	Exposure by inhalation (mg/m^3)			Dermal exposure (mg/day)	
	Typical	Reasonable worst-case	Short term	Typical	Reasonable worst-case

SO	0.004-0.27	7.0	14	0.8	1.4
U	0.002-0.18	≈0	≈0	0.4	0.8

1: SO = Soluble nickel salts considered being all nickel nitrate (worst-case); U = Insoluble nickel species

4.1.1.2.4 Overall conclusions

Comprehensive data on exposure by inhalation of 'total' nickel were available for some scenarios while data were sparse on other scenarios. In general data were sparse on exposure to groups of nickel species and for most scenarios 'total' airborne nickel was considered being all nickel nitrate (worst-case). Most data on exposure by inhalation were reported in terms of the 'total' aerosol fraction and for the assessment an effort was made to convert the data to the inhalable fraction. Within a scenario data on exposure by inhalation of nickel were given, if possible, for sub-groups of workers with similar tasks. By such grouping it proved possible to identify high-risk sub-groups of workers within some scenarios.

No data on dermal exposure were available for the assessment, and for most scenarios (A1-B2, B4) exposure was estimated by analogy to dermal exposure measured for operators involved in the packing of nickel sulphate hexahydrate or nickel hydroxycarbonate. The tasks in packing nickel nitrate is expected to be similar to the tasks in packing nickel sulphate and nickel carbonate. Thus the analogy from nickel sulphate/carbonate packing operators to nickel nitrate packing operators is considered valid for the production of nickel nitrate (scenario A1-A2). For the use of nickel nitrate (scenario B1-B2, B4) the handling of nickel nitrate is expected to be less intensive than in the packing of the chemical. Thus the estimated exposure for these three scenarios is considered biased towards high levels. For the scenario on chemical pre-treatment of metals (scenario B3) the dermal exposure was estimated by analogy to measured exposure in electroplating operations. The tasks in scenario B3 are expected to be rather similar to the tasks in electroplating operations. Thus the analogy is considered valid. The predicted exposure level (EASE) for all scenarios was much higher than the levels estimated by analogy to measured data. However, the predicted exposure levels produced by EASE are intended to be estimates of potential exposure and do not therefore take into account the attenuating effect of gloves and other protective clothing.

It is recognized that more detailed information on exposure by inhalation of dust and by dermal exposure may lead to a more accurate exposure assessment. The estimated exposure levels for the scenarios taken forward to risk characterization are summarized in Table 4.1.1.2.4.A.

Table 4.1.1.2.4.A: Estimated exposure by inhalation of nickel species throughout scenarios taken foreword to risk characterization. Estimated dermal exposure levels are included in the table.

Scenario	**Comment**	**Time scale of exposure**		**Estimated exposure to inhalable nickel (mg/m^3)**								**Dermal exposure (mg/day)**			
		Duration	**Frequency**	**Full shift (8 hour time weighted average)**						**Short-term**		**Typical**		**Reasonable worst-case level**	
		(hr/day)	**(day/year)**	Typical level		Method	Reasonable worst-case level		Method	Level		Method				
A1	Nickel nitrate production from metallic nickel	6-8	200	0.2	SO [1]	Meas. [2]	1.6	SO	Meas.	3.2	SO	Exp. [3]	0.8 [4] 0.4 [4]	SO U	1.4 [4] 0.8 [4]	SO U
A2	Nickel nitrate production from secondary raw materials	6-8	200	0.07 0.05	SO U	Meas.	1.0 0	SO U	Meas.	2.0 0	SO U	Exp.	0.8 [4] 0.4[4]	SO U	1.4 [4] 0.8 [4]	SO U
B1	Nickel nitrate used in the production of catalysts	6-8	200	0.002 0.05	SO U	Meas.	0.3 4.1	SO U	Meas.	0.6 8.2	SO U	Exp.	0.8 [4] 0.4 [4]	SO U	1.4 [4] 0.8 [4]	SO U
B2	Nickel nitrate used in the production of nickel-cadmium batteries	6-8	200	0.015	SO	Meas.	0.3	SO	Meas.	0.6	SO	Exp.	0.8 [4] 0.4 [4]	SO U	1.4 [4] 0.8 [4]	SO U
B3	Nickel nitrate used in chemical pre-treatment of metals	6-8	200	0.025	SO	Meas.	0.05	SO	Meas.	0.1	SO	Exp.	0.04[5]	SO	0.4[5]	SO
B4	Other uses of nickel: chemicals production	6-8	200	0.004-0.27 0.002-0.18	SO U	Ana. [6]	7.0 0	SO U	Ana. [6]	14 0	SO U	Ana. [6]	0.8 [4] 0.4 [4]	SO U	1.4 [4] 0.8 [4]	SO U

1: SO = Soluble nickel considered being all nickel nitrate (worst-case); U = Other nickel species than soluble nickel. 2: The estimate was derived from measured data. 3: 'Expert judgement'. 4: The mass of dust deposited on the skin was estimated by analogy to dermal exposure measured for operators involved in packing nickel sulphate and nickel carbonate. 5: The mass of dust deposited on the skin was estimated by analogy to dermal exposure measured in electroplating operations. 6: The RAR on nickel metal has a scenario for nickel metal in the production of nickel-containing chemicals. The exposure was estimated by analogy to that scenario.

4.1.1.3 Consumer exposure.

There is no reported consumer exposure to nickel nitrate.

4.1.1.4 Exposure of man via the environment.

See the common MvE RAR for the nickel substances (nickel; nickel carbonate; nickel chloride; nickel dinitrate and nickel sulphate): "Humans exposed indirectly via the environment and combined exposure - exposure assessment and risk characterisation".

4.1.1.5 Combined exposure.

See the common MvE RAR for the nickel substances (nickel; nickel carbonate; nickel chloride; nickel dinitrate and nickel sulphate): "Humans exposed indirectly via the environment and combined exposure - exposure assessment and risk characterisation".

4.1.2 Human health effects assessment.

This section deals with the health effect assessment of nickel nitrate. Studies performed with nickel nitrate are described here. Other nickel compounds now under review under EU Regulation 793/93 are nickel metal, nickel sulphate, nickel chloride, and nickel carbonate. The results of studies carried out on other nickel compounds may have relevance for the effect assessment of nickel nitrate. Studies performed with other nickel compounds will be described in either the Risk Assessment reports for the specific compound or in the *Background document in support of the individual Risk Assessment Reports*. Where considered relevant, results obtained from other nickel compounds can be included in the discussion sections, and may influence the final conclusion for nickel nitrate.

Very little information has been provided by the European producers of nickel nitrate. However, a lot of information on nickel and nickel compounds in general has been provided by industry. Much additional data on nickel and nickel compounds have been published. A search in Toxline gave 2538 hits for nickel and toxicity, 5077 hits for nickel and effects, and about 16000 hits for nickel and sensitisation. Much of these data have been reviewed in good quality reviews including UK HSE (1987), IARC (1990), IPCS (1991, 1996), US ATSDR (1995) and a Nordic Expert Group (Aitio 1995). The effects of nickel on the skin have also been reviewed (Maibach & Menné, Eds. 1989). NiPERA in collaboration with Eurométaux have also produced a criteria document for nickel and nickel compounds for the European Commission (NiPERA 1996). Toxicology Excellence for Risk Assessment (TERA) has prepared a toxicological review of soluble nickel salts for Metal Finishing Association of Southern California Inc., US-EPA and Health Canada (TERA 1999). These reviews plus (where considered relevant) the primary literature, have been used widely in this risk assessment report as it is felt that much of the essential data to establish possible hazards and risks of nickel for human health has already been adequately evaluated. This implies that not all the studies cited in this risk assessment report have been checked and studies have often been described in a summary form. When information is cited from reviews, the primary source is given with the notation "quoted from".

Since there is little data on the specific substance under review, the effects have been evaluated using data from other relevant nickel compounds. It is assumed that the nickel cation is the determining factor for systemic toxicity. Ideally, the actual or bioavailable concentration, which is important for the systemic toxicity should form the basis for the effect assessment in both experimental animals and in humans. Nickel exists in different forms, some of which are more bioavailable than others. 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. Ideally, data on the solubility of the nickel compounds in biological fluids are preferable; however, no data are available regarding the solubility of any of the five prioritised nickel compounds in biological fluids. For the purpose of risk characterisation the water solubility will be used as a prediction of the solubility in biological fluids although realising that such a prediction might not be correct as some data indicate that compounds insoluble or slightly soluble in water might be more soluble in biological fluids.

With respect to local effects, the nickel ion may not be responsible for the toxic effects in all situations. Therefore, use of data on other nickel compounds in evaluations of local effects of an individual nickel compound is considered on a case-by-case basis.

When expressing results, the term “significant” is used only if the result is statistically significant at a p-level lower than 0.05.

4.1.2.1 Toxico-kinetics, metabolism and distribution

4.1.2.1.1 Absorption

4.1.2.1.1.1 Animal studies

4.1.2.1.1.1.1 Inhalation

No studies regarding absorption and retention of nickel following inhalation of nickel nitrate have been located.

4.1.2.1.1.1.2 Oral

Following administration of a single dose of 10 mg nickel (nickel nitrate in 5% starch saline solution) by gavage to male Wistar rats, the absorption was 34% (Ishimatsu *et al*. 1995).

4.1.2.1.1.1.3 Dermal

No studies regarding absorption and retention following dermal contact to nickel nitrate have been located.

4.1.2.1.1.2 Human data

No data regarding absorption and retention of nickel nitrate in humans have been located.

4.1.2.1.1.3 In vitro studies

Tanojo et al. (2001) quantified the *in vitro* permeation of several nickel salts (nickel sulphate, nickel chloride, nickel nitrate and nickel acetate) through human stratum corneum from cadaver leg skin by using a continuous flow-through diffusion cell system. An aqueous solution of nickel nitrate hexahydrate (at 1% Ni^{2+} concentration) was used as the donor solution with pure water as the receptor fluid. Nickel concentrations in the donor and receptor fluid, as well as in the stratum corneum were analysed. After 96 hours, 82.5% of the dose was recovered in the donor solution with 0.5% in the receptor fluid and 1% in the stratum corneum; the total recovery was about 84%.

4.1.2.1.2 Distribution and elimination

No data regarding distribution and elimination in experimental animals or in humans following exposure to nickel nitrate have been located.

4.1.2.1.2.1 Transplacental transfer

Transplacental transfer has been demonstrated in rodents following administration of nickel chloride and nickel has been shown to cross the human placenta. These aspects will be further addressed in the *Risk Assessment Report on nickel chloride* as well as in the *Background document in support of the individual Risk Assessment Reports*.

4.1.2.1.2.2 Cellular uptake

According to TERA (1999), nickel can enter animal cells by three different mechanisms: uptake via metal ion transport, systems, diffusion of lipophilic nickel compounds through the membrane, and phagocytosis. 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 transport systems or through membrane diffusion. These aspects are discussed further in the *Background document in support of the individual Risk Assessment Reports*.

4.1.2.1.3 Discussion and conclusions

The toxicokinetics of nickel nitrate have been investigated to a very limited extent.

4.1.2.1.3.1 Absorption

4.1.2.1.3.1.1 Inhalation

No data regarding the absorbed fraction of nickel in humans or experimental animals following inhalation of nickel nitrate have been located.

The deposition of particles in the respiratory tract depends on the particle sizes (MMADs) as well as on other characteristics of the particles, and the absorption of nickel from the respiratory tract into the blood stream depends on the solubility of the nickel compound inhaled. Soluble nickel compounds, such as nickel nitrate, are expected to be absorbed from the respiratory tract following inhalation exposure.

One study of nickel sulphate in rats (Medinsky et al. 1987) using intratracheal instillation of nickel sulphate (as a solution in saline) showed that 50 to 80% of a dose (dependent on the dose) of nickel sulphate can be absorbed from the respiratory tract. Studies in rats using intratracheal instillation of nickel chloride (Carvalho & Ziemer 1982, English et al. 1981, Clary 1975) showed that up to approximately 97% of a dose of nickel chloride can be absorbed from the respiratory tract. By assuming that the absorption of nickel following inhalation exposure to nickel chloride is similar to absorption following intratracheal instillation, the absorption of nickel from the respiratory tract following inhalation of nickel chloride might be as high as about 97%. Furthermore, an inhalation study on nickel sulphate (Benson et al. 1995) showed that clearance of nickel sulphate from the lungs of rats and mice is extensive (up to 99% in rats and 80 to 90% in mice). By assuming that the clearance of nickel sulphate particles (respirable particles, MMADs ranging from 2.0 to 2.4 µm) from the lungs in the inhalation study is due to absorption rather than to deposition or by mucociliary action, the absorption of nickel from the lungs following inhalation of nickel sulphate might be as high as up to 99% (at concentrations up to 0.11 mg Ni/m^3 in rats and up to 0.22 mg Ni/m^3 in mice). For further details, the reader is referred to the *Risk Assessment Reports on nickel sulphate and nickel chloride* as well as to the *Background document in support of the individual Risk Assessment Reports.*

In conclusion, the available data on nickel chloride and nickel sulphate indicate that the absorption of nickel following inhalation of these nickel compounds might be as high as up to 97-99%; it should be noted that the fraction absorbed apparently depends on the concentration of the nickel compound in the inhaled air as well as on the duration of exposure. For the purpose of risk characterisation, a value of 100% will be taken forward to the risk characterisation for the absorbed fraction of nickel from the respiratory tract following exposure by inhalation of nickel nitrate for particulates with an aerodynamic diameter below 5 µm (respirable fraction). For nickel particulates with aerodynamic diameters above 5 µm (non-respirable fraction), the absorption of nickel from the respiratory tract is considered to be negligible as these particles predominantly will be cleared from the respiratory tract by mucociliary action and translocated into the gastrointestinal tract and absorbed. Hence, for the non-respirable fraction, 100% clearance from the respiratory tract by mucociliary action and translocation into the gastrointestinal tract is assumed and the oral absorption figures can be taken.

For further details, the reader is referred to the *Background document in support of the individual Risk Assessment Reports*.

4.1.2.1.3.1.2 Oral

Absorption of nickel following oral ingestion of nickel nitrate has been evaluated in one study in rats (Ishimatsu et al. 1995), which showed an absorption of 34% when nickel nitrate was administered in a 5% starch saline solution. No human data have been located.

The absorption of nickel sulphate following oral exposure can be as high as 27% when nickel sulphate is administered in drinking water to fasting individuals (or to fasting individuals), while absorption seems to be around 1 to 5% when administered together with food and to non-fasting individuals. For further details, the reader is referred to the *Risk Assessment Report on nickel sulphate* as well as to the *Background document in support of the individual Risk Assessment Reports*.

A study on volunteers (Nielsen et al. 1999), in which the nickel compound administered was not specified, showed that 25.8% of the administered dose was excreted in the urine following administration of nickel in drinking water to fasting individuals compared with 2.5% when nickel was mixed into a meal. Based on experimental data from various human studies, Diamond et al. (1998) have used a biokinetic model to estimate nickel absorption; the results showed that estimated nickel absorption ranged from 12-27% of the dose when nickel was ingested after a fast, to 1-6% when nickel was administered either in food, in water, or in a capsule during (or in close proximity to) a meal. For further details, the reader is referred to the *Background document in support of the individual Risk Assessment Reports*.

In conclusion, the available data indicate that the absorption of nickel following administration in the drinking water to fasting individuals might be as high as up to about 25-27% and about 1-6% when administered to non-fasting individuals and/or together with (or in close proximity to) a meal. For the purpose of risk characterisation, a value of 30% will be taken forward to the risk characterisation for the absorbed fraction of nickel from the gastrointestinal tract following oral exposure to nickel nitrate in the exposure scenarios where fasting individuals might be exposed to nickel nitrate. In all the other exposure scenarios, a value of 5% will be used for the absorbed fraction of nickel from the gastrointestinal tract.

For further details, the reader is referred to the *Background document in support of the individual Risk Assessment Reports*.

4.1.2.1.3.1.3 Dermal

When considering dermal absorption, a distinction should be made between penetration of nickel into skin and percutaneous transport, where nickel is transported through the skin and into the blood stream. For further details, the reader is referred to the *Background document in support of the individual Risk Assessment Reports*.

No *in vivo* studies providing specific information about the absorbed fraction of nickel in humans or experimental animals following dermal contact to nickel nitrate have been located. In an *in vitro* study (Tanojo et al. 2001) using human skin (stratum corneum from cadaver leg skin), about 82.5% of the dose was recovered in the donor solution after 96 hours, with about 0.5% in the receptor fluid and 1% in the stratum corneum.

Recent human *in vivo* studies of nickel sulphate and nickel metal (Hostýnek et al. 2001a, 2001b) 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. For further details, the reader is referred to the *Risk Assessment Reports on nickel sulphate and nickel metal*.
In vitro studies using human skin support the findings in the human *in vivo* studies as most of the dose remained in the donor solution and only minor amounts were found in the receptor fluid; the *in vitro* studies also indicate that absorption following dermal contact may have a significant lag time. For further details, the reader is referred to the *Background document in support of the individual Risk Assessment Reports.*

In conclusion, 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. The data are too limited for an evaluation of the absorbed fraction of nickel following dermal contact to nickel nitrate. The *in vitro* study of soluble nickel compounds (nickel sulphate, nickel chloride, nickel nitrate, and nickel acetate) using human skin (Tanojo *et al*. 2001) showed about 98% of the dose remained in the donor solution, whereas 1% or less was found in the receptor fluid and less than 1% was retained in the stratum corneum. According to the revised TGD, the amount absorbed into the skin, but not passed into the receptor fluid, should also be included in the estimate of dermal absorption. For the purpose of risk characterisation, a value of 2% will be taken forward to the risk characterisation for the absorbed fraction of nickel following dermal contact to nickel nitrate.

For further details, the reader is referred to the *Background document in support of the individual Risk Assessment Reports*.

4.1.2.1.3.2 Distribution and elimination

No studies regarding distribution and elimination in humans or in experimental animals following exposure to nickel nitrate have been located.

Generally, nickel tends to deposit in the lungs of workers occupationally exposed to nickel compounds and in experimental animals following inhalation or intratracheal instillation of nickel compounds. 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. Low levels of accumulation in tissues are observed (generally below 1 ppm). A primary site of elevated tissue levels is the kidney. In addition, elevated concentrations of nickel are often found in the lung, also after oral dosing, and in the liver. Elevated nickel levels are less often found in other tissues. Limited information exists on tissue distribution in humans.

Absorbed nickel is excreted in the urine, regardless of the route of exposure. Most ingested nickel is excreted via faeces due to the relatively low gastrointestinal absorption. In humans, nickel excreted in the urine following oral

intake of nickel sulphate accounts for 20-30% of the dose administered in drinking water to fasting subjects or to fasting subjects compared with 1-5% when administered together with food or in close proximity to a meal. From biological monitoring in small groups of electroplaters exposed to nickel sulphate and nickel chloride, the half-life for urinary elimination of nickel has been estimated to range from 17 to 39 hours.

Inhaled nickel particles can be eliminated from the respiratory tract by absorption, by deposition in the lung tissues, by removal via the mucociliary action and subsequently swallowed into the gastrointestinal tract, and by exhalation.

For further details, the reader is referred to the *Background document in support of the individual Risk Assessment Reports.*

4.1.2.2 Acute toxicity

Neither the NIPERA (1997) review nor the TERA (1999) review discusses the acute toxicity of soluble nickel compounds. In the HSE (1987) review one study is mentioned.

4.1.2.2.1 Animal studies

4.1.2.2.1.1 Inhalation

No studies have been found.

4.1.2.2.1.2 Oral

A single LD_{50} study with nickel nitrate hexahydrate has been found (Smyth et al., 1969). An LD_{50} value of 1620 mg Ni-nitrate hexahydrate/kg corresponding to 330 mg Ni/kg was reported. The method generally used is described in an earlier publication by the author (Smyth et al., 1962). Groups of 5 non-fasted Carworth-Wistar male rats, four to five weeks of age and weighing 90 to 120 g were dosed by gastric intubation. Based upon mortalities during a 14-day observation period, the most probable LD_{50} value was estimated. The study method deviates from the Annex V method in several respects. Only one sex was used, and the animals were not fasted prior to dosing.

An acute toxic class method study has been performed by Phycher (2003a, 2003b, 2003c) according to OECD TG 423 (1996 version, also Annex V B.1 tris) with three different nickel nitrate formulations administered by gavage in distilled water. The three formulations were “dry” crystalline nickel dinitrate hexahydrate (20.1% Ni), crystalline nickel dinitrate hexahydrate (19.9% Ni) and a commercial nickel dinitrate solution (13.95% Ni, pH 3.9). The starting dose chosen for the study was 2000 mg/kg bw of nickel dinitrate hexahydrate (407 mg Ni/kg bw). Two animals died at this dose. Therefore a dose level of 200 mg/kg bw of nickel dinitrate hexahydrate (40.7 mg Ni/kg bw) was selected. After dosing, the rats were observed for 15 days. A gross necropsy was performed on all animals. One male animal administered nickel dinitrate hexahydrate died on day 4 post-dosing; clinical symptoms of toxicity included ataxia, decreased reflexes, and laboured respiration. No symptoms of toxicity were observed in the five surviving animals. No mortality and no signs of toxicity were observed among animals given the other two formulations (nickel dinitrate hexahydrate “dry” or nickel dinitrate solution). Option 1 in the test method was followed and testing was stopped at this dose. The studies deviate from the OECD TG 423 (2001) and from the revised Annex V method as a dose level of 200 mg/kg bw has been selected instead of 300 and 500 mg/kg bw, respectively.

Table 4.1.2.2.1A: Summary of acute oral toxicity studies

Species	End point	Dose	Result	Reference
Rat Carworth-Wistar: 5 male	LD_{50}	Nickel dinitrate hexahydrate	1620 mg/kg	Smyth et al. 1969
Rat Sprague-Dawley: 3 male, 3 female	Acute oral toxic class method	200 mg/kg bw Nickel dinitrate hexahydrate crystalline (19.9 % nickel)	1 male died No signs of toxic symptoms in the five surviving animals	Phycher 2003a

Species	End point	Dose	Result	Reference
Rat Sprague-Dawley: 3 male, 3 female	Acute oral toxic class method	200 mg/kg bw Nickel dinitrate hexahydrate crystalline "dry" (20.1 % nickel)	No mortality, no signs of toxic symptoms	Phycher 2003b
Rat Sprague-Dawley: 3 male, 3 female	Acute oral toxic class method	200 mg/kg bw Nickel dinitrate solution (13.95 % nickel), pH 3.9	No mortality, no signs of toxic symptoms	Phycher 2003c

Based on these results nickel nitrate fulfils the Annex VI criteria for classification as Harmful with Xn; R22 (Harmful if swallowed).

4.1.2.2.1.3 Dermal

No data have been found.

4.1.2.2.2 Human studies

No studies have been found.

4.1.2.2.3 Discussion and conclusion for acute toxicity

4.1.2.2.3.1 Inhalation

Animal studies of toxicity via inhalation are lacking, and no human data on the toxicity of nickel nitrate via this route have been found. Thus, it is not possible to reach a conclusion for nickel nitrate alone.

From the background document on nickel compounds it appears that no properly conducted Annex V acute toxicity inhalation tests are available for any nickel compound. However, short-term inhalation studies are available and allow the determination of a LOAEC of 0.7 mg Ni/m^3 for reduced body weight and adverse effects in the respiratory tract (atrophy and inflammation) from the 16-day study of nickel sulphate hexahydrate (NTP, 1996)), which will be used for the risk characterisation. The use of results from this repeated dose study is considered to be a conservative approach, since greater toxicity is expected from repeated exposure (12 exposures during 16 days) compared to a single 4h exposure as in the Annex V test.

The above-mentioned data from the repeated dose study are not directly useful for classification. Based on the oral toxicity, and knowing that the absorption via inhalation is considerably greater than via the oral route, and further considering the observed lethality in a 16-days inhalational study with nickel sulphate, the TC C&L has agreed to classify nickel nitrate as Harmful with Xn; R20 (Harmful by inhalation) [2].

Further testing of acute inhalational toxicity is not considered necessary for the risk assessment of nickel nitrate.

4.1.2.2.3.2 Oral

There is data from one acute LD_{50} oral rat study and three acute oral toxic class method studies on nickel nitrate.

The Smyth *et al*. (1969) study gave an LD_{50} value of 1620 mg Ni-nitrate/kg. The study method deviates from the Annex V method in several important respects. Only one sex was used (males), and the animals were not fasted prior to dosing. Lower LD_{50} values were reported for females than for males for the other soluble nickel compounds, nickel chloride (FDRL 1983a) and nickel sulphate (FDRL 1983b). Therefore, it is possible that a lower LD_{50} value would have been determined for nickel nitrate if the female sex had been included. Furthermore, the uptake following oral exposure is known to depend greatly on the presence of food in the gastrointestinal tract. The uptake in fasting individuals is approximately 30%, while in non-fasting individuals a

[2] This classification is included in the Annex I entry in the 30th ATP which was adopted by a Technical Progress Committee in February 2007, but has not yet been adopted by the Commission or published in the Official Journal.

much smaller fraction is absorbed, estimated as 5% (see section on toxicokinetics for further details). The Smyth *et al*. study, using non-fasted rats, was thus likely to yield a higher LD_{50} value than a study using fasted rats. In conclusion, the Smyth *et al*. study is expected to underestimate the toxicity compared to an Annex V test. The results of the three formulations tested by the acute toxic class method show a result in the range between 200 and 2000 mg/kg.

For the risk characterisation, an oral LD_{50} value of 43 mg Ni/kg, corresponding to 211 mg Nickel nitrate hexahydrate/kg, will be used based on results for nickel chloride (FDRL 1983a).

The TC C&L has agreed to classify nickel nitrate as Harmful with Xn; R22 (Harmful if swallowed) [3].

4.1.2.2.3.3 Dermal

Animal studies of toxicity via dermal contact are lacking, and no human data on the toxicity of nickel nitrate via this route have been found.

From the background document on nickel compounds it appears that dermal acute toxicity data have not been found for any other nickel compounds. Dermal absorption is expected to be very limited, and therefore this endpoint is not considered in the risk characterisation, and classification for acute toxicity via the dermal route is not considered appropriate.

4.1.2.3 Irritation / corrosivity

In the reviews by UK HSE (1987), NIPERA (1996), US ATSDR (1997) and TERA (1999), skin, eye or respiratory irritation of nickel nitrate are not discussed.

4.1.2.3.1 Animal studies

4.1.2.3.1.1 Skin and eye irritation

The skin and eye irritation potential of three different nickel nitrate formulations has been tested in the studies summarised in Table 4.1.2.3.A. The three formulations were “dry” crystalline nickel dinitrate hexahydrate (20.1% Ni), crystalline nickel dinitrate hexahydrate (19.9% Ni) and a commercial nickel dinitrate solution (13.95% Ni, pH 3.9).

The skin irritation potential has been examined in studies performed by the Annex V method (Phycher 2003d, 2003e, 2003f). Nickel nitrate was a skin irritant in the tests.

The eye irritation potential has been examined in studies performed by the Annex V method (Phycher 2003g, 2003h, 2003i). Nickel nitrate was an eye irritant in the tests and irritation was still observed at the end of the 21-day observation period.

Table 4.1.2.3.A: Summary of skin and eye irritation studies

	Species	**Test substance**	**Result**	**Grading (irritation scores)**	**Method**	**Reference**
Skin	Rabbits, Adult New Zealand White: 3 male	Nickel dinitrate hexahydrate crystalline (19.9 % nickel)	Irritant	2.8 (erythema) 1.0 (oedema)	Annex V	Phycher 2003d
Skin	Rabbits, Adult New Zealand White: 3 male	Nickel dinitrate hexahydrate crystalline “dry” (20.1 % nickel)	Irritant	3.1 (erythema) 1.1 (oedema)	Annex V	Phycher 2003e
Skin	Rabbits, Adult New Zealand White: 3 male	Nickel dinitrate hexahydrate solution (13.95 % nickel, pH 3.9)	Irritant	3.1 (erythema) 2.2 (oedema)	Annex V	Phycher 2003f

[3] This classification is included in the Annex I entry in the 30th ATP.

	Species	Test substance	Result	Grading (irritation scores)	Method	Reference
Eye	Rabbits, Adult New Zealand White: 1 female	Nickel dinitrate hexahydrate crystalline (19.9 % nickel)	Irritant	2.0 (corneal opacity) 1.0 (iris lesion) 2.0 (conjunctival redness) 3.0 (conjunctival oedema)	Annex V	Phycher 2003g
Eye	Rabbits, Adult New Zealand White: 1 female	Nickel dinitrate hexahydrate crystalline "dry" (20.1 % nickel)	Irritant	1.0 (corneal opacity) 1.0 (iris lesion) 2.0 (conjunctival redness) 2.7 (conjunctival oedema)	Annex V	Phycher 2003h
Eye	Rabbits, Adult New Zealand White: 1 female	Nickel dinitrate hexahydrate (13.95 % nickel, pH 3.9)	Irritant	1.3 (corneal opacity) 1.0 (iris lesion) 1.0 (conjunctival redness) 2.0 (conjunctival oedema)	Annex V	Phycher 2003i

The results of the skin irritation studies shown above indicate that nickel nitrate is a skin irritant, and fulfils the Annex VI criteria for classification as a skin irritant with Xi; R38 (Irritating to skin).
The results of the eye irritation studies shown above indicate that nickel nitrate is an eye irritant, and fulfils the Annex VI criteria for classification as an eye irritant with Xi; R36 (Irritating to eyes). However, as the effects were not reversible within the 21-day observation period, classification with Xi; R41 (Risk of serious damage to eyes) is warranted.

4.1.2.3.2 Human data

No studies have been found.

4.1.2.3.3 Other data

pH measurements of nickel nitrate solutions are available. A solution of 50 g $Ni(NO_3)_2.6H_2O$ dissolved in 1000 ml water has a pH of 5 (Königswarter & Ebell, 2004). The pH of a commercial nickel nitrate solution is more or less below 1.5 depending on nitric acid content (Henkel, 2004). The classification criteria for corrosivity would lead to a classification as C; R35 for solutions of pH < 2.

4.1.2.3.4 Conclusion

In the Annex V tests in rabbits, nickel nitrate was a skin irritant. Based on this data, classification as Xi; R38 is warranted.

In the Annex V tests in rabbits, nickel nitrate was an eye irritant and the effects were not reversible within the 21-day observation period. Based on this data, classification as Xi; R41 is warranted.

According to information from Industry, nickel nitrate may contain nitric acid either as an additive at a concentration of 10% or in concentrations of 0 – 4% as an impurity from the production process (see Chapter 1.2). The specific concentration limit in Annex I for classification of mixtures containing nitric acid as corrosive with C; R34 is > 5%. The toxicological information in the Safety Data Sheet prepared by one producer of a nickel nitrate solution reflects concerns due to the presence of nitric acid in the product (PCF, 2004).

Some producers of the substance have provisionally classified the substance as C; R34. In some cases, this is based on the fact that the pH is below 2. It should be noted that when classification as corrosive is based on considerations of extreme pH (i.e. < 2) alone, R35 should be applied.

The TC C&L has agreed to classify nickel nitrate as Xi; R38-41[4].

[4] This classification is included in the Annex I entry in the 30th ATP.

4.1.2.4 Sensitisation

4.1.2.4.1 Animal studies

4.1.2.4.1.1 Skin sensitisation

No data regarding skin sensitisation in animals have been located.

4.1.2.4.1.1.1 Conclusion, animal studies, skin sensitisation

From the background document on nickel compounds it appears that it is the nickel ion that causes skin sensitisation. It can therefore be assumed that nickel nitrate is a skin sensitiser in animals.

4.1.2.4.1.2 Respiratory sensitisation

No data regarding respiratory sensitisation in animals have been located.

4.1.2.4.2 Human data

4.1.2.4.2.1 Skin sensitisation

Nickel allergy is induced by skin exposure to nickel ions, which are considered to be exclusively responsible for the immunological effect of nickel (Menné 1994).

Most cases of primary nickel sensitisation are caused by skin contact with metallic items such as ear ornaments, ear stickers, jewellery, jeans buttons, and other nickel releasing items (European Environmental Contact Dermatitis Group 1990).

4.1.2.4.2.1.1 Elicitation of allergic response

There is one study describing elicitation of allergic response in nickel sensitive patients after challenge with nickel nitrate.

Santucci *et al.* (1998) have studied 151 consecutive patients, 96 with positive patch test to nickel sulphate 5% in petrolatum and 55 patients with positive patch test to nickel sulphate 5% in petrolatum and in addition positive patch test to at least one of the metal salts: cobalt chloride, palladium chloride and potassium dichromate. All patients were patch tested with nickel sulphate 5% in petrolatum corresponding to a nickel content of 200µg. 101 patients were patch tested with an aqueous solution of nickel sulphate and an aqueous solution of nickel nitrate corresponding to a nickel content of 47µg. 50 patients were patch tested with an aqueous solution of nickel sulphate and an aqueous solution of nickel nitrate corresponding to a nickel content of 12µg.

All patients had a positive patch test to 200µg nickel as sulphate. 61/101 had a positive patch test to 47µg nickel in nickel sulphate and 59/101 to 47µg nickel in nickel nitrate. In the 12µg group 17/50 had a positive patch test to nickel in nickel sulphate and 23/50 to nickel in nickel nitrate.

4.1.2.4.2.1.2 Thresholds for Sensitisation and elicitation

The LOAEL of elicitation of a response to nickel nitrate after occlusion in nickels sensitive patients is 12µg on a disc with a diameter of 8 mm corresponding to 24 µg/cm^2. From the background document on nickel compounds it appears that it is the concentration of nickel ion that determines the outcome of the patch test. On the basis of the available data it is not possible to set a threshold for elicitation (NOEL) in nickel sensitised individuals. Estimating the risk from a certain exposure must include the dose per unit area of skin exposed (Robinson *et al*., 2000) and the possibility of penetration i.e. duration of exposure and possible occlusion.

There are no data from skin exposure to nickel nitrate to allow an estimate of the dose that may cause skin sensitisation. Based on data from nickel sulphate an empirical threshold of 0.3 µg Ni/cm^2 for both sensitisation and elicitation is suggested for use in the risk characterisation of occupational exposure.

4.1.2.4.2.1.3 Conclusion, human data, skin sensitisation

Nickel nitrate can elicit an allergic reaction in nickel sensitive humans. Based on data from other nickel compound it may also cause sensitisation. In addition, a specific concentration limit of 0.01%, a level 100 times lower than the general concentration limit normally associated with this effect, is also considered to be justified.

In sensitised subjects LOAEL after patch tests with nickel nitrate is 24 µg Ni/cm^2. On the basis of the available data it is not possible to set a threshold for elicitation (NOEL) in nickel sensitised individuals. Based on data from nickel sulphate an empirical threshold of 0.3 µg Ni/cm^2 for both sensitisation and elicitation is suggested for use in the risk characterisation of occupational exposure.

4.1.2.4.2.2 *Respiratory sensitisation*

No data regarding respiratory sensitisation in humans have been located.

4.1.2.4.2.2.1 Conclusion, human data, respiratory sensitisation

There are no data on respiratory sensitisation with nickel nitrate. From the background document on nickel compounds it appears that based on data from nickel metal and nickel sulphate nickel salts when inhaled may cause respiratory sensitisation.

It is not possible to set a threshold for sensitisation or elicitation.

4.1.2.4.3 Conclusion

Nickel nitrate can elicit an allergic reaction in nickel sensitive humans. Based on data from other nickel compound it may also cause sensitisation. Nickel nitrate is classified as R43 with a specific concentration limit of 0.01% in the 30th ATP.

Based on data from nickel sulphate an empirical threshold of 0.3 µg Ni/cm^2 for both sensitisation and elicitation is suggested for use in the risk characterisation of occupational exposure.

Based on data for other related nickel compounds it is concluded that nickel nitrate is a respiratory sensitiser. Nickel nitrate is classified as R42 in the 30th ATP.

4.1.2.5 Repeated dose toxicity

In the reviews by HSE (1987), NIPERA (1997) and TERA (1999), repeated dose toxicity of nickel nitrate is not discussed.

4.1.2.5.1 Animal studies

4.1.2.5.1.1 Inhalation

No data have been found.

4.1.2.5.1.2 Oral

No data have been found.

4.1.2.5.1.3 Dermal

No data have been found.

4.1.2.5.2 Human data

No data have been found.

4.1.2.5.3 Conclusion

No repeated dose toxicity data have been found on nickel nitrate itself. Thus, it is not possible to reach a conclusion for repeated dose toxicity based on data for nickel nitrate alone.

4.1.2.5.3.1 Inhalation

From the background document on nickel compounds it appears that long-term inhalation of insoluble as well as soluble nickel compounds results in adverse effects on the lungs including chronic lung inflammation and fibrosis. A LOAEC of 0.056 mg Ni/m^3 will be used (identified in the 2-year rat study of nickel sulphate by NTP (1996a)).

Chronic lung inflammation and lung fibrosis are serious and potentially irreversible effects. Based on data from other nickel compounds, nickel nitrate is classified as T; R48/23 with a specific concentration limit of ≥ 1% for T; R48/23 and ≥ 0.1 % for Xn; R48/20 in the 30th ATP.

4.1.2.5.3.2 Oral

From the background document on nickel compounds it appears that sufficient oral repeated dose toxicity data are available for nickel sulphate (oral LOAEL of 6.7 mg Ni/kg bw/day based on reduced body weight and increased mortality and a NOAEL of 2.2 mg Ni/kg bw/day from the CRL (2005) study). However, uncertainties remain whether this NOAEL should actually be considered as a NOAEL, as reduced body weight gain (both sexes) and increased mortality (females) occurred to a statistically non-significant extent. These data are considered relevant for the risk assessment of nickel nitrate.

The effects following repeated oral administration of nickel compounds in general do not lead to a need for classification.

4.1.2.5.3.3 Dermal

From the background document on nickel compounds it appears that dermal repeated dose toxicity data are lacking for soluble as well as insoluble nickel compounds. However, dermal absorption is expected to be very limited. Therefore, this endpoint is not considered in the risk characterisation, and no classification for repeated dose toxicity via the dermal route is proposed.

4.1.2.6 Mutagenicity

The genotoxicity of nickel nitrate and other nickel compounds have been reviewed by several organisations including IPCS (1991), IARC (1990), UK HSE (1987), ECETOC (1989), US ATSDR (1997), NiPERA (1996) [5] and TERA (1999). The following tables give a summary of the *in vitro* and *in vivo* data on the mutagenic and genotoxic effects of nickel nitrate. These tables and the discussions are based primarily on the summaries given in the above-mentioned published reviews and other information submitted by Industry.

4.1.2.6.1 *In vitro* studies

4.1.2.6.1.1 DNA Damage and Repair

DeFlora *et. al*. (1984) studied the effects of nickel nitrate on differential toxicity in *E. Coli* to examine effects on DNA repair. The result was negative (quoted in IARC, NiPERA, 1996).

4.1.2.6.1.2 Gene mutations

The studies on gene mutations are summarised in table 4.1.2.6.1.A.

Two studies with nickel nitrate have been conducted with *Salmonella typhimurium*. DeFlora *et al.* (1984) studied the effects in several strains including TA 97, and Marzin & Phi (1985) studied the effect in TA 102 (quoted from NiPERA, 1996). Negative results were seen in both studies.

No studies of the effects of nickel nitrate on gene mutation *in vitro* in eukaryotes are available.

Table 4.1.2.6.1.A: In vitro studies with nickel nitrate on gene mutations.

Species (test system)	End point	Result	Reference	Review
Prokaryotes				
S. typhimurium TA1535, TA 1537, TA1538, TA97, TA98, TA100	reverse mutation	Negative	DeFlora *et. al*. (1984)	IPCS, IARC, NiPERA (1996)
S. typhimurium TA 102	reverse mutation	Negative	Marzin & Phi (1985).	NiPERA (1996)

[5] NiPERA has pointed out that this review was produced by independent scientists for NiPERA and that the conclusions of the report do not necessarily reflect the current position of NiPERA.

4.1.2.6.1.3 Chromosomal effects

The studies on chromosomal effects are summarised in table 4.1.2.6.1.B.

Only two *in vitro* studies with effects on chromosomes are available. The two studies from 1954 and 1963 are listed in IPCS, and both are reported as showing a positive result.

Table 4.1.2.6.1.B: In vitro studies with nickel nitrate on chromosomal effects.

Species/Strain	Test system	Result	Reference	Review
Plants				
Vicia faba	mitotic effects	Positive	Komczynski *et al*. (1963)	IPCS
Pisum	chromosome aberrations	Positive	Van Rosen (1954)	IPCS

4.1.2.6.1.4 Discussion and conclusion, in vitro studies

There are only a very limited number of studies on the *in vitro* genotoxicity of nickel nitrate. The two studies in Salmonella typhimurium (including TA 97 and TA102) are negative, consistent with the results seen for almost all the studies on nickel sulphate and nickel chloride. The data on *in vitro* clastogenicity is also very limited. The studies were carried out in the 1950's and 1960's. No other studies in Pisum have been found for nickel sulphate, chloride or carbonate. The study in *Vicia faba* (Komczynski *et al.* 1963) was carried out with nickel chloride with a similar result.

There is only one study on DNA repair *in vitro* (in bacteria) and no studies on sister chromatid exchanges or cell transformation.

4.1.2.6.2 *In vivo* studies

4.1.2.6.2.1 DNA Damage and Repair

There are no *in vivo* studies on effects on DNA.

4.1.2.6.2.2 Effects on gene mutations

The studies on gene mutations are summarised in table 4.1.2.6.2.A)

Nickel nitrate has been studied in two studies in *Drosophila* (Rasmuson 1985 and Vogel, 1984). The Vogel study (reviewed in IPCS, IARC and NiPERA, 1996) was reported as questionably positive. The Rasmuson study was negative (reviewed in IPCS, IARC).

Table 4.1.2.6.2.A: In vivo studies with nickel nitrate on gene mutation.

Species/Strain	Endpoint	Result	Reference	Review
Insects				
D. melanogaster eggs from C(1)DX y,w,f females X SC Z W^{+}f males	somatic eye colour test	Negative	Rasmuson (1985)	IPCS, IARC, US ATSDR
D. melanogaster	Mutation	Questionably positive	Vogel (1984)	IPCS, IARC

4.1.2.6.2.3 Chromosomal effects

The studies on chromosomal effects are summarised in table 4.1.2.6.2.B.

Nickel nitrate has been reported to induce the frequency of chromosome abnormalities (rings, fragments) in mice after oral administration of 72.2 mg/kg bw (23 mg Ni/kg bw) for 4, 8, 12 or 16 days (Sharma *et al*. 1987). The CAS No. (13138-45-9) given for the substance identifies it as the anhydrous salt. Nickel chloride and nickel sulphate were also studied. There is only limited information in the study description. One exposure level only

was tested, together with a control but no positive control. It is not stated how many animals were studied per group (NiPERA, 2003 quotes 1 animal/group). It is not stated when sampling took place in relation to the final dose. 100 metaphases/animal were scored, but there is no indication whether the scoring was blind. There is no specific mention of whether gaps were scored. The results are shown as single figures (with no mean). The frequency of chromosomal aberrations/cell for nickel chloride ranged from 0.23 to 0.42 as against the control values of 0.02 to 0.06. The results for all three nickel compounds tested peaked at day 12 and were highest for nickel sulphate and lowest for nickel chloride. With only one dose, direct information on a dose-response relationship is not available. NiPERA (1996) reports the results of this study as positive. NiPERA (2003) has evaluated this study as equivocal, based on a significant increase in at least one dose group, but unclear scoring of gaps, insufficient number of animals, single exposure level and no blind scoring. The study is not included in the IPCS, IARC, US ATSDR or the TERA reviews. In the same study, significant increases in inversion of chromosomes in a mosquito (*Anopheles stephensi*) after treatment at 25 μg/ml were also reported.

Deknudt & Léonard (1982) studied nickel nitrate and nickel chloride in the bone marrow micronucleus test and the dominant lethal test. Groups of 40 Balb/C mice were given nickel nitrate hexahydrate intraperitoneally in doses of 28, 56, 112 or 224 mg $Ni(NO_3).6H_2O$/kg. The substance was toxic at the two higher doses, the animals dying immediately or a few hours after treatment. One animal died a week after the dose of 25 mg/kg, and this dose was used for the MN study. Positive and negative control groups were included. Five animals were used per group. The technique used, in particular the timing of the dosing and bone marrow sampling, is not described explicitly in the paper. The authors refer to Schmid (1976) for the methodology. The standard Schmid protocol at this period is two doses at 24 h intervals with bone marrow sampled once, 6 hr after the second dose. (NiPERA, 2003 reports that the study was carried out with 1 treatment and with an unknown sample time). The yield of micronuclei (per 1000) in the nickel nitrate group was 3.20 ± 0.58 compared to 2.60 ± 0.24 in the control group. The positive control group (200 mg/kg cyclophospamide) showed a yield of 46.60 ± 6.08. No figures are given for the NCE/PCE ratio. It is concluded that treatment did not increase the incidence of micronuclei. The study has been included in most of the reviews considered here. It is considered as negative by UK HSE, IARC, IPCS, and NiPERA (1996). It is included in the paper prepared for the Specialised Experts (van Benthem, 1997). The study is not included in the US ATSDR or TERA reviews. NiPERA (2003) has evaluated this study as negative, based on a lack of significant increase at the one exposure groups. They conclude that a follow-up study would be required since the dose-response cannot be evaluated, the sampling time is unknown, and 3 instead of one exposure level would have increased power (NiPERA, 2003).

Sobti & Gill (1989) also tested nickel nitrate, nickel chloride and nickel sulphate in a micronucleus test. Nickel nitrate was given as a single oral dose of 72.2 mg/kg (23 mg Ni/kg) in water to Lacca mice. The number of animals treated per group was not given. Bone marrow samples were taken 6 and 30 hours after treatment, and smears of spermatozoa were made from the epididymis five weeks after the last exposure. It is not clear how many cells were scored per animal, or whether these were scored blind. There is a reference to Robert & Bernard (1982) for slide preparation techniques and to Schmid (1973, 1975) for staining, but no other details are given.

Frequency of micronucleated PCEs in bone marrow cells and in spermatozoa (Sobti & Gill, 1989).

Dose mg/kg	harvest time	Mn-PCEs/1000		NCE/PCE ratio	
		mean	SE	mean	SE
bone marrow					
0	6 h	1.33	0.272	-	
	30 h	1.66	0.272	-	
95	6 h	3.80.	0.815	-	
	30 h	5.00	0.948	-	
Spermatozoa					
0	5 weeks	8.66	0.547		
95	5 weeks	22.66	2.179		

Significant increases ($p<0.05$) in micronuclei were seen at both 6 and 30 hours after treatment. A significant increase ($p<0.01$) in sperm head anomalies was also seen after 5 weeks. The different types of abnormal

spermatozoa were described as Daphnia, polyp, amorphous, giant amorphous and anvil-shaped. The authors note that their results agree with their earlier findings on chromosomal aberrations (Sharma *et al*. 1987). The study is reported as positive in the US ATSDR, NiPERA (1996) and TERA reviews. It is included in the paper prepared for the Specialised Experts (van Benthem, 1997). NiPERA (2003) considers the result equivocal based on significant increases at one dose, but no information on trend, single recommended sampling time, insufficient animals, single exposure level, unclear units of exposure, no blind scoring (NiPERA (2003).

Nickel nitrate has also been tested in the dominant lethal test by Deknudt & Léonard (1982). Jaquet & Mayence (1982) have carried out further studies with *in vitro* embryo cultures to determine the mechanism of pre-implantation loss.

In the micronucleus study described above, Deknudt & Léonard (1982) carried out a dominant lethal tests using the technique of Bateman and Epstein (1971). The dose of 56 mg $NiNO_3.6H_2O$ /kg (11 mg Ni/kg) was the same as described above for the micronucleus test. Each male was caged with 3 females 6 hours after i.p. injection. They were replaced by fresh females 7, 14, 21 and 28 days later.

Results of the dominant lethal test with nickel nitrate (Deknudt & Léonard (1982).

Observations	1st week		2nd week		3rd week		4th week		5th week	
	Controls	Nickel nitrate	Controls	Nickel nitrate	Controls	Nickel nitrate	Controls	Nickel nitrate	Controls	Nickel nitrate
Females mated	102	51	102	51	102	51	102	51	54	51
Pregnant females										
Total	64	14	62	13	69	14	65	10	31	16
%	62.75	27.45 (1)	60.78	25.49 (2)	67.6	27.45 (2)	63.73	19.61 (2)	57.41	31.37 (3)
Implanted embryos										
Total	488	99	452	70	514	73	507	50	239	111
per female	7.63	7.07	7.29	5.38 (2)	7.45	5.21 (4)	7.80	5.00 (4)	7.71	6.94
Live embryos										
Total	403	89	391	54	437	55	405	44	188	91
per female	6.30	6.36	6.31	4.15 (4)	6.33	3.93 (4)	6.23	4.40 (4)	6.06	5.69
Dead embryos										
Total	85	10	61	16	77	18	102	6	51	20
per female	1.33	0.71	0.98	1.23	1.12	1.29	1.57	0.60	1.65	1.25

1) $P < 0.0001$ χ^2 2) $P < 0.001$ χ^2 3) $P < 0.01$ χ^2 4) $P < 0.01$ Mann-Whitney 4) $P < 0.05$ Mann-Whitney
The results for the positive control (200 mg/kg cyclophosphamide) are given in the nickel chloride risk assessment report. These are not shown as statistically significantly different from the controls for any parameter at any time.

The authors note that treatment with nickel nitrate decreased significantly the incidence of pregnant females and, from the second to the fourth week, the mean number of implanted embryos per female. The treatment did not increase the post implantation loss. Whilst these effects could be caused by either clastogenic effects leading to embryonic deaths or by toxicity on germ cells, the absence of clastogenic effects seen in the MN study suggests the effects are due to a toxic effect on male germ cells. The authors suggest that this is consistent with the results of Jacquet & Maynance (1982) (see below). The study has been included in most of the reviews considered here. It is considered as negative by UK HSE, IARC, IPCS, and NiPERA (1996). The study is not included in the US ATSDR or TERA reviews. NiPERA (2003) points out that post-implantation losses were seen in the two-generation reproductive study.

Jacquet & Mayence (1982) carried out a study with doses of 40 and 56 mg $NiNO_3.6H_2O$/kg (8.1 and 11.3 mg Ni/kg) to determine the mechanism of pre-implantation loss of embryos. Treated and control animals were mated with superovulated females, and the number of cleaved eggs and the development of embryos to blastocytes and implantations were counted. Neither the fertilising capacity of spermatozoa nor the development of cultured embryos was influenced by the 40 mg/kg dose. A dose of 56 mg/kg significantly reduced the fertilisation rate, but did not affect the development of two-cell embryos. The results suggest that pre-implantation loss after exposure to nickel is due to toxic effects on spermatids and spermatogonia rather than to zygotic death (Jacquet & Maynance, 1982, quoted from IARC). The study is included in IPCS as a dominant lethal test, although the methodology is not the same as guideline rodent dominant lethal tests. The study is also included by IARC (see quotation above) but as evidence for effects on reproduction and prenatal toxicity.

NiPERA (2003) considers the dominant lethal study as negative for clastogenic activity of nickel.

Table 4.1.2.6.2.B: In vivo studies with nickel nitrate on chromosomal effects.

Species/Strain / Endpoint/ test system	**Route of administration / Dose / No. of doses**	**Result**	**Reference**	**Review**
Mammals – chromosomal aberrations (CA) in bone marrow				
Mouse (Lacca)	oral 72.2 mg/kg [23 mg Ni/kg] for 4, 8, 12 or 16 days.	Positive equivocal	Sharma *et al*., (1987)	NiPERA (1996) NiPERA (2003)
Mammals – micronucleus test (MN) in bone marrow				
Mouse Balb/C	intraperitoneal 56 mg/kg [11.3 mg Ni/kg] two doses, 24 h apart	Negative	Deknudt & Léonard, (1982).	IPCS, IARC, UK HSE, NiPERA (1996, 2003)
Mammals – micronucleus test (MN) in bone marrow and spermatozoa				
Mouse (Lacca)	oral 72.2 mg/kg [23 mg Ni/kg]	Positive equivocal	Sobti & Gill (1989)	US ATSDR, NiPERA (1996), TERA NiPERA (2003)
Mammals – dominant lethal test				
Mouse BalbC	Intraperitoneal 56 mg/kg [11.3 mg Ni/kg] single dose	Negative	Deknudt & Léonard, (1982).	IPCS, IARC, UK HSE NiPERA (1996, 2003)

4.1.2.6.2.4 Discussion and conclusion, in vivo studies

Compared to the relatively limited *in vitro* data on the genotoxicity of nickel nitrate, there are a number of relevant *in vivo* studies. In all the studies considered here, other nickel compounds were tested at the same time as nickel nitrate.

The two *Drosophila* studies tested both nickel chloride and nickel nitrate, and came to the same results for both compounds.

The results from the *in vivo* studies of chromosomal effects are conflicting. In two of the animal studies (Sobti & Gill, 1989, Sharma *et al*., 1987), nickel chloride and nickel sulphate were tested together with nickel nitrate after oral administration with positive results. In the remaining animal study, Deknudt & Léonard (1982) tested nickel chloride and nickel nitrate in the micronucleus test and in a dominant lethal test after intraperitoneal administration with a negative result. The conclusions of these studies, together with other studies with nickel chloride alone, are discussed in more detail in the risk assessment report for nickel chloride.

4.1.2.6.3 Conclusions

There is little data of any kind on the *in vitro* genotoxicity of nickel nitrate. The two studies of gene mutation in S. typhimurium show the same negative effects normally seen for other nickel compounds. The two other tests provide little useful evidence.

The *in vivo* genotoxicity of both nickel chloride and nickel sulphate has been studied more extensively than nickel nitrate. The evidence from the different studies has been discussed in the risk assessment reports for nickel chloride and nickel sulphate.

There is little evidence concerning hereditable effects on germ cells. Whilst there is evidence that nickel ions reach the testes, the effects seen in the Deknudt & Léonard (1982) dominant lethal study may reflect toxic effects on germ cells rather than chromosomal damage.

In a previous draft of this report, the Rapporteur recommended that a classification of nickel nitrate as Muta. Cat. 3; R68 should be considered. NiPERA (2003) states that based on the four animal studies reviewed above it is not possible to conclude that nickel nitrate causes mutations *in vivo*, but that the mutagenicity assessment for nickel nitrate could be derogated to the overall mutagenicity assessment for soluble nickel compounds. The Rapporteur finds the evidence for the *in vivo* genotoxicity of nickel chloride and nickel sulphate convincing. The effects seen with nickel nitrate are very similar. The genotoxicity of soluble nickel compounds has also been reviewed by NiPERA (1996) and TERA (1999). TERA concludes that soluble nickel salts produce chromosomal effects in mammalian cells both *in vitro* and *in vivo*. The NiPERA (1996) report concludes “that it is clear that most Ni compounds are clastogenic *in vitro* and *in vivo* as measured by chromosomal aberrations and micronuclei induction, although in general the elicited responses are weak.”

The opinion of the Specialised Experts has been sought with regard to this classification proposal at their meeting in April 2004. The Specialised Experts concluded that nickel sulphate, nickel chloride and nickel nitrate should be classified as Muta. Cat. 3; R68 (European Commission, 2004). This conclusion is based on evidence of *in vivo* genotoxicity in somatic cells, after systemic exposure. Hence the possibility that the germ cells are affected cannot be excluded. The Specialised Experts did not consider that further testing of effects on germ cells was practicable (European Commission, 2004).

Further testing in an *in vivo* comet assay in lung cells after inhalational exposure is also considered to be unnecessary for the purposes of risk characterisation. A positive result would not alter the conclusions for the classification as a mutagen, and a negative result would not be regarded as sufficient evidence to justify the use of a threshold approach in the carcinogenicity risk characterisation. Hence, further testing for this effect would not produce additional information that would significantly change the outcome of this risk assessment.

Nickel nitrate is classified as Muta. Cat. 3; R68 in the 30th ATP.

4.1.2.7 Carcinogenicity

4.1.2.7.1 Animal data

4.1.2.7.1.1 Inhalation

No studies regarding carcinogenicity of nickel nitrate following inhalation exposure or intratracheal instillation in experimental animals have been located.

4.1.2.7.1.2 Oral

No data regarding carcinogenicity of nickel nitrate following oral administration in experimental animals have been located.

4.1.2.7.1.3 Dermal

No data regarding carcinogenicity following dermal contact to nickel nitrate in experimental animals have been located.

4.1.2.7.1.4 Other routes of administration

No data regarding carcinogenicity following exposure by other routes of administration of nickel nitrate in experimental animals have been located.

4.1.2.7.1.5 Promoter studies

No data regarding the promoting effect of nickel nitrate in experimental animals have been located.

4.1.2.7.1.6 Discussion and conclusions, carcinogenicity in experimental animals

4.1.2.7.1.6.1 Inhalation

No studies regarding carcinogenicity of nickel nitrate following inhalation exposure or intratracheal instillation in experimental animals have been located.

Inhalation studies on nickel oxide (NTP 1996b) and nickel subsulphide (NTP 1996c) showed some evidence and clear evidence, respectively, for carcinogenic activity following inhalation in rats, and there was equivocal evidence for nickel oxide in female mice. In contrast, similar inhalation studies on nickel sulphate (NTP 1996a) showed no evidence of carcinogenic activity following inhalation of nickel sulphate hexahydrate in rats and mice.

The results of the NTP studies on nickel sulphate, nickel oxide, and nickel subsulphide raise the question of whether soluble forms of nickel differ from insoluble forms of nickel in carcinogenic potential or in potency in experimental animals following exposure by inhalation; however, the available data are not sufficient for an evaluation of this question. For further details, the reader is referred to the *Background document in support of the individual Risk Assessment Reports.*

No other data considered as being relevant for the conclusion on the carcinogenicity of nickel nitrate in experimental animals following inhalation have been located.

In conclusion, the available data on carcinogenicity of various nickel compounds is considered as being insufficient for a conclusion on the carcinogenic potential of nickel nitrate in experimental animals following inhalation.

4.1.2.7.1.6.2 Oral

No data regarding carcinogenicity of nickel nitrate following oral administration in experimental animals have been located.

The carcinogenicity of nickel sulphate following oral administration has been studied in two old non-guideline studies with rats and dogs; no neoplasms were revealed in either rats or dogs in these studies. An oral (gavage) OECD 451 carcinogenicity study with rats did not show any tumorogenic potential of exposure to nickel sulphate. Data on other nickel compounds are limited to a drinking water study of nickel acetate in rats and mice in which no exposure-related neoplasms was observed.

In conclusion, given that there is sufficient oral carcinogenicity data to show that nickel sulphate does not show any carcinogenic potential in experimental animals following oral administration, a similar conclusion is drawn for nickel nitrate.

4.1.2.7.1.6.3 Dermal

No data regarding carcinogenicity following dermal contact to nickel nitrate in experimental animals have been located.

Data on other nickel compounds are limited to a study in male hamsters in which no tumours developed in the buccal pouch, oral cavity, or intestinal tract following painting on the mucosa of the buccal pouches with α-nickel subsulphide.

In conclusion, the available data are too limited for an evaluation of the carcinogenic potential in experimental animals following dermal contact to nickel nitrate.

4.1.2.7.1.6.4 Other routes of administration

No data regarding carcinogenicity following exposure by other routes of administration of nickel nitrate in experimental animals have been located.

Data on other nickel compounds show that these compounds, with a few exceptions, produce local tumours following injection at various sites to experimental animals.

In conclusion, the available data show that nickel compounds, with a few exceptions, produce local tumours following injection at various sites to experimental animals. It should be noted that these routes of administration are irrelevant for human beings who will only be exposed via inhalation, oral intake or dermal contact to nickel sulphate. However, the positive findings in these studies might be considered as part of the weight of the evidence when evaluating the carcinogenic potential of nickel nitrate to human beings.

4.1.2.7.1.6.5 Promoter studies

No data regarding the promoting effect of nickel nitrate in experimental animals have been located.

Data on nickel sulphate, nickel chloride, and nickel metal indicate that these compounds might have a promoting effect.

In conclusion, the available data indicate that nickel sulphate, nickel chloride, and nickel metal might have a promoting effect in combination with selected initiators. However, such information is difficult to use with respect to evaluating the carcinogenic potential of nickel nitrate.

4.1.2.7.1.7 Conclusion

Inhalation
The available experimental animal data on carcinogenicity of various nickel compounds is considered as being insufficient for a conclusion on the carcinogenic potential of nickel nitrate in experimental animals following inhalation.

Oral exposure
A well-conducted OECD 451 study in rats did not show any carcinogenic potential of nickel sulphate following oral administration. On this basis, nickel nitrate is not expected to show any carcinogenic potential after oral exposure.

Dermal exposure
The available data concerning dermal exposure are too limited for an evaluation of the carcinogenic potential in experimental animals following dermal contact to nickel nitrate. However, as oral exposure to nickel nitrate is not expected to show any carcinogenic potential, there are good reasons to assume that cancer is not a relevant end-point with respect to dermal exposure either.

4.1.2.7.2 Human studies

Since 1990, starting with the report of the International Committee on Nickel Carcinogenesis in Man (Doll *et al.*, 1990), many of the epidemiological cancer studies among nickel exposed workers have addressed four groups of nickel species: sulphidic, oxidic, and metallic nickel, and water-soluble nickel salts. In order to improve the quality of the exposure data, the nickel industry has developed a sequential leaching technique that identifies these four forms of nickel in dust and aerosols (Zatka *et al.*, 1992). Nickel nitrate is highly soluble in water (IARC 1990).

No epidemiological study has addressed the potential carcinogenic effect of nickel nitrate specifically.

In general, water-soluble nickel can cause cancer in humans, and most of the evidence is based on workers exposed to nickel sulphate, or to the combination of nickel sulphate and nickel chloride. It is generally recognised that the nickel ion (Ni^{2+}) is the active agent in the carcinogenic effect of water-soluble nickel salts. As a consequence, the evidence for carcinogenicity of nickel sulphate should be relevant also for the evaluation of nickel nitrate.

For a description of the evidence for carcinogenicity of water-soluble nickel salts the reader is referred to risk assessment documents for nickel sulphate. An evaluation of the carcinogenicity to humans of nickel nitrate should be based on the presumption that the effect of the nickel ion is similar whether it comes from nickel nitrate or another soluble nickel salt.

4.1.2.7.3 Overall conclusion for carcinogenicity

The Rapporteur considers that nickel nitrate should be classified in Category 1, known to be carcinogenic to man. This proposal has been reviewed by the Specialised Experts at their meeting in April , 2004. The Specialised Experts concluded that nickel sulphate and nickel chloride should be considered as human carcinogens (Carc. Cat. 1). The data was considered to be sufficient to establish a causal association between the human exposure to the substances and the development of lung cancer. There was supporting evidence for this conclusion from more limited data on nasal cancer. In drawing this conclusion regarding lung cancer, it was recognised that the epidemiological data showed a clear exposure response relationship for water-soluble compounds, consistency across and within studies and time periods, and high strength of association. Improved exposure characterisation based on personal air sampling and improved analysis of the water-soluble fractions added to the reliability of the findings. Confounding factors such as co-exposure to insoluble nickel compounds and smoking were adequately addressed, and did not lower the level of confidence in reaching the conclusion.

The Specialised Experts also agreed that nickel nitrate should be classified as Carc. Cat. 1. In reaching this conclusion the Specialised Experts recognised that the water solubility of this compound was sufficiently similar to that of nickel sulphate and nickel chloride to justify the same classification.

The TC C&L has agreed to classify nickel nitrate as Carc. Cat. 1; R49 (May cause cancer by inhalation), as there is no concern for carcinogenic potential with other routes of administration[6].

4.1.2.8 Toxicity for reproduction

No relevant studies regarding nickel nitrate have been found. Thus it is not possible to reach conclusions for reproductive and developmental toxicity for nickel nitrate alone.

From the background document on nickel compounds it appears that relevant data is available for other nickel compounds. These data on other nickel compounds are used, as the basic assumption is made that after intake nickel compounds (including nickel nitrate) are changed and that it is the nickel ion that is the determining factor for the reproductive toxicity.

No effects on fertility have been found in generation studies on nickel chloride or nickel sulphate using dose levels up to around 50 mg Ni/kg bw/day. Effects on male sex organs in rats and mice have been found in 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 will be taken forward to the risk characterization.

The potential for effects on sex organs has not been sufficiently investigated, as sperm quality and oestrus cyclicity either was not investigated or the highest dose level did not induce any signs of toxicity in the adult animals. Therefore, to be able to draw clear conclusions regarding the potential for effects on sex organs further studies using higher dose levels and including these end points would be relevant. However, there is no reason to expect that such testing would lead to lower NOAELs than the ones already determined for effects on sex organs. Therefore, the results of such testing are unlikely to influence the outcome of the risk assessment.

No standard prenatal developmental toxicity studies via either the oral or inhalation routes were located. The available studies on nickel chloride, nickel sulphate and an unspecified nickel salt provide consistent evidence of increased postimplantation/perinatal lethality in rats after oral exposure. Based on an OECD TG 416 two-generation study on nickel sulphate, a NOAEL of 1.1 mg Ni/kg bw/day was identified. As this NOAEL is below the equivocal LOAEL of 1.33 mg Ni/kg bw/day for nickel chloride, the NOAEL that will be used for developmental toxicity for regulatory purposes is set to 1.1 mg Ni/kg bw/day. This value will be taken forward to the risk characterisation.

There is consistent evidence of developmental toxicity (stillbirth, postimplantation/perinatal lethality) in rats dosed with nickel chloride as well as evidence of similar effects in rats dosed with nickel sulphate at dose levels not causing maternal toxicity. The TC C&L has agreed to classify nickel nitrate as Repr. Cat. 2; R61[7].

Although there is a lack of a standard prenatal developmental toxicity studies (OECD 414) via either the oral or inhalation routes, there is not considered to be urgent need for further testing for developmental toxicity if nickel compounds is classified in Category 2 for developmental toxicity.

[6] This classification is included in the Annex I entry in the 30th ATP.
[7] This classification is included in the Annex I entry in the 30th ATP.

4.1.3 Risk characterisation.[8]

4.1.3.1 General aspects

This assessment deals with the production and use of nickel nitrate. The scenarios considered are shown in Table 4.1.3.1.A below. Three of the industrial uses are processes (B1, B2, B4) where nickel nitrate is used as a starting material, but where other nickel compounds can also be used.

There is no known consumer exposure to nickel nitrate.

Table 4.1.3.1.A. Scenarios for the risk characterisation.

Scenario		**Occupational exposure**	**Consumer exposure**	**Indirect exposure**
A1	Nickel nitrate production from metallic nickel	yes	no	yes
A2	Nickel nitrate production from secondary raw materials	yes	no	yes
B1	Nickel nitrate used in the production of catalysts	yes	no	yes
B2	Nickel nitrate used in the production of NiCd batteries	yes	no	yes
B3	Nickel nitrate used in chemical pre-treatment of metals	yes	no	yes
B4	Other uses of nickel: chemicals production	yes	no	yes

4.1.3.1.1 Exposure assessment summary

Occupational exposure to nickel nitrate is described in chapter 4.1.1.2. Occupational exposure to nickel nitrate occurs primarily by inhalation and by dermal exposure. Direct oral exposure is considered to be negligible and is ignored in this risk characterisation.

There is no known consumer exposure to nickel nitrate.

The occupational exposures in the industrial production and use of nickel nitrate are summarised in Table 4.1.1.2.4.A. The values for inhalational and dermal exposure used in the risk characterisation are shown in Tables 4.1.3.1.1.A and 4.1.3.1.1.B respectively.

4.1.3.1.1.1 Inhalational exposure.

Table 4.1.3.1.1.A: Estimated exposure to nickel nitrate by inhalation.

Scenario		**Speciation (1)**	**Estimated exposure to inhalable nickel (mg/m³)**				
			Full shift (8 hour time weighted average)			**Short-term**	
			Typical level	**Worst-case level**	**method (2)**	**mg/m³**	**method (2)**
			mg/m³	**mg/m³**			
A1	Nickel nitrate production from metallic nickel	SO	0.2	1.6	Meas.	3.2	Exp.
A2	Nickel nitrate production from secondary raw materials	SO U	0.07 0.05	1.0 0	Meas.	2.0 0	Exp.

[8] Conclusion (i) There is a need for further information and/or testing.
Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.
Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

B1	Nickel nitrate used in the production of catalysts	SO U	0.002 0.05	0.3 4.1	Meas.	0.6 8.2	Exp.
B2	Nickel nitrate used in the production of NiCd batteries	SO	0.015	0.3	Meas.	0.6	Exp.
B3	Nickel nitrate used in chemical pre-treatment of metals	SO	0.025	0.05	Meas.	0.1	Exp.
B4	Other uses of nickel: chemicals production	SO U	0.004-0.27 0.002-0.18	7.0 0	Ana.	14 0	Ana.

1: SO = Soluble nickel considered to be all nickel nitrate (worst-case); U = Insoluble nickel.
2: Meas. = Estimate derived from measured data; Exp. = Expert judgement; Ana. = Analogy to scenario for nickel metal in the production of nickel-containing chemicals from nickel metal RAR.

The estimated inhalation exposures for five of the six processes (A1 – A2, B1 – B3) are based on measured data. The typical exposure levels for nickel nitrate are based on measurements of the total nickel exposures, taking into account available speciation information. The levels are expressed as soluble and insoluble nickel species. In the first production process (scenarios A1) exposure is to a variety of different nickel species. The exposure is assumed to be entirely to nickel nitrate (worst-case). For two of the use scenarios involving electrolysis (scenarios B2 & B3), most of the exposure is to soluble nickel. In the case of nickel catalyst production, the proportion of soluble nickel is a very small proportion of the total nickel exposure. For this risk assessment, the "soluble nickel" fraction is assumed to be entirely nickel nitrate.

For the scenario where no data is available (B4), estimates have been made by analogy to the production of chemicals using metallic nickel (see nickel metal risk assessment report).

For all scenarios except one, the "worst-case" and the "short-term" levels are calculated on the basis that the total nickel exposure is regarded as exposure to nickel nitrate, i.e. these figures ignore speciation estimates. In the case of catalyst production, (scenario B3) the proportion of soluble nickel in the exposure is very low (about 3%). In the worst-case situation the high end of the range of soluble nickel proportions (6%) is used to estimate exposure to soluble nickel (i.e. nickel nitrate) (see 4.1.1.2.3.3.1).

"Short-term" exposures are calculated as twice the "worst-case" full-shift exposures in all cases.

The typical levels are below the OEL of 0.1 mg Ni/m^3 in force in most European countries[9] for four of the scenarios (A2, B1, B2 & B3). The OEL is exceeded in the remaining "typical" levels and in all the "worst-case" scenarios.

As discussed in the toxicokinetics summary below, inhaled nickel particles is exhaled or leads to absorption either via the lungs (for the respirable fraction) or to oral absorption, following mucociliary action to the gastrointestinal tract. Werner *et al.* (1999) has shown that the respirable fraction of aerosols collected in the Kristiansand refinery is small (2 – 6.8%).

4.1.3.1.1.2 Dermal exposure.

Table 4.1.3.1.1.B: Estimated dermal exposure to nickel nitrate.

Scenario		**Dermal exposure**						
		Speciation (1)	**Typical**			**Worst-case**		
			mg/day	**µg/cm²**	**method (2)**	**mg/day**	**µg/cm²**	**method (2)**
A1	Nickel nitrate production from metallic nickel	SO U	0.8(3) 0.4(3)	0.4(5) 0.2(5)	Ana.	1.4(3) 0.8(3)	0.7(5) 0.4(5)	Ana.

[9] In some countries the OEL is lower. In Denmark it is 0.01 mg Ni/m^3, in Austria, Germany and Norway it is 0.05 mg Ni/m^3.

A2	Nickel nitrate production from secondary raw materials	SO U	0.8[3] 0.4[3]	0.4[5] 0.2[5]	Ana.	1.4[3] 0.8[3]	0.7[5] 0.4[5]	Ana.
B1	Nickel nitrate used in the production of catalysts	SO U	0.8[3] 0.4[3]	0.4[5] 0.2[5]	Ana.	1.4[3] 0.8[3]	0.7[5] 0.4[5]	Ana.
B2	Nickel nitrate used in the production of NiCd batteries	SO U	0.8[3] 0.4[3]	0.4[5] 0.2[5]	Ana.	1.4[3] 0.8[3]	0.7[5] 0.4[5]	Ana.
B3	Nickel nitrate used in chemical pre-treatment of metals	SO U	0.04 [4]	0.048 [6]	Ana.	0.4 [5]	0. 48 [6]	Ana.
B4	Other uses of nickel: chemicals production	SO U	0.8[3] 0.4[3]	0.4[5] 0.2[5]	Ana.	1.4[3] 0.8[3]	0.7[5] 0.4[5]	Ana.

1: SO = Soluble nickel considered to be all nickel nitrate (worst-case); U = Other nickel species than soluble nickel.
2: Ana: Analogy to other scenarios.
3: Analogy to measured data for operators involved in the packing of nickel sulphate and nickel carbonate
4: Analogy to dermal exposure measured in electroplating operations.
5: The exposure is given for both forearms and hands, including the fingers and back of the hands. For a man, the average mean surface area of the forearms and hands is 1980 cm^2.
6: The exposure is given for both hands, including the fingers and back of the hands. For a man, the average mean surface area of the hands is 840 cm^2.

There is no measured data on dermal exposure for any of the scenarios considered.

The dermal exposure for the use of nickel nitrate in chemical pre-treatment of metals (scenario B3) is estimated by analogy to the measured nickel-plating data. The tasks in nickel plating are expected to be rather similar to the tasks in chemical pre-treatment of metals. Thus the analogy is considered valid. The data measured in nickel-plating were collected for typical tasks, but no information was given on the use of personal protective equipment (gloves etc.).

All the other exposure levels have been estimated by analogy to measured data for operators involved in the packing of nickel sulphate hexahydrate and nickel hydroxcarbonate. The tasks in packing nickel sulphate/carbonate are expected to be similar to the tasks in packing nickel nitrate. Thus the analogy is considered valid for the production of nickel nitrate (scenario A1-A2). The handling of nickel nitrate as a feedstock (scenario B1-B2, B4) is expected to be less intensive than in the production (packing) of the chemical. Thus the estimated exposure for these scenarios (B1-B2, B4) is considered biased towards high levels. It is noted that the data measured for nickel sulphate/carbonate packing operators were collected for typical tasks, and the workers wore cotton overalls and rigger-type gloves.

The absorption by the dermal route is low (2%, see 4.1.3.1.2.1) and systemic effects from this route are not considered to be of concern.

4.1.3.1.1.3 Oral exposure.

Occupational exposure to nickel nitrate by the direct oral route is considered to be negligible as it is assumed that this is prevented by personal hygiene measures.

As discussed in the toxicokinetics summary below, inhaled nickel particles are exhaled or lead to absorption either via the lungs (for the respirable fraction) or to oral absorbtion, following mucociliary action to the gastrointestinal tract. This systemic absorption is ignored in the risk characterisation.

4.1.3.1.2 Effects assessment summary.

There is very little data for nickel nitrate and much of the data used in this risk characterisation are based on data from studies carried out using other soluble nickel compounds. Details of the source of the data are shown in the summary of the health effects of nickel nitrate in the following sections.

The endpoints and the NOAELs/LOAELs used are shown in Table 4.1.3.1.2.A below.

Table 4.1.3.1.2.A: Summary of effects.

Toxicological endpoint	**Inhalation (or respiratory tract)**	**Dermal (or eye)**	**Oral**
Acute toxicity	No data for single exposure. Toxic by inhalation based on oral acute data, toxico kinetic considerations and repeated exposure study (16 days inhalation study) Xn; R20 LOAEC: 0.7 mg/m^3	No data: acute toxicity considered to be low.	LD_{50} = 43 mg Ni/kg bw Xn; R22
Irritation / corrosivity	Inconclusive with regard to respiratory tract irritation	Skin irritant, Xi; R38 Specific concentration limit of 20% for R38 . Severe eye irritant R41	
Sensitisation	Respiratory sensitiser: R42	Skin sensitiser: R43 Specific concentration limit of 0.01% for R43. Empirical elicitation threshold 0.3 µg/cm^2 Empirical sensitisation threshold 0.3 µg/cm^2	Elicitation: LOAEL (oral challenge) = 0.012 mg Ni/kg bw
Repeated dose toxicity	T; R48/23 Specific concentration limit of 1% for T; R48/23 LOAEC = 0.056 mg Ni/m^3 (lung inflammation, fibrosis)	Not possible to determine. Not of concern due to low absorption	LOAEL = 6.7 mg Ni/kg bw/day (decreased survival rate (females), reduced body weight gain (both sexes)) NOAEL = 2.2 mg Ni/kg bw/day (however, associated with a slight decrease in body weight gain (both sexes) and survival in females)
Mutagenicity	Muta. Cat. 3; R68.		
Carcinogenicity	Carc. Cat. 1; R49	-	-
Fertility impairment	No data Calculated NOAEC: 0.55 mg/m^3	No data. Not of concern due to low absorption	No LOAEL NOAEL = 2.2 mg Ni/kg bw/day
Effects on male sex organs	LOAEC = 5.6 mg Ni/m^3 NOAEC = 0.45 mg Ni/m^3	No data. Not of concern due to low absorption	LOAEL = 5.6 mg Ni/kg bw/day NOAEL = 2.2 mg Ni/kg bw/day
Developmental toxicity	Repr. Cat. 2; R61		
	No data Calculated NOAEC: 0.277 mg/m^3	No data. Not of concern due to low absorption	LOAEL = 2.2 mg Ni/kg bw/day NOAEL = 1.1 mg Ni/kg bw/day

4.1.3.1.2.1 Toxicokinetics.

There is very little data on the toxicokinetics of nickel nitrate. The following values are taken from data from nickel sulphate and other soluble nickel compounds.

A value of 100% is used for the absorbed fraction of nickel from the respiratory tract following exposure by inhalation of nickel nitrate for particulates with an aerodynamic diameter below 5 µm (respirable fraction). For nickel particulates with aerodynamic diameters above 5 µm (non-respirable fraction), the absorption of nickel from the respiratory tract is considered to be negligible as these particles predominantly will be cleared from the respiratory tract by mucociliary action and translocated into the gastrointestinal tract and absorbed. Hence, for the non-respirable fraction, 100% clearance from the respiratory tract by mucociliary action and translocation into the gastrointestinal tract is assumed and the oral absorption figures can be taken.

A value of 30% is used for the absorbed fraction of nickel from the gastrointestinal tract following oral exposure to nickel nitrate in the exposure scenarios where fasting individuals might be exposed to nickel nitrate. In all the other exposure scenarios, a value of 5% is used for the absorbed fraction of nickel from the gastrointestinal tract.

Absorption of nickel following dermal contact to various nickel compounds can take place to a limited extent, with a large part of the applied dose remaining on the skin surface or in the stratum corneum. A value of 2% is taken as the absorbed fraction of nickel following dermal contact to nickel nitrate.
Generally, nickel tends to deposit in the lungs of workers occupationally exposed to nickel compounds and in experimental animals following inhalation or intratracheal instillation of nickel compounds. 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. Low levels of accumulation in tissues are observed (generally below 1 ppm). A primary site of elevated tissue levels is the kidney. In addition, elevated concentrations of nickel are often found in the lung, also after oral dosing, and in the liver. Elevated nickel levels are less often found in other tissues. Limited information exists on tissue distribution in humans.

Absorbed nickel is excreted in the urine, regardless of the route of exposure. Most ingested nickel is excreted in the faeces due to the relatively low gastrointestinal absorption. In humans, nickel excreted in the urine following oral intake of nickel chloride accounts for 20-30% of the dose administered in drinking water to fasting subjects compared with 1-5% when administered together with food or in close proximity to a meal. From biological monitoring in small groups of electroplaters exposed to nickel sulphate and nickel chloride, the half-life for urinary elimination of nickel has been estimated to range from 17 to 39 hours.

Inhaled nickel particles can be eliminated from the respiratory tract either by exhalation, by absorption in the respiratory tract, or by removal due to mucociliary elimination.

4.1.3.1.2.2 Acute toxicity

No valid study of the oral toxicity of nickel nitrate is available. The available data indicates acute oral toxicity at much higher levels than is seen for other soluble nickel salts. An LD_{50} for acute oral toxicity of 43 mg Ni/kg based on data from nickel chloride is used for this risk characterisation. Nickel nitrate is classified as Xn; R22.

No data for acute inhalational toxicity of nickel nitrate has been found. Considering the acute oral toxicity of the substance and the potential for absorption via the respiratory tract and observed lethality in a 16-days inhalational study with nickel sulphate, nickel nitrate is classified as Xn; R20.

For the purpose of this risk characterisation, the LOAEC for local effects in the respiratory tract of 0.7 mg Ni/m^3 from the 16-day repeated dose toxicity study of nickel sulphate by NTP (1996a) is used. The use of this LOAEC is considered to be a conservative approach, since greater toxicity is expected from repeated exposure (12 exposures during 16 days) compared to a single 4h exposure as in the Annex V test.

There is no data for acute dermal toxicity. There is no concern for systemic effects from the dermal route of exposure.

4.1.3.1.2.3 Irritation/corrosivity.

Nickel nitrate is classified as Xi; R38-41, with a specific concentration limit of 20% for R38.

There is also a concern for respiratory irritation. This concern is however considered to be more appropriately covered by the risk assessment for repeated dose effects.

4.1.3.1.2.4 Sensitisation

There are two effects of relevance for the risk characterisation: the induction of nickel allergy in non-sensitive people, and the elicitation of allergic reactions in people already sensitive to nickel.

Nickel nitrate is a skin and respiratory sensitiser. There is evidence that nickel nitrate can elicit skin sensitisation in humans, and is considered to be able to induce skin sensitisation by analogy with other nickel compounds. The evidence for respiratory sensitisation is based on analogy with nickel sulphate. Nickel nitrate is classified as R42/43 and to add specific concentration limits of 0.01% for R43

The thresholds for sensitisation and elicitation are assumed to be the same as for nickel sulphate. On the basis of the available data it is not possible to set a scientifically based threshold (NOEL) for elicitation or sensitisation in nickel-sensitised individuals. Based on data from Uter *et al*. (1995) an empirical threshold for elicitation and sensitisation of 0.3 µg/cm^2 is used in the quantitative risk characterisation. If the exposure is not under occlusion, the potential risk of elicitation of an allergic response may be less.

It is not possible to establish a NOAEL for oral challenge in patients with nickel dermatitis. The LOAEL established after provocation of patients with empty stomach is 12µg/kg body weight (Nielsen *et al.* 1999). It should be noted that this dose is the acute LOAEL in fasting patients on a 48h diet with reduced nickel content. A cumulative LOAEL may be lower and a LOAEL in non-fasting patients is probably higher because of reduced absorption of nickel ions when mixed in food.

4.1.3.1.2.5 Repeated dose toxicity.

There is no data on repeated dose toxicity of nickel nitrate. When soluble nickel salts are inhaled, the main target is the respiratory system, where serious effects are induced in the form of chronic lung inflammation and fibrosis. Nickel nitrate is classified as T; R48/23 with a specific concentration limit of 1% for T; R48/23.

The LOAEC of 0.056 mg Ni/m^3 from the 2-year NTP study of nickel sulphate is used for risk characterisation for repeated dose toxicity via inhalation.

The NOAEL of 2.2 mg Ni/kg bw/day and LOAEL of 6.7 mg Ni/kg bw/day for nickel sulphate following oral administration are also used for nickel nitrate. However, uncertainties remain whether this NOAEL should actually be considered as a NOAEL, as reduced body weight gain (both sexes) and increased mortality (females) occurred to a statistically non-significant extent.

It is not possible to determine a NOAEL/LOAEL for the dermal route based on the available information. There is, however, no concern for systemic effects from the dermal route of exposure due to the low absorption. .

4.1.3.1.2.6 Mutagenicity

There is some evidence indicating that nickel nitrate is genotoxic *in vivo.* Nickel nitrate is classified as Muta. Cat. 3; R68 on the basis of the Specialised Experts' conclusion. This conclusion was based on evidence of in vivo genotoxicity in somatic cells, after systemic exposure. Hence the possibility that the germ cells are affected cannot be excluded (European Commission, 2004).

As there is concern for the genotoxic effects of nickel nitrate in somatic cells, the carcinogenicity risk characterisation is carried out using a non-threshold approach (see below).

There are remaining uncertainties with regard to the mutagenicity for nickel nitrate for effects on germ cells, but the Specialised Experts did not consider that further testing was practicable (European Commission, 2004).. Further information is not considered likely to have an impact on the risk reduction measures and thereby the regulation of the substance. As a result, further studies are not required at this time. This can be expressed as a **conclusion (i) "on hold"**.

4.1.3.1.2.7 Carcinogenicity.

Nickel nitrate is classified as Carc. Cat. 1; R49 on the basis of the Specialised Experts' conclusion that nickel nitrate should be classified as a human carcinogen (Carc. Cat. 1), as they recognised that the water solubility of this compound was sufficiently similar to that of nickel sulphate and nickel chloride to justify the same classification (European Commission, 2004).

As nickel nitrate is also classified as Muta. Cat. 3; R68, the risk characterisation is carried out using a non-threshold approach.

A unit risk for cancer following inhalation has been calculated by a number of bodies.

The US EPA has estimated the lifetime cancer risk from exposure to nickel refinery dust as 2.4×10^{-4} / μg/m^3, the midpoint of a range from 1.1×10^{-5} to 4.6×10^{-4} / μg/m^3 (US EPA, 1991a). The US EPA has also estimated the lifetime cancer risk from exposure to nickel subsulfide. Since nickel subsulfide is a major component of nickel refinery dust and has been shown to produce the highest incidence of tumours for nickel compounds in animals (supported by in vitro studies), the incremental unit risk estimate of nickel refinery dust [2.4×10^{-4} / μg/m^3] may be used with a multiplication factor of 2 to account for the roughly 50% nickel subsulfide composition. An inhalation unit risk of 4.8×10^{-4} / μg/m^3 (Range $2.2 \times 10^{-5} – 9.2 \times 10^{-4}$) was thus obtained for nickel subsulfide (US EPA, 1991b).

WHO (1999) has made an estimate of unit risk on the basis of the report of lung of lung cancer in workers first employed between 1968 and 1972 and followed through 1987 in Norway. 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 3.8×10^{-4} / μg/m^3 were calculated. This figure is the estimate accepted by the CSTEE in their opinion on the Commission Ambient Air Position Paper (CSTEE, 2001).

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 using a linear non-threshold approach (Lepicard *et al*., 1997). The epidemiological studies of occupational exposure led to a unit risk estimate of 2.5×10^{-4} / μg/m³. 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 of 4.0×10^{-5} / μg/m³ for nickel oxide and 3.0×10^{-4} / μg/m³ for nickel subsulfide (quoted from European Commission, 2000).

The Canadian Health Authorities (CEPA, 1994) estimate exposure in relevant environmental media is compared to quantitative estimates of cancer potency, expressed as the concentration or dose that induces a 5% increase in the incidence of or mortality due to relevant tumours ($TD_{0.05}$, i.e. exposure/potency indices) to characterize risk. The estimates of the $TD_{0.05}$ for inhaled "oxidic", "sulphidic", and "soluble" nickel (combined) for lung cancer mortality ranged from 0.04 to 1.0 mg/m^3 [mean 0.33 mg/m^3]. The $TD_{0.05}$ for lung cancer mortality for "soluble" nickel, estimated based on data for the Falconbridge cohort, was also within this range of values (i.e., 0.07 mg/m^3).

The lifetime dose that theoretically will cause cancer in 25% of the exposed population (HT 25) can also be calculated from the unit risk estimates shown above (Sanner *et al*., 2001, Sanner, 2002). The dose from 1 μg/m^3 continuous daily exposure is 1 μg/m^3 x 20 m^3/day x (1/70 kg) = 0.286 μg/kg/day. The risk estimate range is then divided by this dose, to generate an oral slope factor in units of inverse dose.

Table 4.1.3.1.2.B: Calculated HT25 estimates (Sanner, 2002).

Source of estimate	**Estimate**	**HT 25 (μg/kg/day**
US EPA, refinery dust; midpoint	2.4×10^{-4} / μg/m^3	298
US EPA, nickel subsulfide; high	9.2×10^{-4}/ μg/m^3	78
WHO unit risk	3.8×10^{-4}/ μg/m^3	188
CEPN	2.5×10^{-4}/ μg/m^3	286
CEPA data ($TD_{0.05}$)	0.33 mg/m^3	470
Falconbridge ($TD_{0.05}$)	0.07 mg/m^3	100
Nickel oxide (NTP, 1996b)		484
Nickel subsulphide (NTP, 1996c)		53

1) The details of these calculations by Sanner (2002) are not included here.

The risk characterisation is based on the WHO unit risk estimate. This figure is the estimate accepted by the CSTEE in their opinion on the Commission Ambient Air Position Paper (CSTEE, 2001) The exposures that resulted in the increased lung cancer frequencies that were used as basis for the epidemiological studies represent complex mixtures of different nickel species that may have varied from study to study as well as within a study. From these studies it is not possible to identify the risk of the individual nickel species. The risk estimation is therefore based on the estimated total exposure to nickel species. It is apparent that the HT25 data presented above differ by factor of about 9 and that the WHO risk estimate used is close to the average of the numbers presented. Thus, if the complex mixtures representing the exposure scenarios are similar to those in the epidemiological studies and the dose response is linear also at low doses, the actual lifetime cancer risk does probably do not differ from the calculated risk by a factor of more than 3 (Sanner, 2002).

The risk characterisation shown below is based on the HT25 dose descriptor for humans based on epidemiological studies (Sanner, 2002). The figure used is taken from the figure in WHO (1999) and is 188 μg/kg/day

The lifetime increased cancer risk at a workplace exposure level of 1 mg/m^3 is equal to 95 x 10^{-3}. A workplace exposure of 1 mg/m^3 corresponds to 200 μg/kg/day assuming a bodyweight of 70 kg and that a worker is breathing 13.9 m^3 during the working day. The exposure has to be divided with 2.8 if the exposure is distributed over the whole lifetime and not only during 5 days a week and 48 weeks a year and a working period of 40 years (7/5 x 52/48 x 75/40 = 2.8).

Exposure level 1 mg/m^3 :	1 mg/m^3 x 13.9 m^3/day x (1 / 70 kg)	= 200 μg/kg bw/day
Occupational lifetime increased cancer risk level:	(200 / 2.8) / (188 / 0.25)	= 95x10^{-3}.

Whilst this calculation is based on the HT25 values shown earlier, the estimate does not presume an internal dose and the figure for the lifetime increased cancer risk at an exposure level of 1 mg/m^3 of 95 x 10^{-3}, is based directly on the WHO unit risk estimate corrected for the difference between continuous and workplace exposures.

The exposures in some scenarios involve mixed exposure to different nickel species. Since the effects seen are due to the total nickel exposure rather than to nickel nitrate alone, the lifetime increased cancer risk level is based on the total nickel levels.

Short-term exposure is not considered relevant in this assessment. Worst-case exposure is also ignored, as this exposure level does not reflect levels of lifetime exposure.

The methodology for the calculation is generally accepted and based on the WHO figure for the cancer risk. This figure is in turn based on epidemiology data gathered mostly under exposure conditions similar to many of those considered here.

The estimate is based on exposure to a mixture of nickel species. In the Ambient Air Position Paper (European Commission, 2000) Industry argued that the WHO estimate is based mainly on the nickel subsulfide exposure. The carcinogenic potential of nickel subsulfide is at least an order of magnitude higher than that of nickel oxide (i.e. NTP data). Hence, the occupational cancer risk of nickel based on a linear extrapolation should be modified when applied to ambient air (European Commission, 2000). The figures shown in Table 4.1.3.1.2.B indicate that the differences between the different estimates are fairly small. In particular the HT25 of 100 μg/kg bw/day calculated from the $TD_{0.05}$ for lung cancer mortality for "soluble" nickel, estimated based on data for the Falconbridge cohort is less than a factor 2 below the WHO estimate of 188 μg/kg bw/day. The Rapporteur does not consider that the differences in exposure evaluated here are such as to invalidate the use of the WHO estimate.

The OEL in EU Member States for soluble nickel ranges from 0.01 to 0.1 mg/m^3 as nickel (see Table 2.4.A). These levels correspond to increased lifetime cancer risk of 1 and 10 x 10^{-3} respectively. However, as the OEL values are based on other factors than strictly health based issues (e.g. technical and economical considerations), these values cannot be used as an indicator of concern in the scenarios.

In the Ambient Air Position paper (European Commission, 2000) Industry argued that threshold-based carcinogenesis should be considered. They suggest that a threshold-based extrapolation shows a threshold as occurring between 600 and 1100 ng Ni/m^3. The threshold levels suggested by Industry of 0.001 mg/m^3 or less are still substantially lower than the estimated exposures seen in the different scenarios.

Additional arguments have been put forward by NiPERA (2002). Basing their calculations on the results of the NTP studies, after adjusting for particle size and deposition/clearance differences between animals and humans, the highest concentration to which rats were exposed in the NTP bioassay (0.1 mg Ni/m^3 MMAD 2.2 um) is equivalent to 2-3 mg Ni/m^3 of workplace dust ("inhalable fraction" size particles) (Hsieh *et al.,* 1999; Yu *et al.,* 1998; Yu *et al.,* 2001). Based on these models, the differences in exposure levels between animals and humans cannot explain why rats exposed to nickel sulphate hexahydrate did not get tumours in the NTP study while workers exposed to mixtures of nickel compounds (containing nickel sulphate) did in the epidemiological studies. Still, if the rat data were relevant for humans, a workplace exposure above 0.1-0.2 mg Ni/m^3 may induce sufficient respiratory tract inflammation that could enhance the tumorigenicity of inhalation carcinogens such as sulphidic or oxidic nickel, acid mists, soluble cobalt compounds, or cigarette smoke (NiPERA, 2002). However, the present knowledge of the mechanisms and the exposure levels of water-soluble nickel that lead to the carcinogenic effect is incomplete.

4.1.3.1.2.8 Reproductive toxicity.

There is no data on the reproductive toxicity of nickel nitrate. Nickel nitrate is classified as Repr. Cat. 2; R61 on the basis of the data for nickel sulphate and nickel chloride.

The NOAEL of 2.2 mg Ni/kg bw/day for fertility and effects on male sex organs and a NOAEL of 1.1 mg/kg bw/day for developmental toxicity for nickel sulphate are also used for nickel nitrate.

Similarly, NOAECs for fertility and effects on male sex organs of 0.45 mg Ni /m^3 and a calculated NOAEC of 0.277 mg Ni /m^3 is also taken from the data for nickel sulphate.

4.1.3.1.2.9 Groups of particular concern.

The main group of people where there is particular concern are those who are already nickel-sensitive. Much of the nickel allergy on the general population is due to prolonged and close contact with nickel-releasing metal objects. EU legislation has come into force that is intended to prevent future exposure to this type of objects leading to nickel allergy. Experience in Denmark suggests that this legislation may well be largely effective in preventing further cases of nickel allergy. There are however already a substantial proportion of the general population who are already nickel-sensitive, and this is a group especially at risk from both dermal and oral exposure to nickel.

No genetic variations that influence adverse reactions to nickel have been identified (UK EGVM, 2003).

There is no data on which to judge whether children are a group that is particularly sensitive to the adverse effects of nickel.

4.1.3.1.2.10 Completeness of the database.

Whilst there is little data on which to evaluate the specific effects of nickel nitrate, data is available from nickel sulphate and nickel chloride.

There is no data on acute inhalational toxicity, but further testing is not considered relevant as this effect can be adequately assessed using other data from repeated dose studies with nickel sulphate.

There is no basis on which to evaluate threshold values for respiratory sensitisation; however, further testing is unlikely to provide data that would have any impact on relevant risk reduction measures.

There are remaining uncertainties with regard to the mutagenicity for nickel nitrate for effects on germ cells, but the Specialised Experts did not consider that further testing was practicable. Further information is not considered likely to have an impact on the risk reduction measures and thereby the regulation of the substance. As a result, further studies are not required at this time.

There is no need for testing for developmental toxicity as classification of nickel nitrate in Category 2 for developmental toxicity has been agreed. The potential for effects of nickel nitrate on fertility has not been sufficiently investigated. However, there is no reason to expect that further testing would influence the outcome of the risk assessment.

Whilst most of the data in this risk characterisation is taken from studies on nickel sulphate or nickel chloride rather than on nickel nitrate, the Rapporteur considers that this is an adequate basis for the risk characterisation, and no other additional toxicology studies are considered necessary for this risk assessment.

4.1.3.2 Risk characterisation for Occupational exposure.

Occupational exposure to nickel nitrate may occur by inhalation of aerosols containing nickel nitrate or by skin contact.

Occupational exposure to nickel nitrate directly by the oral route is considered to be negligible as it is assumed that this is prevented by personal hygiene measures. Some of the nickel nitrate in air can be transported by mucociliary action to the gastrointestinal tract. There is little data on which to base estimates for the exposure to nickel via this latter route. The oral absorbtion of nickel is low and systemic occupational exposure to nickel by this route is considered to be negligible.

When a N(L)OAEC from an inhalational animal experimental study is used as a starting point for comparison with a human inhalation exposure scenario, possible differences in the particle size distribution between the animal experiment and the human scenario need to be considered. The controlled exposure used for animal exposure typically consists of a rather uniform particle size distribution in the region of respirable particle sizes while also coarser particles are part of the occupational exposure, typically measured as total or inhalable dust. Thus the exposure levels from the different exposure situations may not be quite comparable with respect to the respirable fractions.
Particles in the respirable size are to a greater extent deposited in the lung and subjected to pulmonary absorption than larger particles that are deposited in the upper respiratory tract. Therefore, considering the inhalable occupational exposures as if they were of respirable size would tend to overestimate the pulmonary exposure and the risk to the workers with respect to pulmonary toxicity.
On the other hand, when evaluating the risk for pulmonary toxicity it should also be kept in mind that recent models concerning lung deposition of particles show that a considerable higher pulmonary deposition of respirable particles occur in humans compared to rats (Netherlands RIVM 2002). This aspect would then cause an under estimation of the risk to workers when extrapolation to humans is made from inhalation toxicity studies with rats.

More specific data regarding particle sizes in the occupational exposure would reduce the first point of this problem as more precise estimation of the respirable fraction could be made. However, based on the available data on the occupational exposure it has not been possible for the rapporteur to make estimations regarding respiratory fractions for the occupational scenarios and therefore the issue regarding differences in particle size distribution can only be addressed in a qualitative manner in the risk characterisation.

The risk characterisation for occupational exposure to nickel nitrate is shown for each of the relevant toxicological endpoints. The exposure estimates which are used for this risk characterisation are shown in Table 4.1.3.1.1.A and 4.1.3.1.1.B.

The data for the different effects is summarised in Table 4.1.3.1.2.A. There is inhalation data from either nickel nitrate or nickel sulphate for all relevant endpoints except fertility and developmental toxicity. For developmental toxicity, a value has been calculated from the oral NOAEL for nickel sulphate for this effect. There is little data related to dermal exposure, but there is no concern for systemic effects following this route of exposure.

4.1.3.2.1 Acute toxicity

4.1.3.2.1.1 Acute inhalational toxicity.

There is agreement to classify nickel nitrate as Xn; R20. The risk characterisation for acute inhalational toxicity from the estimated short term exposures presented in table 4.1.1.2.4.A is based on the LOAEC of 0.7 mg Ni/m^3 for reduced body weight and adverse effects in the respiratory tract (atrophy and inflammation) in the 16-day repeated dose toxicity rat study on nickel sulphate by NTP (1996).

The MOS is estimated on the basis of the calculated short-term exposures (see 4.1.3.1.1). These are estimated a) on the basis of twice the estimate of the “worst-case” full-shift exposure and b) an assumption (in most cases) that the whole of the nickel exposure is due to soluble nickel. These factors contribute to a more conservative value of the MOS, since at least some of the exposure will be due to less toxic nickel species.

Table 4.1.3.2.1.A: Occupational risk assessment for acute inhalational toxicity.

Scenario		Short term [1]		
		mg Ni/m^3	MOS [2]	Conclusion
A1	Nickel nitrate production from metallic nickel	3.2	0.22	**iii**
A2	Nickel nitrate production from secondary raw materials	2.0	0.4	**iii**
B1	Nickel nitrate used in the production of catalysts	0.6	1.2	**iii**
B2	Nickel nitrate used in the production of NiCd batteries	0.6	1.2	**iii**
B3	Nickel nitrate used in chemical pre-treatment of metals	0.1	7	**ii**
B4	Other uses of nickel: chemicals production	14	0.05	**iii**

1): Estimated short-term exposure to inhalable soluble nickel considered to be all nickel nitrate (worst-case) (from table 4.1.1.2.4.A)
2): Based on a NOAEC of 0.7 mg Ni/m^3 from data for nickel sulphate (from Table 4.1.3.1.2.A). This is considered to be a very conservative approach.

The MOS is estimated on the basis of the calculated short-term exposures (see 4.1.3.1.1). These are estimated a) on the basis of twice the estimate of the "worst-case" full-shift exposure (normally measured) and b) an assumption (in most cases) that the whole of the nickel exposure is due to soluble nickel. This should be considered as a conservative approach, since at least some of the exposure will be due to less toxic nickel species.

Other aspects to be considered in relation to the MOS value is inter- and intraspecies differences in susceptibility and the use of a LOAEC value for rather severe effects (inflammation, epithelia cell degeneration and atrophy) instead of a NOAEC value. However, a LOAEC from a repeated toxicity study is used and greater toxicity is to be expected from repeated exposure (12 exposures during 16 days) compared to a single 4h exposure as in the Annex V test, Therefore, the use of a repeated dose study as a basis for the risk characterisation for acute effects is also considered conservative.

For interspecies differences for local effects an assessment factor of 3 is considered appropriate while an assessment factor of 5 is used for intraspecies differences in worker populations. Furthermore, a factor of 3 is used for LOAEC to NOAEC extrapolation. An overall assessment factor of 3 x 5 x 3 = 45 is however to a certain extent counterbalanced by the above mentioned conservative assumptions with regard to exposure and with regard to the use of a LOAEC from a repeated toxicity study and not an acute study. All together an overall assessment factor of 5 seems appropriate and a MOS < 5 is considered of concern with respect to occupational acute exposure.

There is no concern for scenario B3 (**conclusion (ii)**). **Conclusion (iii)** applies to scenarios A1, A2, B1, B2 and B4.

4.1.3.2.1.2 Acute dermal toxicity.

There is no concern for systemic effects following this route of exposure (**conclusion (ii)**).

4.1.3.2.2 Irritation and corrosivity

There is agreement to classify nickel nitrate as a skin irritant at concentrations > 20%. There is concern for this effect for exposures to solid nickel nitrate and nickel nitrate in concentrations > 20%. Personal protective equipment, properly selected and worn, will significantly reduce exposure. As classification for this effect will lead to appropriate risk reduction measures, **conclusion (ii)** applies to all workplace situations.
There is agreement to classify nickel nitrate as a severe eye irritant (Xi; R41). There is concern for this effect, but personal protective equipment, properly selected and worn, will significantly reduce exposure. As classification for this effect will lead to appropriate risk reduction measures, **conclusion (ii)** applies to all workplace situations.

Some producers of the substance market nickel nitrate containing significant concentrations of nitric acid, either as an additive or as an impurity. The nitric acid content can justify classification as C; R34. In these cases,

appropriate classification of the product is required, as classification for this effect will lead to appropriate risk reduction measures.

There is some concern for respiratory irritation. However, these concerns are better addressed under repeated dose toxicity.

4.1.3.2.3 Sensitisation

Nickel nitrate is a skin and respiratory sensitiser, and there is agreement to classify the substance as R42/43..

4.1.3.2.3.1 Skin

Based on patch test data from Uter *et al*. (1995) an empirical threshold for elicitation and sensitisation of 0.3 $\mu g/cm^2$ has been defined. This effect concentration can be used as a starting point for a quantitative risk characterisation for the working population. The 0.3 $\mu g/cm^2$ comes from patch test studies with nickel sulphate under occlusion for 48 hours. Using this figure for risk evaluation of occupational exposure that is at most semi occluded (e.g. inside gloves) for 8 hours per day represents a worst-case scenario.

Scenario B3 (nickel nitrate used in chemical pre-treatment of metals) has the lowest typical dermal exposure of 0.04 mg/day for exposure to soluble and other nickel compounds. This corresponds to 0.048 $\mu g/cm^2$/day. For all the other scenarios the typical exposure to soluble nickel was 0.4 $\mu g/cm^2$/day. Thus the MOS values for all scenarios range from 0.75 to 6.2 (typical exposure). The worst-case exposure to soluble and insoluble nickel was 0.48 $\mu g/cm^2$/day for scenario B3. For all other scenarios the worst-case exposure to soluble nickel was 0.7 $\mu g/cm^2$/day. Thus the MOS values for all scenarios range from 0.43 to 0.63 (worst-case exposure). Although the typical and worst-case exposure for most scenarios is slightly higher than the empirical threshold of 0.3 $\mu g/cm^2$ this is considered acceptable (**conclusion (ii)**) as the threshold is based on evidence from human studies involving prolonged and close contact to nickel.

4.1.3.2.3.2 Respiratory tract

Nickel nitrate is considered to be a respiratory sensitiser in humans. From the data available it is not possible to determine a no-effect level or exposure-response relationship. Thus it is not possible make a quantitative evaluation of the risk. However, given the severe nature of this effect, and that once the hypersensitive state is induced in an individual, then even low levels of exposure might induce an asthmatic response, there is cause for concern. **Conclusion (iii)** applies to all workplace situations resulting in inhalational exposure.

4.1.3.2.4 Repeated dose toxicity

4.1.3.2.4.1 Repeated dose Inhalational Toxicity

A 2-year inhalational LOAEC in rats of 0.056 mg Ni/m^3 for lung inflammation and fibrosis is taken from data for nickel sulphate. This LOAEC is used for comparison with inhalational occupational exposure estimates.

When evaluating the MOS considerations should be given to the conservative approach with respect to the exposure evaluation, where the whole nickel exposure is considered to be due to soluble nickel nitrate. Further, considerations should be given to inter- and intra species variation in susceptibility and to the use of a LOAEC value as a starting point. At the LOAEC rather severe effects on the respiratory tract and that data indicates that adverse effects may occur at lower levels.

An assessment factor of 3 is used for interspecies differences in susceptibility for local effects and a factor 5 is used for intraspecies differences among workers. For LOAEC to NOAEC extrapolation an assessment factor of 3-5 is considered appropriate. All together an overall assessment factor of 50 is considered appropriate and thus a MOS < 50 is considered to be of concern for repeated occupational exposure.

Table 4.1.3.2.4.A: Occupational risk assessment for repeated dose inhalational toxicity.

Scenario		**Typical Full shift (8 hr TWA)**			**Worst-case Full shift (8 hr TWA)**		
		mg Ni/m^3	**MOS [1)]**	**Conclusion**	**mg Ni/m^3**	**MOS [1)]**	**Conclusion**
A1	Nickel nitrate production from metallic nickel	0.2	0.28	**Iii**	1.6	0.035	**iii**
A2	Nickel nitrate production from	0.07	0.8	**Iii**	1.0	0.06	**iii**

	secondary raw materials						
B1	Nickel nitrate used in the production of catalysts	0.002	28	**Iii**	0.3	0.19	**iii**
B2	Nickel nitrate used in the production of NiCd batteries	0.015	3.7	**Iii**	0.3	0.19	**iii**
B3	Nickel nitrate used in chemical pre-treatment of metals	0.025	2.2	**Iii**	0.05	1.12	**iii**
B4	Other uses of nickel: chemicals production	0.004-0.27	0.21-14	**Iii**	7.0	0.008	**iii**

1): Based on a LOAEC of 0.056 mg Ni/m^3 from data for nickel sulphate (from Table 4.1.3.1.2.A).

The values of the MOS for "typical exposures range from 0.21 to 28. **Conclusion (iii)** applies to all workplace situations resulting in inhalational exposure.

4.1.3.2.4.2 Repeated dose dermal Toxicity

There is no concern for systemic effects following this route of exposure (**conclusion (ii)**).

4.1.3.2.5 Mutagenicity

Nickel nitrate is classified as Muta. Cat. 3; R68, as the possibility that the germ cells are affected cannot be excluded.

There is concern (**conclusion (iii)**) for somatic cell mutagenicity linked to inhalational carcinogenicity.There are remaining uncertainties with regard to the mutagenicity for nickel nitrate for effects on germ cells. The conclusions of the Specialised Experts were that further testing for effects on germ mutagenicity was not considered practicable. Further information is unlikely to have an impact on the risk reduction measures and thereby the regulation of the substance. As a result, further studies are not required at this time. This can be expressed as a **conclusion (i) "on hold"**.

4.1.3.2.6 Carcinogenicity

4.1.3.2.6.1 Carcinogenicity after inhalational exposure

The risk characterisation shown below is based on a lifetime increased cancer risk at an exposure level of 1 mg/m^3 of 95 x 10^{-3}. This figure is taken from the unit risk estimate of 3.8 x 10^{-4} per µg/m^3 (WHO, 1999) corrected for the difference between continuous exposure and occupational exposure. The figures in the table show the lifetime cancer risk x 10^{-3}.

Short-term and worst-case exposures are not considered relevant in this assessment.

Table 4.1.3.2.6.A: Estimated full shift (8 hour time weighted average) typical exposure to nickel nitrate and other nickel species by inhalation and the corresponding lifetime cancer risks (Sanner, 2002).

Scenario		**Speciation (1)**	**Inhalable nickel (mg/m^3) - typical level**	**Lifetime cancer risk (10^{-3})**	**Conclusion**
A1	Nickel nitrate production from metallic nickel	SO	0.2	19	**iii**
A2	Nickel nitrate production from secondary raw materials	SO U	0.07 0.05	12 (2)	**iii**
B1	Nickel nitrate used in the production of catalysts	SO U	0.002 0.05	5 (2)	**iii**
B2	Nickel nitrate used in the production of NiCd batteries	SO	0.015	1.4	**iii**

B3	Nickel nitrate used in chemical pre-treatment of metals	SO	0.025	2.4	**iii**
B4	Other uses of nickel: chemicals production	SO U	0.004-0.27 0.002-0.18	0.6-43	**iii**

1: SO = Soluble nickel considered to be all nickel nitrate (worst-case); U = Insoluble nickel species.
2: SO and U have been added and the risk calculated for the total nickel exposure.

The WHO unit risk estimate of 3.8×10^{-4} used for calculating of the lifetime cancer risk in the table is most probably derived from occupational nickel exposure measurements measured as "total dust". The exposure level for the exposure scenarios 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 order of magnitudes rather than exact values.

There is a concern for carcinogenicity in all the full shift scenarios (**conclusion (iii)**).

4.1.3.2.6.2 Carcinogenicity after dermal exposure.

As the carcinogenicity is only related to inhalational exposure, there is no concern for carcinogenicity following dermal exposure (**conclusion (ii)**).

4.1.3.2.7 Toxicity for reproduction

4.1.3.2.7.1 Effects on fertility after inhalational exposure

As there is no appropriate data for nickel nitrate, a NOAEC of 0.55 mg/m^3 for effects on fertility has been calculated from an oral NOAEC of 2.2 mg Ni/kg bw/day for nickel sulphate. A NOAEC of 0.45 mg/m^3 for effects on sperm and oestrus cyclicity from a repeated dose study with nickel sulphate is used as the basis for this risk characterisation. A possible LOAEC for effects after inhalation was 1.6 mg Ni/m^3 .

When evaluating the MOS, considerations should be given to the conservative approach with respect to the exposure evaluation, where the whole nickel exposure is considered to be due to soluble nickel nitrate. Considerations to inter and intra species differences in susceptibility should be given. Further, it should be taken into account that the NOAEC for fertility is probably higher than the one used as the NOAEC value was the highest dose used in the study. It should also be noticed that only limited data concerning a possible effect on sex organs are available.

When using an interspecies factor of 10 and an intraspecies factor of 5 an overall factor of 50 would be obtained. However, due to the conservatism in relation to exposure values and because the NOAEC value used was the highest tested dose level an overall assessment factor of 10 seems more appropriate.

Values of the MOS < 10 for effects on fertility and sex organs are considered of concern for workers.

Table 4.1.3.2.7.A: Occupational risk assessment for effects on male sex organs (surrogate for fertility).

Scenario		**Typical Full shift (8 hr TWA)**			**Worst-case Full shift (8 hr TWA)**		
		mg Ni/m^3	**MOS [1)]**	**Conclusion**	**mg Ni/m^3**	**MOS [1)]**	**Conclusion**
A1	Nickel nitrate production from metallic nickel	0.2	2.3	**iii**	1.6	0.3	**iii**
A2	Nickel nitrate production from secondary raw materials	0.07	6.4	**iii**	1.0	0.45	**iii**
B1	Nickel nitrate used in the production of catalysts	0.002	225	**ii**	0.3	1.5	**iii**
B2	Nickel nitrate used in the production of NiCd batteries	0.015	30	**ii**	0.3	1.5	**iii**

B3	Nickel nitrate used in chemical pre-treatment of metals	0.025	18	**ii**	0.05	9	**iii**
B4	Other uses of nickel: chemicals production	0.004-0.27	1.7-110	**ii-iii**	7.0	0.06	**iii**

1): Based on a NOAEC of 0.45 mg Ni/m^3 from data for nickel sulphate (Table 4.1.3.1.2.A).

The values of the MOS for the "typical" exposure scenarios are between 1.7 and 225. Scenario B4 has a MOS value ranging from 1.7 to 110. The exposure for this scenario is based on data for the production of chemicals from metallic nickel and may not accurately reflect the actual exposure. It is noted that scenario B4 covers an enormous range of processes (see section 4.1.1.2.3.4) and **conclusion (ii)** applies to some processes of that scenario.

The MOS values for the "worst-case" full shift exposures are all less than 10, and in three cases, less than 1.

It can be debated whether **conclusion (i)-on hold** would be more appropriate than **conclusion (iii)** for this end-point given the uncertainties regarding a proper NOAEC-value and proper studies for examining this end-point. However, as all the **conclusion (iii)** scenarios for the fertility end-point are also **conclusion (iii)** for developmental toxicity for (which a lower NOAEC value is used) this is academic, as risk reduction measures for these scenarios are already recommended.

4.1.3.2.7.2 Effects on fertility after dermal exposure

There is no concern for systemic effects following this route of exposure (**conclusion (ii)**).

4.1.3.2.7.3 Developmental toxicity after inhalational exposure

As there is no appropriate data for nickel nitrate, a NOAEC of 0.277 mg/m^3 for effects on developmental toxicity has been calculated from an oral NOAEC of 1.1 mg Ni/kg bw/day for nickel sulphate.

When evaluating the MOS the conservative approach with respect to the exposure evaluation where the whole nickel exposure is considered to be due to soluble nickel nitrate should be considered. Also the uncertainties with regard to route-to-route extrapolation, severity of the effect, and inter- and intraspecies variations should be taken into account.

An assessment factor of 10 is used for interspecies differences in susceptibility and a factor of 5 is used for intraspecies differences in the worker populations. Further a factor of 2-3 accounting for severity of the effects (death of foetuses) should be considered. However, such a factor is considered outweighed by the above mentioned conservative assumptions with regard to exposure values and the conservative absorption factors used in the route-to-route extrapolations. This leads to an overall assessment factor of 50 and thus a MOS < 50 is considered to be of concern for workers.

Table 4.1.3.2.7.C: Occupational risk assessment for developmental toxicity after inhalational exposure.

Scenario		**Typical Full shift (8 hr TWA):**			**Worst-case Full shift (8 hr TWA)**		
		mg Ni/m^3	**MOS (1)**	**Conclusion**	**mg Ni/m^3**	**MOS (1)**	**Conclusion**
A1	Nickel nitrate production from metallic nickel	0.2	1.4	**Iii**	1.6	0.17	**iii**
A2	Nickel nitrate production from secondary raw materials	0.07	4.0	**Iii**	1.0	0.28	**iii**
B1	Nickel nitrate used in the production of catalysts	0.002	139	**Ii**	0.3	0.9	**iii**
B2	Nickel nitrate used in the production of NiCd batteries	0.015	18	**Iii**	0.3	0.9	**iii**
B3	Nickel nitrate used in chemical pre-treatment of metals	0.025	11	**Iii**	0.05	5.5	**iii**
B4	Other uses of nickel: chemicals production	0.004-0.27	1.0-69	**ii-iii**	7.0	0.04	**iii**

1): Based on a calculated NOAEC of 0.277 mg Ni/m^3.

The values of the MOS for the “typical” exposure scenarios are between 1.0 and 139. Scenario B4 has the lowest MOS value, and the exposure for this scenario is based on data for the production of chemicals from metallic nickel and may not accurately reflect the actual exposure. It is noted that scenario B4 covers an enormous range of processes (see section 4.1.1.2.3.4) and **conclusion (ii)** applies to some processes of that scenario.

The MOS values for the “worst-case” full shift exposures are all less than 10, five scenarios are less than 1.

4.1.3.2.7.4 Effects on developmental toxicity after dermal exposure

There is no concern for systemic effects following this route of exposure (**conclusion (ii)**).

4.1.3.2.8 Summary of risk characterisation for workers

Table 4.1.3.2.8.A: Summary of risk characterisation for occupational exposure.

Non-quantitative effects:
Conclusion (i) "on hold" applies to all workplace scenarios for germ cell mutagenicity, and **conclusion (iii)** for somatic cell mutagenicity linked to cancer.
Conclusion (ii) applies to all workplace scenarios involving dermal and eye exposure for irritation, and to all scenarios for skin sensitisation (induction and elicitation).
Conclusion (iii) applies to all workplace scenarios involving respiratory sensitisation.

Scenario	**Acute toxicity**		**Repeated dose toxicity**			**Carcinogenicity**		**Fertility**			**Developmental toxicity**		
	Inhalational	**Dermal**	**Inhalation – full-shift**		**Dermal**	**Inhalation Full shift**	**Dermal**	**Inhalation Full shift**		**Dermal**	**Inhalation Full shift**		**Dermal**
	Short-term	**Typical / Worst-case**	**Typical**	**Worst-case**	**Typical / Worst-case**	**Typical**		**Typical**	**Worst-case**	**Typical / Worst-case**	**Typical**	**Worst-case**	**Typical / Worst-case**
A1: Nickel nitrate production from metallic nickel	**iii**	**ii**	**iii**	**iii**	**ii**	**iii**	**ii**	**iii**	**iii**	**ii**	**iii**	**iii**	**ii**
A2: Nickel nitrate production from secondary raw materials	**iii**	**ii**	**iii**	**iii**	**ii**	**iii**	**ii**	**iii**	**iii**	**ii**	**iii**	**iii**	**ii**
B1: Nickel nitrate used in the production of catalysts	**iii**	**ii**	**iii**	**iii**	**ii**	**iii**	**ii**	**ii**	**iii**	**ii**	**ii**	**iii**	**ii**
B2: Nickel nitrate used in the production of NiCd batteries	**iii**	**ii**	**iii**	**iii**	**ii**	**iii**	**ii**	**ii**	**iii**	**ii**	**iii**	**iii**	**ii**
B3: Nickel nitrate used in chemical pre-treatment of metals	**ii**	**ii**	**iii**	**iii**	**ii**	**iii**	**ii**	**ii**	**iii**	**ii**	**iii**	**iii**	**ii**
B4: Other uses of nickel: chemicals production	**iii**	**ii**	**iii**	**iii**	**ii**	**iii**	**ii**	**ii-iii**[1]	**iii**	**ii**	**ii-iii**[1]	**iii**	**ii**

1) It is noted that scenario B4 covers an enormous range of processes (see section 4.1.1.2.3.4) and **conclusion (ii)** applies to some processes of that scenario.

4.1.3.3 Risk characterisation for Consumers.

There is no known consumer exposure to nickel nitrate.

4.1.3.4 Risk characterisation for Man via environment.

See the common MvE RAR for the nickel substances (nickel; nickel carbonate; nickel chloride; nickel dinitrate and nickel sulphate): "Humans exposed indirectly via the environment and combined exposure - exposure assessment and risk characterisation".

4.1.3.5 Combined Exposure.

See the common MvE RAR for the nickel substances (nickel; nickel carbonate; nickel chloride; nickel dinitrate and nickel sulphate): "Humans exposed indirectly via the environment and combined exposure - exposure assessment and risk characterisation".

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

Risk assessment concerning the properties listed in Annex IIA of Regulation 1488/94

4.2.1 Exposure assessment

See section 4.1.1

4.2.2 Effects assessment:

Hazard identification and Dose (concentration) - response (effect) assessment

4.2.2.1 Explosivity

Nickel dinitrate has no explosive properties.

4.2.2.2 Flammability

No data is available for the flash point, flammability or autoflammability of nickel dinitrate. This information is regarded as "not applicable" in two HEDSET submissions (HEDSET 2000a, 2000b) (see Chapter 13.4).

The US Coastguard (1984-5) includes under Fire potential "Contact of solid with wood or paper may cause fires" Hawley's Condensed Chemical Dictionary (1987) includes: "Hexahydrate dangerous fire risk." (quoted from HSDB, 2003).

4.2.2.3 Oxidising potential

Nickel dinitrate is an oxidiser (see Chapter 1.3.3).

4.2.3 Risk characterisation

There is no concern for explosive properties of nickel dinitrate. **Conclusion (ii)** applies.

Nickel dinitrate gives concern for flammability. Compliance with proper risk reduction measures should be adequate to meet the concern for this property. **Conclusion (ii)** applies to all workplace situations.

Nickel dinitrate is an oxidiser (see Chapter 1.3.3). Compliance with proper risk reduction measures should be adequate to meet the concern for this property. Conclusion **(ii)** applies to all workplace situations.

5. CONCLUSIONS/RESULTS

5.1 ENVIRONMENT

Not included in this report.

5.2 HUMAN HEALTH

5.2.1 OCCUPATIONAL ASSESSMENT

(X) i) There is need for further information and/or testing

(X) ii) There is at present no need for further information and/or testing or for risk reduction measures beyond those which are being applied

(X) iii) There is a need for limiting the risks: risk reduction measures which are already being applied shall be taken into account

Conclusion (i) (on hold) is reached because:

- There is a need for further studies to evaluate the possible effects of nickel nitrate on germ cells, but further testing is not considered practicable.

Conclusion iii) is reached because:

- The risk assessment has shown that for certain endpoints (acute toxicity, respiratory sensitisation, repeated dose toxicity, carcinogenicity, effects on fertility and development) effects on human health cannot be excluded following inhalational exposure for the following scenarios:

Scenario	Acute toxicity	Respiratory sensitisation	Repeated dose toxicity		Carcino-genicity [1]	Fertility		Develop-mental toxicity	
	Inhalational Short -term		Inhalation – full-shift		Inhalation Full shift Typical	Inhalation Full shift		Inhalation Full shift	
			Typical	Worst-case		Typical	Worst-case	Typical	Worst-case
A1: Nickel nitrate production from metallic nickel	iii	iii	iii	iii	iii	iii	iii	iii	iii
A2: Nickel nitrate production from secondary raw materials	iii	iii	iii	iii	iii	iii	iii	iii	iii
B1: Nickel nitrate used in the production of catalysts	iii	iii	iii	iii	iii		iii		iii
B2: Nickel nitrate used in the production of NiCd batteries	iii	iii	iii	iii	iii		iii	iii	iii
B3: Nickel nitrate used in chemical pre-treatment of metals		iii	iii	iii	iii		iii	iii	iii
B4: Other uses of nickel: chemicals production	iii	iii	iii	iii	iii	iii [2]	iii	iii [2]	iii

1: Includes somatic cell mutagenicity linked to inhalational cancer.
2: The scenario covers an enormous range of processes (see section 4.1.1.2.3.4). **Conclusion (ii)** applies to some processes.

Conclusion ii) is reached because:

- For all other scenarios for inhalational exposure for effects on acute toxicity, fertility and development and for all scenarios for dermal exposures for acute and repeated dose toxicity, irritation, skin sensitisation, carcinogenicity and reproductive toxicity there is no need for limiting the risks taking into account the risk reduction measures that are already being applied.

5.2.2 CONSUMER ASSESSMENT

There is no known consumer exposure to nickel nitrate.

5.2.3 INDIRECT EXPOSURE VIA THE ENVIRONMENT

5.2.4 *See the common MvE RAR for the nickel substances (nickel; nickel carbonate; nickel chloride; nickel dinitrate and nickel sulphate): "Humans exposed indirectly via the environment and combined exposure - exposure assessment and risk characterisation"*.COMBINED EXPOSURE

See the common MvE RAR for the nickel substances (nickel; nickel carbonate; nickel chloride; nickel dinitrate and nickel sulphate): "Humans exposed indirectly via the environment and combined exposure - exposure assessment and risk characterisation".

5.2.5 PHYSICOCHEMICAL PROPERTIES

( )	i)	There is need for further information and/or testing
(X)	ii)	There is at present no need for further information and/or testing or for risk reduction measures beyond those which are being applied
( )	iii)	There is a need for limiting the risks: risk reduction measures which are already being applied shall be taken into account

Conclusion ii) is reached because:

- Nickel dinitrate is an oxidiser and there is concern for flammability. However, compliance with proper risk reduction measures should be adequate to meet the concerns. Nickel dinitrate is not explosive.

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7. APPENDICES

7.1 EUSES RISK CHARACTERISATION RESULT TABLE

To be included

7.2 EUSES SUMMARY REPORT

To be included

7.3 IUCLID DATA SET

To be included

7.4 NEW ANNEX I ENTRY TO DIR. 67/548

Index No	Chemical name	Notes related to substances	EC No	CAS No	Classification	Labelling	Concentration limits	notes related to preparations
028-012-00-1	nickel dinitrate [1] nitric acid, nickel salt [2]	E	236-068-5 [1] 238-076-4 [2]	13138-45-9 [1] 14216-75-2 [2]	O; R8 Carc Cat 1; R49 Muta. Cat. 3; R68 Repr. Cat. 2; R61 T; R48/23 Xn; R20/23 Xi; R38-41 R42/43 N; R50-53.	O; T; N R: 49-61-23/25-8-38/41-42/43-48/23-50/53 S: 53-45-60-61	C≥25%: T, N; R49-61-20/22-38-41-42/43-48/23-50/53 20%≤C<25%: T, N; R49-61-38-41-42/43-48/23-51/53 10%≤C<20%: T, N; R49-61-41-42/43-48/23-51/53 5%≤C<10%: T, N; R49-61-36-42/43-48/23-51/53 2.5%≤C<5%: T, N; R49-61-42/43-48/23-51/53 1%≤C<2.5%: T; R49-61-42/43-48/23-52/53 0.5%≤C<1%: T; R49-61-43-48/20-52/53 0.25%≤C<0.5%: T; R49-43-48/20-52/53 0.1 %≤C<0.25 %: T; R49-43-48/20 0.01%≤C<0.1%: Xi; R43	

This new Annex I entry is included in the 30th. ATP