Nickel carbonate

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EINECS-No.: 222-068-2

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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0. OVERALL RESULTS OF THE RISK ASSESSMENT

0.1 OVERALL CONCLUSIONS FOR ENVIRONMENT:

Not included in this report.

0.2 OVERALL CONCLUSIONS FOR HUMAN HEALTH

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 carbonate 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 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 carbonate.

0.2.3 INDIRECT EXPOSURE VIA THE ENVIRONMENT

0.2.4 *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".

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:

- There is no reason for concern with respect to the physico-chemical properties of nickel carbonate.

1. GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

1.1.1 Nickel carbonate and nickel hydroxycarbonate.

The identity of the commercially available substance "nickel carbonate" is complicated.

The name "nickel carbonate" is most often used as a common class name rather than to identify the simple salt $NiCO_3$. Most of the commercial "nickel carbonates" are basic salts described more appropriately as nickel hydroxycarbonates or basic nickel carbonates with a general formula $xNiCO_3.yNi(OH)_2.zH_2O$ (NiPERA, 1996).

The following Table lists a series of substances ranging from different nickel carbonates, through a number of nickel hydroxycarbonates with decreasing proportions of carbonate to hydroxide, to nickel hydroxide. Information on the hydrates is also included. The information in this Table is based mainly on Laine (2002a).

Table 1.1.A: nickel carbonates, nickel hydroxycarbonates and nickel hydroxide.

Name	Formula	CAS No.	EC No.	Hydrate	CAS No.
Carbonic acid, nickel (2+)salt	$NiCO_3$	3333-67-3	222-068-2 (1)	$NiCO_3 \cdot H_2O$ $NiCO_3 \cdot 6H_2O$	51944-07-1 (2) 18195-55-6 (2)
Carbonic acid, nickel salt,	$CH_2O_3.x$Ni.	16337-84-1	240-408-8.		
"Nickel carbonate hydroxide"		142164-39-4		"Nickel Carbonate Hydroxide, Hydrate"	155775-31-8
	$4NiCO_3.Ni(OH)_2$ (x = 4:y = 1)	152008-07-6			
	$3NiCO_3.Ni(OH)_2$ (x = 3:y = 1)	128024-15-7		$3NiCO_3.Ni(OH)_2.2.5H_2O$	158970-34-4
	$Ni(CO_3)_{0-1.5}(OH)_{0-3}$	342774-56-5			
[μ-[carbonato(2-)-O:O']] dihydroxy trinickel	$NiCO_3.Ni(OH)_2$ (x = 1:y = 1)	65405-96-1	265-748-4	$NiCO_3.Ni(OH)_2.H_2O$ $NiCO_3.Ni(OH)_2.2H_2O$	97564-53-9 (2) No CAS No. (2)
	$3NiCO_3.4Ni(OH)_2$ (x = 3:y = 4)	148522-90-1			
pentanickel dicarbonate hexahydroxide	$2NiCO_3.3Ni(OH)_2$ (x = 2:y = 3)	12122-15-5	(3)	$2NiCO_3.3Ni(OH)_2.4H_20$	12244-51-8 (4)
[carbonato(2-)] tetrahydroxytrinickel; Basic nickel carbonate;	$NiCO_3.2Ni(OH)_2$ (x = 1:y = 2)	12607-70-4	235-715-9 (1)	$NiCO_3.2Ni(OH)_2.H_2O$ $NiCO_3.2Ni(OH)_2.2H_2O$ $NiCO_3.2Ni(OH)_2.3H_2O$ $NiCO_3.2Ni(OH)_2.4H_2O$ (6) $NiCO_3.2(OH)_2.4.5H_2O$ $NiCO_3.2Ni(OH)_2.6H_2O$	39380-74-0 (2, 5) 201366-93-0 (2) No CAS No. (2) 39430-27-8 (2) 52931-56-3 (2) 77114-11-5 (2)
	$NiCO_3.3Ni(OH)_2$ (x = 1:y = 3)	12274-86-1		$NiCO_3.3Ni(OH)_2.4H_2O$	12011-88-0
	$NiCO_3.13Ni(OH)_2$ (x = 1:y = 13)	404866-99-5		$NiCO_3.13Ni(OH)_2.3H_2O$	12011-89-1

nickel dihydroxide [7]	$Ni(OH)_2$	12054-48-7	235-008-5		

1) Also included in TSCA Inventory.
2) As the anhydrous salt is included in EINECS, this hydrate is by implication included in EINECS.
3) CAS No. 12122-15-5 is not included in EINECS. NiPERA (1996) gives the EC No. 235-715-9 for both the 2:3 and the 1:2 hydroxycarbonates.
4) Antonsen (1996) and Lascelles *et al*. (1991) give CAS No. 29863-10-3 for this compound.
5) A substance with this CAS No. is marketed in the US. The chemical formula given for the marketed substance is $NiCO_3.Ni(OH)_2$, the 1:1 hydroxycarbonate. The 1:1 hydroxycarbonate is not in TSCA and is shown with CAS No. 65405-96-1 in the Table above.
6) This is a naturally occurring mineral, zaratite (Grandjean, 1986, quoted in IARC, 1990).
7) An additional substance in EINECS, nickel hydroxide, CAS No. 11113-74-9, EC No. 234-348-1 has the molecular formula NiOH, and is a nickel (1+) compound.

Other substances not included in the EINECS or TSCA inventories include nickel bicarbonate and a number of hydrated nickel carbonate-nickel oxide compounds (Laine, 2002a). These are shown in Table 1.1.B.

Table 1.1.B: Other related substances and their hydrates not included in EINECS or in the TSCA Inventory (Laine, 2002a).

CAS Number	Structural formula / Name
17237-93-3	$Ni(HCO_3)_2$
12012-03-2	$NiCO_3$ $2NiO.6H_2O$
12012-04-3	$NiCO_3.3NiO.H_2O$
12012-05-4	$NiCO_3.13NiO.16H_2O$
12012-06-5	$NiCO_3.16NiO.21H_2O$
12012-07-6	$NiCO_3.21NiO.14H_2O$
12012-08-7	$NiCO_3.21NiO.18H_2O$

Nickel carbonate with CAS No.: 3333-67-3 is included in the European Customs Inventory of Chemical Substances (ECIS, 1997) with the number 20729. Basic nickel carbonate with CAS No.: 39430-27-8 is also included in ECIS with the number 25626. This CAS Number refers to the tetrahydrate of the 1:2 nickel hydroxycarbonate, [carbonato(2-)] tetrahydroxytrinickel with CAS No. 12607-70-4 (EC No. 235-715-9).

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 2836 99 18, the second 2836 99 19. Both relate to "other" carbonates, and hence, some other metal carbonate can be included in this CN number.

1.1.2 Commercially produced nickel carbonate.

Nickel hydroxide carbonate contains approximately 47 - 51 % nickel. However the composition of nickel hydroxide carbonate (basic nickel carbonate) can vary (IPCS, 1991).

Nickel carbonate is available mainly as hydroxycarbonates, such as basic nickel carbonates (IARC, 1990). IARC (1990) lists two substances as "basic nickel carbonates". These are the 2:3 basic carbonate with CAS No. 12122-15-5 and the 1:2 basic carbonate with CAS No. 12607-70-4 (EC 235-715-9).

Antonsen (1996) states that the commercial material of nickel carbonate, CAS 3333-67-3 "is the basic salt $2NiCO_3.3Ni(OH)_2$. $4H_20$, CAS No. 29863-10-3". Lascelles *et al*. 1991 points out that "the industrially important compound is the bright green, rhombic basic nickel carbonate approximating to $2NiCO_3.3Ni(OH)_2$ $4H_20$, CAS No. 29863-10-3, Mr 587.57." This salt is the tetrahydrate of the 2:3 basic carbonate mentioned in IARC. According to Laine (2002a), the CAS No. of this tetrahydrate salt is 12244-51-8 rather than the CAS No. 29863-10-3 given by both Antonsen (1996) and Lascelles *et al*. (1991).

NiPERA (1996) lists a number of compounds under "oxidic" nickel. These include nickel carbonate with CAS No. 3333-67-3 and EC No. 222-068-2. The tetrahydrate of the 2:3 nickel hydroxycarbonate (CAS No. 12244-51-8 from Table 1.1.A) is shown with CAS No. 12122-15-5 and EC No. 235-715-9. This would appear to be an error, as this CAS No. corresponds to the anhydrous 2:3 nickel hydroxycarbonate (see above) and the EC No. to the 1:2 nickel hydroxycarbonate. NiPERA (1996) finally includes the 1:2 nickel hydroxycarbonate as both the anhydrous form and the tetrahydrate. These are both shown with CAS No. 12607-70-4 and EC No. 235-715-9. The 1:2 nickel hydroxycarbonate tetrahydrate is also listed a second time, this time with the CAS No. 39430-27-8, no EC number and including the synonym "zaratite" with a note that this is a naturally occurring mineral. The 1:1 nickel hydroxycarbonate is not listed by NiPERA (1996).

"Nickel carbonate" is manufactured in Europe by three producers. One, OMG, has filed HEDSET data on nickel carbonate, CAS No. 3333-67-3, EC No. 222-068-2 as a HPVC (European Commission, 2002a). The substance is actually a basic nickel carbonate. The chemical composition of the nickel hydroxycarbonate can be expressed as the molar ratio between $Ni(OH)_2$ and $NiCO_3$. The $Ni(OH)_2/NiCO_3$ -molar ratio in the typical, commercially available product varies between 1 and 2.

In two series of measurements the average $Ni(OH)_2/NiCO_3$ molar ratio varied around 1.5 according to confidential information received by the rapporteur from the main manufacturers. More information is available in the derogation statement and in a confidential annex, available to member states on request to the Danish EPA. These figures should be compared to the 1.5 ratio for the $2NiCO_3.3Ni(OH)_2$ described by Antonsen (1996) and Lascelles *et al*. (1991) as the commercial nickel basic carbonate and the 2.0 ratio for the $NiCO_3 \cdot 2Ni(OH)_2$ basic carbonate included in EINECS and the TSCA inventory.

Pharmacie de France have submitted a HEDSET on Nickel, [carbonato(2-)]tetrahydroxytri- (CAS No.: 12607-70-4, EC No.: 235-715-9) with $Ni(OH)_2/NiCO_3$-molar ratio = 2, as a LPVC (European Commission, 2002b). In addition, Königswarter and Ebel, Germany, are included in the derogation statement as producers, and Umicore, Belgium as importers, although neither are shown in ESIS (European Commission, 2002b).

For the purpose of this report, the Rapporteur has followed the conclusions of IARC (1990) and NiPERA (1996) listings, and regards both the 2:3 basic carbonate (CAS No. 12122-15-5) and the 1:2 basic carbonate (CAS No. 12607-70-4, EC 235-715-9) as the commercial product. Further details of the 2:3 and the 1:2 nickel hydroxycarbonates are shown in section 1.1.4.

1.1.3 Administrative Considerations.

Nickel carbonate (CAS No. 3333-67-3, EC No. 222-068-2) is included in the fourth list of priority substances (EC, 2000b) under Council Regulation (EEC) 793/93 (EEC, 1993b).

Two "nickel carbonates" were included in ECOIN, the Core Inventory which formed a starting point for EINECS. These are a nickel carbonate, Carbonic acid, nickel (2+)salt, with CAS No. 3333-67-3 (EC No. 222-068-2) and the 1:2 nickel hydroxycarbonate, [carbonato(2-)] tetrahydroxytrinickel with CAS No. 12607-70-4 (EC No. 235-715-9). Both these substances are listed in the TSCA inventory.

Substances included in ECOIN did not have to be specifically notified to EINECS by EEC producers and manufacturers. The final EINECS listing includes two additional "nickel carbonates". These are a second nickel carbonate, Carbonic acid, nickel salt, (CAS No. 16337-84-1, EC No. 240-408-8) and a second nickel hydroxycarbonate, the 1:1 compound: [μ-[carbonato(2-)-O:O']] dihydroxy trinickel (CAS No. 65405-96-1, EC No. 265-748-4). Neither of these substances are included in the TSCA inventory.

For reasons that remain unclear, the "industrially important compound ….. approximating to $2NiCO_3.3Ni(OH)_2$ $4H_20$," (Lascelles *et al*. , 1991) and generally recognised as the commercially available material (see section 1.1.2 above) was not included in ECOIN, was not notified to EINECS and is not in the TSCA inventory.

For substances included in EINECS, the EC numbers shown in Table 1.1.A apply to all the hydrates of these substances. 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." As this rule indicates, the EINECS numbers for the anhydrous forms represent by implication all the corresponding hydrated forms in Table 1.1.A above.

The HPV commercial product made in Europe is nickel hydroxycarbonate. Unlike the other nickel compounds reviewed by the Rapporteur, due to variations in the production process, the products can have varying $Ni(OH)_2/NiCO_3$ -molar ratios. The Rapporteur regards this substance as an Existing Chemical, and for administrative purposes, the commercial product is considered to be the 1:2 hydroxycarbonate, [carbonato(2-)] tetrahydroxytrinickel, (CAS No. 12607-70-4) which is also included in the TSCA Inventory. The tetrahydrate of this substance is also included in ECIS (1997).

This risk assessment covers the commercially produced "nickel carbonate" as it is put on the market. The conclusions of this risk assessment with regard to hazard identification cover all relevant nickel carbonates and hydroxycarbonates. Risk assessment and risk reduction recommendations apply to the actual production processes and the actual uses of the commercially produced and marketed substances.

1.1.4 Substance Identification.

Table 1.1.C: Substance Identification: 2:3 and 1:2 nickel hydroxycarbonates.

CAS No.:	12122-15-5	12607-70-4
EINECS No.:	-	235-715-9 [3]
IUPAC Name:	pentanickel dicarbonate hexahydroxide	trinickel monocarbonate tetrahydroxide
Synonyms:		Basic nickel carbonate;
Molecular formula:	$C_2H_6Ni_5O_{12}$	$CH_4Ni_3O_7$
Structural formula:	$2NiCO_3.3Ni(OH)_2$ (2:3)	$NiCO_3.2Ni(OH)_2$ (1:2)
Molecular weight:	515.52	304.12

Table 1.1.D: Hydrates of 2:3 nickel hydroxycarbonate.

Species	CAS No.	Molecular weight	Stability Range
$2NiCO_3.3Ni(OH)_2$	12122-15-5	515.52	n.a. (1)
$2NiCO_3.3Ni(OH)_2.4H_20$	12244-51-8	587.57	n.a. (1)

1) Information not available.

Table 1.1.E: Hydrates of 1:2 nickel hydroxycarbonate.

Species	CAS No.	Molecular weight	Stability Range
$NiCO_3.2Ni(OH)_2$	12607-70-4	304-12	230 – 250 ºC
$NiCO_3.2Ni(OH)_2.H_2O$	39380-74-0	322.13	n.a. (1)
$NiCO_3.2Ni(OH)_2.2H_2O$	201366-93-0	340.15	n.a. (1)
$NiCO_3.2Ni(OH)_2.3H_2O$	-	358.16	n.a. (1)
$NiCO_3.2Ni(OH)_2.4H_2O$	39430-27-8	376.17	n.a. (1)
$NiCO_3.2(OH)_2.4.5H_2O$	52931-56-3	385-19	n.a. (1)
$NiCO_3.2Ni(OH)_2.6H_2O$	77114-11-5	412.21	n.a. (1)

1) See Figure 1.3.B (Laine, 2003b).

1.2 PURITY / IMPURITIES, ADDITIVES.

Laboratory reagent grades may contain 47.5% or 45% Ni; industrial grades, in the form of green powders or wet pastes contain approximately 45% nickel (Inco, 1981-2, Pharmacie Centrale, 1988, quoted in IARC, 1990). Impurities most likely present in significant amounts are the anions Cl^- or $SO_4^=$ and the cations Na^+ or K^+, depending on the production method (NiPERA, 1996).

As basic nickel carbonates are always produced by precipitation of nickel salt solutions with solutions of an alkali metal carbonate, the CO_3^+/OH^- ratio in the product, and therefore its alkalinity, can vary within a wide range (NiPERA, 1996).

An example of the purity of commercially produced nickel hydroxycarbonate is shown in Table 1.2.A (Laine, 2003b).

Table 1.2.A: Purity of a commercially available nickel hydroxycarbonate (Laine, 2003b)

	CAS-No [1].	**Name**	**Value**
Purity:		Nickel	> 47 %
Impurities:		Cobalt	<10 ppm
		Iron	<10 ppm
		Lead	<1 ppm
		Copper	<1 ppm
		Zinc	<1 ppm
		Cadmium	<1 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 hydroxycarbonate can be sold as a "wet" product, i.e. the filtered precipitate is not dried (see chapter 2.1.1.1.). In this case the nickel content of the product is lower (15 – 25%) (Königswarter & Ebell, 2003).

1.3 PHYSICO-CHEMICAL PROPERTIES

Table 1.3.A: Summary of the physico-chemical properties of commercially available nickel hydroxycarbonate tetrahydrate (1)

	Value	**Comment**	**Reference**
Physical State:	Solid	light-green powder	NiPERA (1996).
Melting Point:		decomposes to form CO_2, H_2O and NiO in temperature range 120 °C – 350°C	Laine (2004b)
Boiling Point:	not applicable	does not form liquid phase	Laine (2004b)
Density:	0.7 –0.8 g/cm^3 2.6 g/cm^3 2.9 kg/m^3	bulk density	OMG Harjavalta Nickel (2003) NiPERA (1996) (2) Laine (2004b)
Vapour Pressure	not applicable	does not form liquid phase	Laine (2004b)
LogK_{ow}	not applicable	nickel hydroxycarbonate does not dissolve in ether, water or n-octanol.	OMG (2004)
Water Solubility:	 Insoluble virtually insoluble	see also section 1.3.2 below. soluble in alcohol, NH_4OH. dissolves in acids with evolution of carbon dioxide	 NiPERA (1996) Lascelles *et al.* (1991)
Surface Tension	not applicable	does not form liquid phase	Laine (2004b)
Flash Point	not applicable	does not form liquid phase. Nickel hydroxycarbonate does not burn.	Laine (2004b)
Autoflammability	not autoflammable	Nickel hydroxycarbonate	Laine (2004b)

	Value	Comment	Reference
		does not burn	
Flammability	not flammable	thermal decomposition is endothermic	OMG Harjavalta Nickel (2003), Laine (2004b)
Explosive Properties	not explosive	thermal decomposition is endothermic	OMG Harjavalta Nickel (2003), Laine (2004b)
Oxidising Properties	not oxidising		Laine (2004b)
Viscosity	not applicable	does not form liquid phase	Laine (2004b)

1) shown by NiPERA (1996) as $C_2H_6NiO_{12}.4H_2O$ with molecular mass of 587.57.
2) quoted from Dean (1973).

Additional physical chemical data is available from NiPERA on the tetrahydrate of the 1:2 basic nickel carbonate (zaratite).

Table 1.3.B: Summary of the physico-chemical properties of the tetrahydrate of carbonic acid, nickel salt, basic (CAS No. 12607-40-4, EC No. 235-715-9) (Zaratite)

	Value	Comment	Reference
Physical State:	Solid	light-green powder	NiPERA (1996).
Melting Point:		decomposes	NiPERA (1996)
Boiling Point:			NiPERA (1996)
Density:	2.6 g/cm^3		NiPERA (1996)
Water Solubility:	Insoluble	soluble in alcohol, NH_4OH	NiPERA (1996)

1.3.1 Conversion factors:

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

1.3.2 Water solubility of nickel carbonates.

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

The solubility of $NiCO_3$ (EC No. 222-068-2) in water is rather low, the solubility product $K_{SP} = 6.565 \cdot 10^{-9}$ (Gmelin, 1966). A second source states the solubility product to be $K_{SP} = 1.42 \cdot 10^{-7}$ (CRC, 2000). Thus a reasonable value for, e.g., risk assessment purposes is suggested to be $K_{SP} = 10^{-7}$ - 10^{-8} , which will constitute a conservative approach (Carlsen, 2001).

It has been reported (Gmelin, 1966) that the solubility increases with increasing carbon dioxide partial pressure (Table 1.3.C) (Carlsen, 2001)

Table 1.3.C: Solubility of $NiCO_3$ as a function of CO_2 partial pressure (Gmelin, 1966, quoted from Carlsen, 2001).

$P(CO_2)$	0	0.4055	0.9613
eq/L	0.00078	0.0270	0.03731

The basic nickel carbonates are generally noted as being insoluble in water, whereas they are reported to be very soluble in diluted acidic solution (Carlsen, 2001).

Additional information is available from the Transformation test carried out in OECD 203 aqueous medium (Skeaff & King, 2002). This test was carried out on nickel hydroxycarbonate produced by OMG (i.e. the commercial product). The solubility was measured at pH 6 in 10:1 OECD 203 medium and pH 8 in regular OECD 203 medium, so these figures do not reflect water solubility in the normal sense of saturated solubility in

distilled water. The solubility at pH 6 was 22 – 46 mg/L and 5.5 – 9.3 mg/L at pH 8. This shows that the substance fulfils the criteria for classification for the aquatic environment as N; R50-53.

1.3.3 Thermogravimetric analysis.

In thermogravimetric analysis, a sample is heated to a certain temperature and loss of weight is observed during heating. Both the 2:3 and the 1:2 nickel hydroxycarbonates form nickel oxide when heated to 800 °C.

The commercially available nickel hydroxide carbonate looses 36% of its weight during heating. The results are shown in Figure 1.3.D. The theoretical weight loss of the nickel hydroxycarbonate with a chemical composition of $2NiCO_3.3Ni(OH)_2.4H_2O$ is 36% (Laine, 2003d).

Nickel hydroxide carbonate hexahydrate ($NiCO_3.2Ni(OH)_2.6H_2O$) looses 45 % of its weight during heating (Laine, 2003d). These results are shown in Figure 1.3.E (data from Atlas of Thermoanalytical Curves, 1995).

Figure 1.3.D: Thermogravimetric measured from the commercially available nickel hydroxide carbonate (Laine, 2003d)

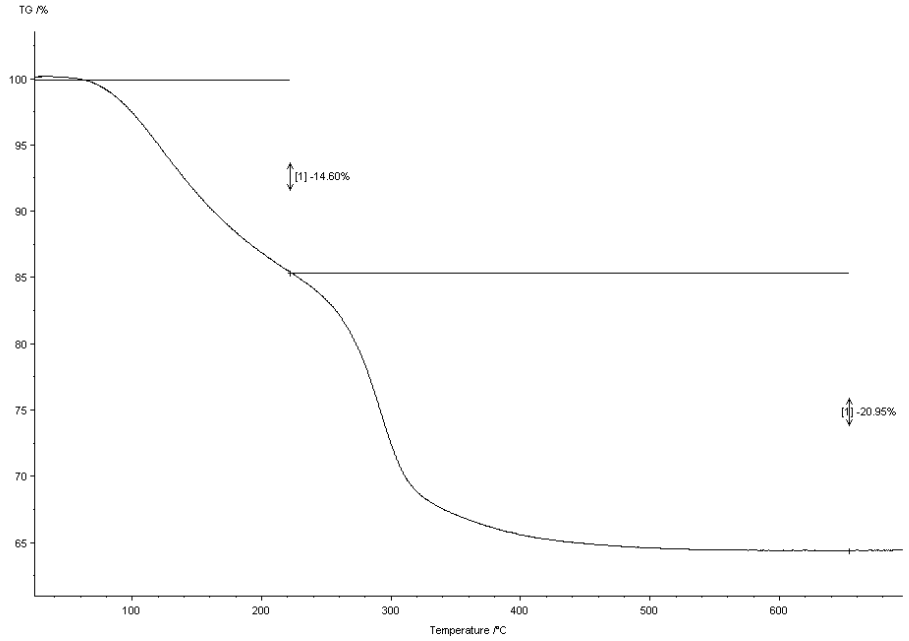
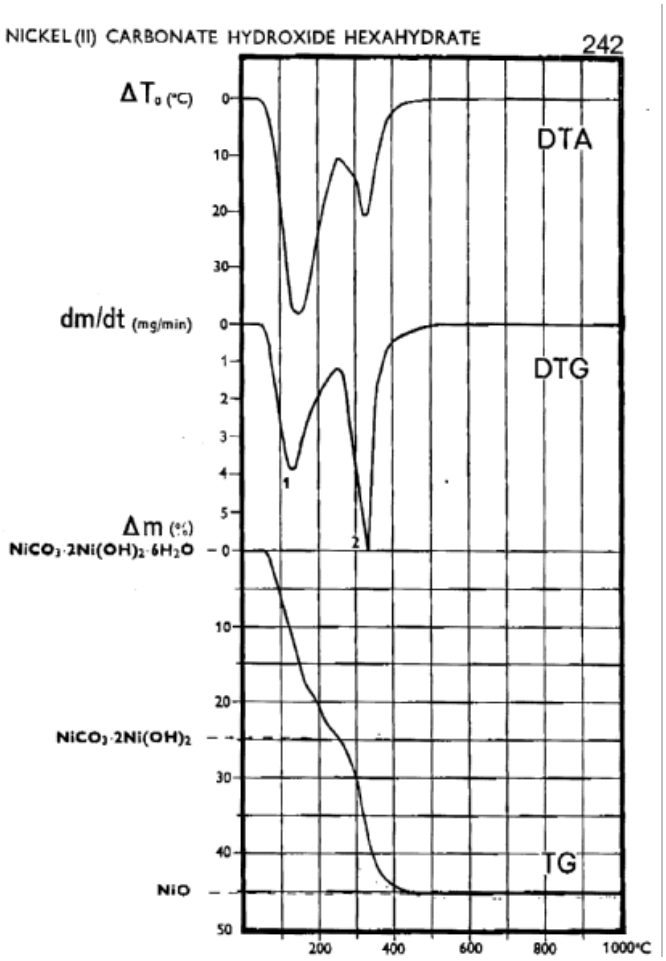


Figure 1.3.E: Thermogravimetric curve of (1:2) nickel hydroxide carbonate hexahydrate (Atlas of Thermoanalytical Curves, 1995).



1.3.4 Summary

The data on physico-chemical properties for the different forms of nickel carbonate are limited. 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 carbonate is not included as a specific entry in the UN Recommendations on the Transport of Dangerous Goods (UN, 2001), ADN (UN ECE, 2001a) or ADR (UN ECE 2001b).

According to Laine (2001), nickel carbonate is transported under UN No. 3077: Environmentally Hazardous Substance, Solid, N.O.S. Hazard Class 9, 12c. Packaging group III. The product is not considered as hazardous when carried by sea (IMDG/GGVSee).

1.4.1.2 Classification according to Directive 67/548/EEC.

Nickel carbonate is included in Annex I to Directive 67/548/EEC. The entry (028-010-00-0) was last updated in the 25th Adaptation to technical progress (EC 1998b).

Classification			
Carc. Cat. 3; R40	**Xn; R22**	**R43**	**N; R50-53**
Labelling			
Symbols	Xn; N		

R Phrases	22-40-43-50/53
S-Phrases	(2-)22-36/37-60-61

Note that the entry formally identifies the substance by its CAS and EC numbers (3333-67-3, 222-068-2).

NiPERA (1996) also lists two other substances, not mentioned in Annex I as included in the same Annex I entry (028-010-00-0). These are the 1:2 nickel hydroxycarbonate, with the EINECS name: [carbonato(2-)] tetrahydroxytrinickel), CAS and EC Nos. 12607-70-4 and 235-715-9, and 2NiCO3.3Ni(OH)2.4H2O shown with CAS No. 12122-15-5 and EC No. 235-715-9 (for comments on these CAS & EC Nos. see section 1.1.2 above).

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

The revised entry for nickel carbonate (028-009-00-5) in Annex I of Council Directive 67/548/EEC in the 30th. ATP is[1]:

Classification							
Carc. Cat. 1; R49	Muta. Cat. 3; R68	Repr. Cat. 2; R61	T; R48/23	Xn; R20/22	Xi; R38	R42/43	N; R50-53

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

The Annex I entry to include all the EINECS-listed “nickel carbonate” substances:
Carbonic acid, nickel (2+)salt, (EC No. 222-068-2, CAS No. 3333-67-3),
Carbonic acid, nickel salt, (EC No. 240-408-8, CAS No. 16337-84-1),
[μ-[carbonato(2-)-O:O’]] dihydroxy trinickel, (EC No. 265-748-4, CAS No. 65405-96-1)
[carbonato(2-)] tetrahydroxytrinickel; Basic nickel carbonate; (EC No. 235-715-9, CAS No. 12607-70-4).

The entry does not include specific concentration limits.

The revised entry for Annex I to Directive 67/548/EEC 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

The nickel carbonates belong 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 document in support of the individual Risk Assessment Reports*.

Zaratite (CAS No. 39430-27-8) is a naturally occurring mineral form of basic nickel carbonate, tetrahydrate ($NiCO_3.2Ni(OH)_2.4H_2O$) (Grandjean, 1986, quoted in IARC, 1990).

2.1 PRODUCTION

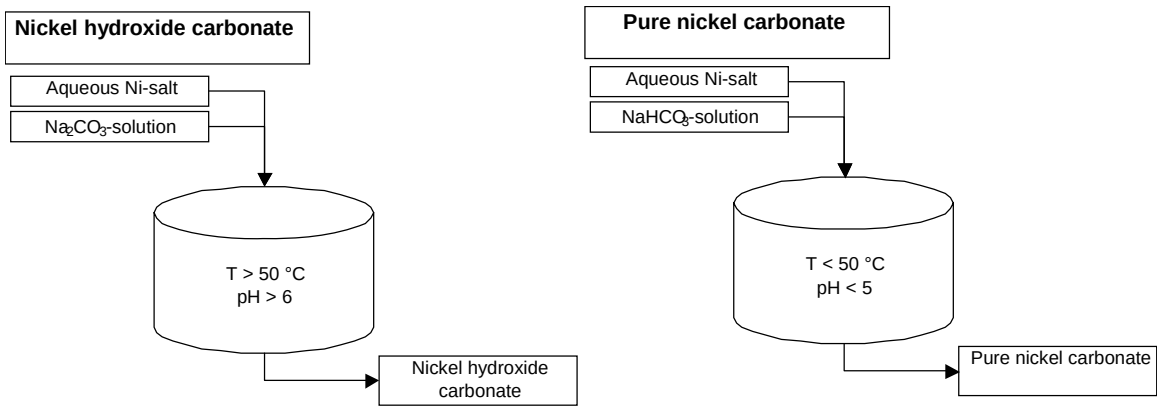
2.1.1 Production methods.

Commercial basic nickel carbonate is made by precipitation from a nickel solution, usually the sulphate, with sodium carbonate. The exact composition of the product depends on the temperature and the concentration of the components in solution (Lascelles *et al*. 1991).

As nickel hydroxycarbonates are always produced by precipitation of nickel salt solutions with solutions of an alkali metal carbonate, the CO_3^{2-}/OH^- ratio in the product can vary within a wide range (NiPERA, 1996).

Nickel hydroxycarbonate is produced at high temperature (> 50 °C) and pH (> 6). Nickel is fed as an aqueous salt (e.g. sulphate, chloride or nitrate) and the precipitation reagent is usually Na_2CO_3 or some other alkali metal carbonate (Laine, 2003d).

There are differences in the manufacturing conditions and precipitation agents used for the production of pure nickel carbonate and nickel hydroxycarbonates. These are shown schematically in Figure 2.1.A (Laine, 2003). Figure 2.1.A: Simplified flow charts of nickel hydroxide carbonate production and pure nickel carbonate production (Laine, 2003d).



Nickel carbonate is produced at lower temperatures (< 50 °C) and at lower pH (< 5) than production of basic nickel carbonates. Alkaline bicarbonates are also used instead of carbonates.

Nickel hydroxycarbonate is mainly produced from either nickel sulphate or nickel nitrate.

2.1.1.1 Nickel hydroxycarbonate production from soluble nickel salts.

Nickel hydroxycarbonate is prepared from nickel sulphate obtained by leaching nickel matte (Laine, 2001).

Nickel matte is produced from sulphidic nickel ores by beneficiation and smelting as described in Chapters 2.1.1. to 2.1.3 of the nickel metal report. The matte, the product of the smelting process, is leached in three steps at the nickel refinery: two atmospheric leaching step and one pressure leaching step, as described in Chapter 2.1.4.2.1 of the nickel metal report. After further purification (described in Chapter 2.1.1.1 of the risk assessment report for nickel sulphate), the product is a pure nickel sulphate solution. This pure nickel sulphate solution is then fed

to either nickel metal production by hydrogen reduction, nickel metal production by electro winning, pure nickel sulphate hexahydrate production, or to production of nickel hydroxycarbonate (Laine, 2001).

In the production of nickel hydroxycarbonate by OMG the main raw materials are nickel sulphate and caustic soda, which acts as precipitation agent. Sodium carbonate is added to the nickel sulphate prepared as described above. The precipitate is washed and precipitated on a band filter. Following this, the nickel carbonate is dried by a spray drier. Finally the product is packed. Most of the product is packed in large bags, although some bulk packing in tank vehicles occurs (Laine, 2001)

Because of dust problems with dried nickel carbonate, therefore the use of at least a P3 class respirator mask is required (Laine, 2001).

Nickel hydroxycarbonate is also produced by precipitation from a nickel sulphate solution with nickel carbonate by a batch process. The precipitate is filtered on a belt filter and washed with water. The product is either sold as a "wet" product, or the nickel hydroxycarbonate is dried in an spray drier (Königswarter & Ebell, 2003).

The production process at PCF is very similar to the processes described above, except that nickel nitrate (obtained by leaching nickel metal or commercially available nickel) is usually used as the starting material instead of nickel sulphate. For internal use, the product is used wet from the filter. The commercial product is dried and packed in drums (PCF, 2003).

2.1.1.2 Nickel carbonate production.

Nickel carbonate can be prepared by the oxidation of nickel powder in ammonia and dioxide. Boiling away the ammonia causes precipitation of pure nickel carbonate (Antonsen, 1996).

Nickel carbonate is not known to be produced in the EU.

2.1.2 Production volumes

The country that produces nickel carbonate in the largest volume in the EU is Finland (ERAMET-SLN, 1989 quoted in IARC, 1990).

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

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

	1994	**1998**	**1999**	**2000**
Calculated as nickel hydroxycarbonate hydrate	4500	5000	7000	6500
Calculated as Ni	2100	2350	3300	3050

The realistic worst-case figures for nickel hydroxycarbonate export are shown below.

Table 2.1.2.B: Export of nickel hydroxycarbonate to non-EU countries (tons / year) (Laine, 2003c).

	1994	**1999**	**2000**
Calculated as nickel hydroxycarbonate hydrate	n.a. (1)	1500	750
Calculated as Ni	n.a. (1)	700	350

1) Information not available.

The country outside the EU producing large volumes of nickel carbonate is Japan (ERAMET-SLN, 1989 quoted in IARC, 1990).

No figures for world production of nickel carbonate are available. No estimate of the proportion of EU production compared to world production of nickel carbonate can be made in the absence of this data.

Umicore in Belgium imports nickel (hydroxy)carbonate to the EU. Import started slowly in 2001 (Laget, 2003). No other figures are available for imports of nickel carbonate to the EU. Nickel carbonates or basic carbonates are not registered individually in customs statistics (ECIS, 1997). Hence information on exports of nickel hydroxycarbonate is not available from this source (Laine, 2003a).

2.1.3 Production sites

Nickel carbonate was produced in the EU at 3 sites in Germany, 2 each in France, Italy and the UK, and one each in Belgium and Spain (Chemical Information Services Ltd. 1988, quoted in IARC, 1990). There are only two manufacturers in Europe (Laine, 2001, quoting from 1999 Directory of Chemical producers – United States, Menlo Park, CA).

Information on the companies currently producing nickel hydroxycarbonate in the EU is shown in the Table below. The Table also shows the raw materials and the products produced.

Table 2.1.3.A: Nickel hydroxycarbonate producing companies in Europe (Laine, 2003b).

Company	Location	Raw materials	Products
OMG Kokkola Chemicals Oy	Kokkola, Finland	nickel sulphate from nickel refinery	nickel hydroxycarbonate
Pharmacie Centrale de France	La Voulte sur Rhone, France	nickel nitrate(1)	nickel hydroxycarbonate
Königswarter & Ebell	Hagen, Germany	nickel sulphate	nickel hydroxycarbonate(2)

1) Nickel nitrate is usually used.
2) Nickel hydroxycarbonate may be sold as a “wet” product.

Nickel hydroxycarbonate was produced at Norddeutsche Affineriet in Germany and a HEDSET submitted to the ECB, but this production has now ceased (Laine, 2003a).

Nickel carbonate was also produced outside the EU at 6 sites in the US and Japan, 3 sites in India, 2 sites each in Argentina and Mexico, and one site each in Brazil, Canada and Switzerland. (Chemical Information Services Ltd. 1988, quoted in IARC, 1990).

2.2 USE PATTERN

2.2.1 Current Use Pattern

Nickel hydroxycarbonate is used in several applications (Laine, 2003d):

- in the manufacture of catalysts
- Zn/Ni-electrogalvanizing
- as a neutralizing compound in nickel electroplating solution
- in the manufacture of certain nickel pigments
- in the manufacture of NiO by thermal decomposition

These are very similar to the uses of nickel carbonate described by Lascelles *et al*. (1991) and Antonsen (1996).

Table 2.2.1.A: Realistic worst-case use of nickel hydroxycarbonate in the EU (t / year).

	1994	1999	2000
Calculated as nickel hydroxycarbonate hydrate	n.a. (1)	5500	5750
Calculated as Ni	n.a. (1)	2500	2700

1) Information not available.

Annual worldwide use of nickel carbonate in 1994 was 5000 t. The price was $4.00 /kg (Antonsen, 1996).

Approximately 70% is used for plating, 20% for catalyst production, 5% for pigment production and 5% for other uses (Laine, 2003c).

High purity nickel carbonate is mainly used in electronic components (IPCS, 1991).

Information from the Danish Product Registry (2001) shows that nickel carbonate containing products are used for “manufacture of metal articles” and for “research and development”. Information from the Swedish Product Registry shows that nickel carbonate is used as a “metal surface treatment agent” (Kemi, 2002).

2.2.1.1 Nickel hydroxycarbonate used in the production of catalysts

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

ECMA (2002) has provided information on catalyst manufacturing feedstocks used by different nickel catalyst producers. Nickel carbonate is a minor feedstock as a source of the nickel used in catalyst production compared to the use of nickel metal, nickel nitrate or nickel chloride. Information from ECMA about the amounts used in nickel catalyst production suggests that the figures for estimated use in this risk assessment report are reasonable.

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

2.2.1.2 Nickel hydroxycarbonate used in electroplating.

Nickel electroplating and zinc-nickel galvanisation have been described in the risk assessment reports for nickel metal, nickel sulphate and nickel chloride. These reports include details of the composition of many of the electroplating baths used. Nickel carbonate functions both as a source of nickel ions and as a neutralizing compound in the nickel electroplating solutions.

2.2.1.3 Nickel hydroxycarbonate used in the synthesis of other nickel containing chemicals.

Black nickel oxide, a finely divided, pure nickel monoxide, is produced by calcining nickel hydroxycarbonate at 600 °C (Antonsen, 1981, quoted from IARC, 1990). Nickel oxide sinter (a coarse, somewhat impure form of nickel monoxide) is manufactured by decomposing nickel hydroxycarbonate (Sibley, 1985, quoted from IARC, 1990). Nickel hydroxycarbonate is used in the manufacture of NiO by thermal decomposition (Laine, 2003d). No other information has been supplied by Industry about this method of production.

Nickel chloride can be produced from nickel carbonate. This process is used by Inco, but is not carried out in the EU. This production is also carried out by other companies in Asia (Taiwan). There are no significantly imports to the EU from this process. (Eramet, 2002).

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

Nickel sulphate has been described as produced by the reaction of nickel carbonate and dilute sulphuric acid. (Antonsen, 1981, quoted in IARC, 1990). In describing the feedstocks used in the production of nickel sulphate, NiPERA (1996) also describes the use of nickel carbonate. Nickel sulphate is not produced by this process in the EU (Meyer-Wulf, 2002).

Nickel carbonate is used in the manufacture of certain nickel pigments (Antonsen, 1996, Lascelles *et al*. 1991, Laine, 2003d). According to Eurocolour, (an umbrella organisation under CEFIC representing EU colourant manufacturers) only nickel oxide and nickel hydroxide are used in the production of dyes and pigments (Eurocolour, 2002).

Nickel carbonate is used in the preparation of coloured glass (Antonsen, 1996). Nickel carbonate is used in the preparation of many speciality nickel compounds (Antonsen, 1996, Lascelles *et al*. 1991). No further information is available on these production processes.

Nickel carbonate is used in the production of nickel powder (Antonsen, 1981, quoted in IARC, 1990). This use is not included in the later version of the description of nickel carbonate uses (Antonsen, 1996).

2.2.2 Recycling

The major uses of nickel carbonate described above result in the production of catalysts, plated products and other nickel-containing chemicals. In these processes nickel carbonate is converted into other nickel-containing compounds. Nickel catalysts and many plated products are recycled. The recycling of these products is described in Chapter 2.2.3. of the Risk Assessment report for metallic nickel. This recycling process is intended to recover nickel rather specifically nickel carbonate.

2.2.3 Discontinued Uses of the Substance

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

2.2.4 Industrial and use categories for nickel carbonate

Tables 2.2.4.A and 2.2.4.B show the amounts of nickel carbonate used in the EU and the industrial and use categories.

Table 2.2.4.A: Tonnes / year calculated as nickel hydroxycarbonate hydrate. Data for 1999 and 2000.

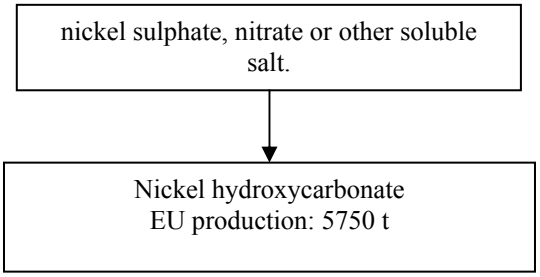
	1999		2000	
	Tonnes / year	%	Tonnes / year	%
Production (1)	7000		6500	
Import (2)	0		0	
Export (3)	1500	21%	750	12%
Used in the EU (4)	5500	79%	5750	88%

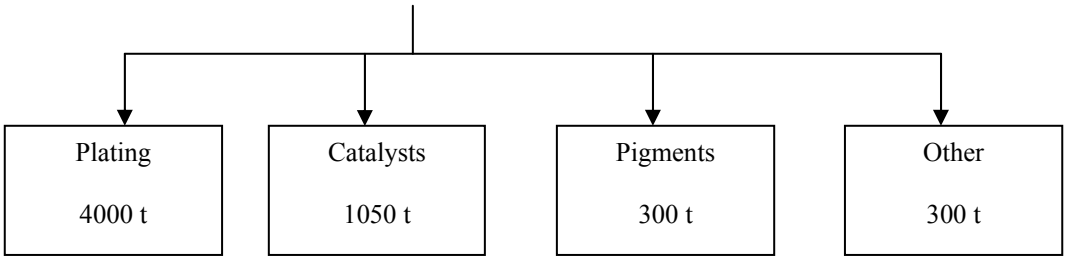
1): Realistic worst-case data from table 2.1.2.A
2). No import has been reported.
3): Realistic worst-case data from table 2.1.2.B (export).
4). Realistic worst-case data from table 2.2.1.A (use).

Table 2.2.4.B: Industrial and use categories (figures for 2000).

Scenario	Lifecycle Stage	Industry category	Use category	Main category	Tonnes / year	%
A1	Production	IC8 (Metal extraction, refining and processing)	UC55 (Others)	MC 1c	5750	
B1	Processing	IC3 (Basic chemical used in synthesis)	UC 33 (Intermediates, other salts, catalysts)	MC3	1450	25%
B3		IC8 (Metal extraction, refining and processing)	UC 17 (Electroplating agents)	MC3	4000	70%
		IC 15 (Others)	UC 55 (Others)	MC3	300	5%

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





2.3 TRENDS

No information indicating any significant trend in nickel hydroxycarbonate use is available.

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 carbonate is included in Annex I to the Directive (EEC, 1992a) with a harmonised classification (for details of the classification, see Chapter 1.4.1.2). The classification was first introduced in the 15th. Adaptation to technical progress (EEC, 1991a). The current listing, which now includes classification for dangers to the environment, is included in the 25th. Adaptation (EC, 1998b). A revised Annex I entry 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).

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, replacing Directive 88/379/EEC (EEC, 1988).

Classification of hazards of preparations containing nickel carbonate is based on the general rules set out in the Directive.

2.4.1.3 National Initiatives.

Nickel carbonate, like other nickel compounds (see *Background document in support of the individual Risk Assessment Reports*), is included in the Danish list of undesirable substances (Danish EPA, 2000).

2.4.2 Protection of workers.

The occupational use of nickel carbonate 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, 1998a).

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.

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

Country/Body	mg/m^3 as nickel [(1)]	Comments

Austria	0.5	nickel carbonate in the form of inhalable dust or inhalable droplets
Belgium	1.0	
Denmark	0.05 insoluble 0.01 soluble	There is no specific OEL for nickel carbonate Arbejdstilsynet (2000)
France		VME (Valeur Moyenne d'exposition)
Finland	0.1	nickel carbonate (IUCLID, 2002)
Germany	0.5	nickel carbonate. TRK (Technische Richtkonzentrationen) [2, 3] (TRGS 900, 2000)
Greece		
Ireland		
Italy		
Luxembourg		
The Netherlands	0.1	nickel carbonate
Portugal		
Spain		
Sweden	0.1	nickel carbonate
United Kingdom	0.1	MEL (Maximum Exposure Limit) based on 'total inhalable' aerosol as measured with the seven-hole sampler. UK HSE (2000). UK HSE would regard nickel carbonate as an insoluble nickel compound
EU (proposed)		NiPERA (1996) Proposal under discussion in SCOEL. This does not include a specific figure for nickel carbonate.
Norway		
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 in respirable form as dusts or aerosols, 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 caused by nickel and nickel compounds (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). Nickel carbonate is not specifically listed in TRGS 905.

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

Unlike metallic nickel or the other soluble salts reviewed (nickel sulphate, nickel chloride and nickel nitrate), it is not clear what the recommended OEL is for nickel carbonate in all countries.

Some countries include nickel carbonate as a specific entry. These are shown in the Table above. Other countries do not have a specific reference to "carbonate", but have values for "soluble" and "insoluble" The UK HSE considers that the carbonate should be regarded as insoluble. No specific guidance on this point is given in Denmark. No figures are given for the other EU countries in the Table above because of this uncertainty.

Nickel carbonate is currently classified as a Category 3 Carcinogen. Category 3 carcinogens are not 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). 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 this Directive when these changes come into force.

This classification does however bring the substance into the scope of 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). 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.

The possibility for young people to work with nickel carbonate and nickel carbonate-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 in Annex I to Directive 67/548/EEC includes S22 (Do not breath dust); S36/37 (wear suitable protective clothing and gloves); S60 (This material and/or its container must be disposed of as hazardous waste and S61 (Avoid release to the environment. Refer to special instructions/Safety data sheet).

2.4.3 Protection of consumers.

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

2.4.4 Emissions to water

Legislation relating 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 document in support of the individual Risk Assessment Reports*.

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 document in support of the individual Risk Assessment Reports.*

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 chapter 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 document in support of the individual Risk Assessment Reports*.

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 wastewater from the cleaning of exhaust gases. For further details, see *Background document in support of the individual Risk Assessment Reports*.

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 relating 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 chapter 2.4.4.1 above.

Annex III includes an indicative list of the main polluting substances to be taken into account if they are relevant for fixing emission values. Metals and their compounds are included as item 5 in the list for emissions to air.

In Finland, the IPPC Directive is implemented by the Environmental Protection Act (2000/86) (Finland, 2000). See Chapter 2.2.5.4 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 document in support of the individual Risk Assessment Reports.*

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 carbonate 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.

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 chapter 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, 1991b) 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 document in support of the individual Risk Assessment Reports*.

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 carbonate 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 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 hydroxycarbonate:

- at the workplace and
- indirectly via the environment.

Humans may be exposed to nickel hydroxycarbonate 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 hydroxycarbonate, either as a solid or in solution.

4.1.1.1.2 Respiratory exposure.

Respiratory exposure to nickel hydroxycarbonate occur s only in an occupational exposure context, by inhalation of aerosols containing nickel hydroxycarbonate.

4.1.1.1.3 Oral exposure.

Oral exposure to nickel from nickel hydroxycarbonate occurs either by ingestion of nickel aerosols at the workplace, or by indirect exposure to nickel hydroxycarbonate 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 hydroxycarbonate may occur by skin contact or by inhalation of aerosols containing nickel hydroxycarbonate. 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 exposure complicates 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 indicates 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 occupational exposure assessment

The production and use of nickel hydroxycarbonate 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 hydroxycarbonate production from soluble nickel salts
B1	Use of nickel hydroxycarbonate	15	55	Nickel hydroxycarbonate used in the production of catalysts
B2		8	17	Nickel hydroxycarbonate used in electroplating
B3		3	33	Nickel hydroxycarbonate used in the synthesis of other nickel containing chemicals

A: 3=Chemical industry: chemicals used in synthesis. 8=Metal extraction industry, refining and processing industry. 15=Others.
B: 17=Electroplating agents. 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, 1992; 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***	**Correction factor 1.0 m/s***
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**	NA***
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

*Ambient air velocity; **Inlet losses recovered and included in sample; ***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 were 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 and 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. 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 carbonate 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.

The division of nickel species into the four classes described about reflects the nickel species (which also include nickel carbonyl) that can be found in the production of metallic nickel, mainly in the refinery process. As shown in chapter 2, production and use of nickel carbonate is not directly related to the refinery process. Nickel carbonate is generally considered to form part of the oxidic fraction (NiPERA, 1996). There is information available concerning the behaviour of nickel carbonate in the separation processes described above. Basic nickel carbonate ($Ni_x(OH)_y(CO3)_z$) is partially leached in the soluble nickel fraction. As the leaching process is very slow, it may also continue into the second leach, causing false positives in the second, sulphidic, group. Precipitated nickel hydroxides or carbonates can also be leached in the metallic nickel fraction (Zatka *et al*. 1992). No quantitative estimates of the amounts of basic nickel carbonate leached in these fractions is given by Zatka *et al*.. Bolt *et al*., (2002) show that only 10% of nickel carbonate is leached by citric acid solution at pH 4 after 20 minutes. There is no data for the loss of nickel carbonate in the metallic fraction. On the basis of this data, nickel carbonate is considered to be mainly present in the oxidic fraction.

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 scenarios.

4.1.1.2.2.1 Scenario A1 – Nickel hydroxycarbonate production from soluble nickel salts

As already mentioned (section 2.1.1.1) nickel hydroxycarbonate is prepared from a nickel solution, usually the sulphate, by adding caustic soda as precipitation agent. The nickel hydroxycarbonate is washed and precipitated on a band filter. Following this, the nickel hydroxycarbonate is dried by a spray drier. Finally the product is packed in the form of powder, paste or granules. 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. The production of nickel hydroxycarbonate by the company OMG is a continuous, closed, hydrometallurgical (water based) process. The production of the chemical involves several processes and 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, 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.

4.1.1.2.2.1.1 Exposure by inhalation – nickel species

The production of nickel carbonate may cause an emission of aerosols. Hughson (2004) measured exposure to inhalable dust in a chemical plant. In the chemical plant nickel sulphate solution was used to produce nickel sulphate hexahydrate and nickel hydroxycarbonate. The dust was analysed for the content of soluble and insoluble nickel. The reported data are listed below. As a percentage of total nickel the dust had a content of insoluble nickel ranging from 27% to 50%. The median of the medians is considered a typical content of nickel (≈40%), while a content of 100% is considered a worst-case situation. It is noted that the data reported by

Hughson (2004) are combined exposure for the packing of nickel sulphate and nickel carbonate. Thus the data are not considered useful for an estimate of the worst-case percentage of insoluble nickel.

Process[1]	N	Exposure			Content of total Ni as % of dust	Content of insoluble Ni as % of total Ni
		Dust (mg/m^3)	Soluble Ni (μg/m^3)	Insoluble Ni (μg/m^3)		
Packing of Ni sulphate	4	0.5[2] (0.2-0.7)[3]	4 (2-11)	2 (2-4)	2 (0.7-5)	35 (27-50)
Packing of Ni carbonate	4	0.4 (0.3-5.9)	6 (1-41)	3 (1-20)	1 (0.5-4.7)	41 (29-50)

1: 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 exposure are a combination of both processes. 2: Median. 3: Range

4.1.1.2.2.1.2 Exposure by inhalation – measured exposure levels

Current data (Table 4.1.1.2.2.1.A) on occupational exposure were obtained from industry and 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. Data from industry (HEDSET Comp. #1) characterise exposure as measured for a continuous, closed and water-based process. The tabulated data are given for sub-groups of workers with similar tasks. As observed data are sparse with little information available on specific tasks characterised by the 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). It appears that the current exposure to 'total' nickel ('total' aerosol fraction) ranged from a median or mean level of 0.1 mg/m^3 to 1.6 mg/m^3. In terms of the inhalable aerosol fraction current 'total' nickel exposure ranged from a median or mean level of 0.009 mg/m^3 to 4.0 mg/m^3. It has to be emphasized that the quality of the data is not ideal: the number of samples and the range of exposure is not known for one set of data (HSE-40) and the data from HEDSET Comp. #1 are inconsistent by the upper limit of exposure being less than the stated 95th percentile. For the assessment an emphasis was put on the recent data from Comp. #1 and Hughson (2004). Thus the perhaps historic data of HSE-40 did not enter the following calculations. The median of the data collected at Comp. #1 was ~0.25 mg/m^3 of inhalable 'total' nickel while the median was 0.009 mg/m^3 for the small data set reported by Hughson (2004). The median of the large data set (0.25 mg/m^3) is considered an estimate of the typical exposure level. The 95th percentile of the data collected at Comp. #1 was ≈0.9 mg/m^3 inhalable 'total' nickel, and this level is considered 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 estimated short-term exposure is 2×0.9 mg/m^3=1.8 mg/m^3.

Table 4.1.1.2.2.1.A: Scenario A1: Nickel hydroxycarbonate production from soluble nickel salts – 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	Nickel hydroxycarbonate production including steps of filtration, drying and packaging	24	1994-1999	Personal [1] /Static [1]	'Total'	0.013-0.15	0.10	0.37 [5]	0.03-0.4	0.25	0.93 [5]
HSE-40*	Packaging of nickel hydroxycarbonate	NA	1985	Personal [2]	'Total'	NA [3]	1.6 [4]	NA	NA	4.0[4]	NA
Hughson, 2004	Packaging of nickel hydroxycarbonate	4	2004	Personal [6]	Inhalable				0.002-0.061	0.009	0.061

*: As quoted by NIPERA (1996). 1: 37-mm closed face filter cassette (presumably). 2: 25-mm closed face filter cassette. 3: Not available. 4: Arithmetic mean. 5: Note that the percentile exceeds the upper range thus indicating inconsistent data. 6: The IOM-sampler.

4.1.1.2.2.1.3 Exposure by inhalation - modelled data (EASE 2.0)

Packaging of nickel hydroxycarbonate might be considered a common task in the production of the chemical. Thus the typical and the reasonable worst-case exposures were modelled for this task. Any manipulation, such as packaging, of a dry material enter 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 hydroxycarbonate 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 hydroxycarbonate
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 hydroxycarbonate 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). Local ventilation (LEV) is very common in the packaging of powders and the pattern-of-control was specified as LEV present.
Model output:
Conclusion: The predicted dust exposure to nickel hydroxycarbonate is 2-5 mg/m^3.

The predicted exposure levels (typical and reasonable worst case) were rather similar to the measured exposure levels as tabulated in Table 4.1.1.2.2.1.A. The measured data provide more detailed information than the EASE model, and the measured data are used for the assessment. The estimated exposure by inhalation of nickel hydroxycarbonate 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 hydroxycarbonate in the production of the substance.

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 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)	
U	40	0.25	0.10	100	0.9	0.9	1.8
SO	60	0.25	0.15	≈0	0.9	≈0	≈0

1: U = Other nickel species than soluble nickel. SO = Soluble nickel.

4.1.1.2.2.1.4 Dermal exposure – measured exposure levels

Hughson (2004) did a comprehensive study on occupational dermal exposure to nickel in a refinery where nickel hydroxycarbonate and nickel sulphate are produced from leaching of nickel matte using nickel sulphate. 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 shifts, 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 $\mu g/cm^2$ (the typical exposure level), while the 90^{th} percentile is 0.7 $\mu g/cm^2$ (the reasonable worst-case exposure level). For insoluble nickel the median is 0.2 $\mu g/cm^2$ (the typical exposure level), while the 90^{th} percentile is 0.4 $\mu g/cm^2$ (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 hydroxycarbonate
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 hydroxycarbonate is 0.1-1 mg/cm^2/day.

The level of dermal exposure in the nickel hydroxycarbonate production from soluble nickel salts was estimated by two approaches, (i) by measured data 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 hydroxycarbonate 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). Thus the measured 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 hydroxycarbonate from soluble nickel salts. 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 0.25 mg/m^3; such exposure was observed for a sub-group of workers with the tasks of nickel hydroxycarbonate production. The reasonable worst-case exposure level was estimated to be 0.9 mg/m^3 as observed for a sub-group of workers with the tasks of nickel hydroxycarbonate production. Data on nickel species in workroom air were available and as a percentage of 'total' nickel the content of insoluble nickel species was estimated at a level of 40% (typical exposure) and 100% (worst case exposure). For the assessment insoluble nickel is considered being all nickel hydroxycarbonate (worst-case).

For the production of nickel hydroxycarbonate measured data were available on dermal exposure to soluble and insoluble nickel. The exposure was estimated by two approaches, (i) from measured data and (ii) by modelling. The predicted exposure level was much higher than the level estimated from 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. Thus it appears prudent to take the exposure estimated from measured data forward to the risk characterization. In conclusion the estimated levels of exposure to nickel hydroxycarbonate 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	0.15	≈0	≈0	0.8	1.4
U	0.10	0.9	1.8	0.4	0.8

1: SO = Soluble nickel salts. U = Other nickel species than soluble nickel.

4.1.1.2.3 Use of nickel hydroxycarbonate

4.1.1.2.3.1 Scenario B1 – Nickel hydroxycarbonate 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 2.2.1.2. More detailed descriptions are given in chapter 2.2.1.5.2 of the risk assessment report for nickel metal and with additional information shown in Appendix 7.7.

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, for sub-groups of workers (sub-scenarios)

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 hydroxycarbonate 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 insoluble nickel ranged from 94 % to ~99 %. The basic nickel carbonates are generally noted as insoluble in water, whereas they are reported to be very soluble in diluted acidic solutions (see section 1.3.2), and data from Zatka *et al*. (1992) and Bolt *et al*. (2002) indicate that nickel hydroxycarbonate is found mainly in the insoluble oxidic fraction. By analogy the data reported by Warner (1984) were considered useful for a rough estimate of exposure by inhalation of insoluble nickel in the catalyst production from nickel hydroxycarbonate. When used as a starting material, nickel carbonate will constitute a substantial part of the exposure at the early stages of catalyst production. Other insoluble species expected to be present are metallic nickel and/or nickel oxide. For the assessment, insoluble nickel was considered being all nickel hydroxycarbonate (worst-case). For the assessment the median (96.5 %) of the data (Table 4.1.1.2.3.1.A) was considered typical while the upper limit of the range (~99 %) was considered a reasonable worst-case. It has to be emphasized that the validity of the analogy of catalyst production from nickel hydroxycarbonate 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).

Type of sampler	**N**	**Exposure level (µg/m^3)**				**Nickel speciation (%)**	
		Soluble nickel		**Other nickel species than soluble nickel**		**Soluble nickel [1,3]**	**Insoluble nickel [2]**
		Range	**Average (SO)**	**Range**	**Average (U)**		
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 insoluble nickel is considered being all nickel hydroxycarbonate (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	1986-1987	Personal[1]	<10-1560	20
Workers not exposed to soluble nickel	49	1986-1987	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 hydroxycarbonate were obtained from industry and tabulated by sub-groups of workers with similar tasks (Table 4.1.1.2.3.1.C). 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. 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 hydroxycarbonate 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. 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 characterized by the data. For such data sets the sub-groups of workers with similar tasks were characterized by a rather general description of the conditions in the production. Other sets of data had more detailed information on sub-groups of workers with similar tasks, but the strategy in collecting the data included an approach of static sampling. Consequently the data may not be valid as estimates of personal exposure. Including all sets of data collected by personal or personal/static sampling it appears that current exposure to 'total' nickel ('total' aerosol fraction) ranged from a median or mean level of less than 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. The samples for this specific sub-group 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 ranged from a median or mean level of less than 0.005 mg/m^3 to 0.98 mg/m^3. Not taking static sampling data into account the median of the median or mean levels was estimated to be 0.09 mg/m^3 (the typical exposure level). Such exposure was observed for a sub-group of workers with the rather non-specific 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. It is noted 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=4; 195 observations) was 4.4 mg/m^3. Such upper limit of exposure was reported for large data set (127 observations) for a sub-group of workers with the task of catalyst production. The median exposure for this sub-group was rather 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). Thus it seems prudent to consider the indicated level of 4.4 mg/m^3 as an estimate of the reasonable worst-case exposure. The estimated reasonable worst-case exposure level was the upper limit of exposure reported for a sub-group of workers with the tasks of catalyst production. 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 $2 \times 4.4 = 8.8$ 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 from nickel hydroxycarbonate – 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. #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
	Catalyst production, tabletting, packaging and cleaning	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 prod., extrusion and packing	NA	NA	Personal [2+]	'Total'	NA	<0.004	NA	NA	<0.005	NA
	Catalyst prod., extrusion and packing	NA	NA	Static [2+]	'Total'	NA	<0.007	NA	NA	<0.008	NA
HEDSET Comp. #4	Catalyst prod., preparation of solution	8	2000	Personal [3+]	'Total'	0.017-0.13	0.054	0.13	0.04-0.33	0.14	0.33
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 [7,9]	NA	-	-	-
	Misc duties	1	1990-1993	Personal /Static [4]	'Total'	-	0.68 [5]	-	-	-	-
	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	'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	-	-	-
HSE-16, 1985*	Production of NiO catalysts	NA	1985	Personal [3]	'Total'	NA	<0.10-.39 [5,8]	NA	NA	<0.25-0.98 [5,8]	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: range of mean exposure concentrations. 9: Note that the average is high by contrast to the upper limit of the range.

4.1.1.2.3.1.3 Exposure by inhalation – modelled data (EASE 2.0)

As observed from Table 4.1.1.2.3.1.C granulating may cause a high level of airborne dust, as measured by static sampling. 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 typical exposure levels are rather similar to the measured exposure levels 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 from nickel hydroxycarbonate.

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 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)	
U	96.5	0.09	0.09≈0.09	99	4.4	4.4	8.8
SO	3.5	0.09	0.003	1	4.4	0.04	0.1

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

4.1.1.2.3.1.4 Dermal exposure – measured and modelled exposure levels

No measured data seem available for the scenario. Hughson (2004) did a comprehensive study on occupational dermal exposure to nickel in a refinery where nickel hydroxycarbonate and nickel sulphate is produced from leaching of nickel matte using nickel sulphate. The dermal exposure was measured during packing of the final products. Since nickel hydroxycarbonate is used as feedstock for catalyst production, nickel hydroxycarbonate

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 solid data were available for the assessment of exposure by inhalation of 'total' nickel in the catalyst production from nickel hydroxycarbonate. 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 by inhalation of dust. However the information was scarce on tasks characterized by the measured data and a very detailed classification of sub-groups was not possible. The estimated reasonable worst-case exposure level (4.4 mg/m^3) to 'total' nickel was observed for a sub-group of workers with the tasks of catalyst production, while the typical exposure level (0.09 mg/m^3) was observed for sub-groups of workers with the tasks of catalyst production. No data on nickel species in workroom air were available. By analogy data on airborne insoluble nickel species (as a percentage of 'total' nickel) in the catalyst production from nickel sulphate were considered valid for airborne insoluble nickel species in the catalyst production from nickel hydroxycarbonate. As a worst-case insoluble nickel species were considered being all nickel hydroxycarbonate. It is recognized that the validity of such analogy remains unknown.

For the catalyst production from nickel hydroxycarbonate no data were available on dermal exposure and the exposure was estimated by two approaches, (i) by analogy to dermal exposure measured in the production (packing) of nickel hydroxycarbonate and nickel sulphate and (ii) by modelling. The dermal exposures estimated by analogy to nickel hydroxycarbonate packing operators were much less than predicted values generated by the EASE model. 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. Nickel hydroxycarbonate is used as feedstock for catalyst production. Exposure in nickel hydroxycarbonate packing is most likely a conservative estimate of the exposure to the chemical in catalyst production as the chemical is used as feedstock. Thus the estimated exposure by analogy to nickel hydroxycarbonate packing operators are taken forward to the risk characterization. In conclusion the estimated levels of exposure to nickel hydroxycarbonate 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**
U	0.09	4.4	8.8	0.4	0.8
SO	0.003	0.04	0.1	0.8	1.4

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

4.1.1.2.3.2 Scenario B2 – Nickel hydroxycarbonate used in electroplating

In a typical nickel electroplating shop, nickel exposures of the workers arise from the aerosolization of electrolyte during the plating process and soluble nickel is considered the predominant group of nickel species in workplace aerosols. Details of the processes involved in nickel plating are given in section 2.2.1.2 and in the risk assessment reports for nickel metal and nickel sulphate. The nickel-containing materials in this scenario take the form of nickel salts for plating solutions in electrolytic or electroless plating, and in electroforming. For electrolytic plating and electroforming nickel metal products, generally massive in form, are used for anodes.

Different methods of nickel plating are common including manual plating, semi-automatic and automatic plating. Manual plating is a series of tanks that contain the appropriate plating and cleaning solutions. Parts are placed on racks or hangers and manually transferred from tank to tank. This type of plating process is labour intensive and, as platers spend a larger proportion of their working time at the tanks, there is a relatively higher risk of exposure. However, the use of this method is declining because of the high costs associated with labour intensive processes. In semi-automatic plating, parts are manually loaded on to jigs and then the operator moves the jigs between the baths using an overhead hoist in a predetermined sequence. The operator usually stands on a platform by the side of the plating line. This method usually results in lower exposure than manual plating as the operators can distance themselves from the plating solutions for large amounts of time. The main difference between automatic and semi-automatic plating is that the movement of the jigs is controlled electronically in automatic plating and therefore the operator spends very little time near the plating solutions, except when there is a problem with the process. Within the overall scenario workers may not have similar tasks. As an effort to identify tasks with high risk of exposure the available data on measured 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.

4.1.1.2.3.2.1 Exposure by inhalation – nickel species

Soluble nickel predominates in electroplating shops, but there is some evidence to suggest that lesser amounts of relatively less soluble nickel compounds may be present under some circumstances. Tsai *et al*. (1996a) have reported data on exposure to inhalable aerosols for two electroplating shops (A and B) in North America. Some of the samples were analysed for content of four groups of nickel species and the reported data are summarized below (Table 4.1.1.2.3.2.A). Kiilunen *et al*. (1997b) reported that soluble nickel predominated the occupational exposure in Finnish electroplating shops (Table 4.1.1.2.3.2.B). For a specific electroplating shop in Finland Tola *et al*. (1979) reported that most of the airborne nickel was in the form of soluble nickel sulphate, but the observation was not supported by detailed data.

Table 4.1.1.2.3.2.A: Nickel speciation data for inhalable aerosols collected from two electroplating shops (A and B) in North America (Tsai et al., 1996a).

Shop	N	Exposure level (µg/m^3)				Nickel speciation (%)				
		Soluble (SO)	Sulfidic (SU)	Oxidic (O)	Metallic (M)	Soluble[1]	Sulfidic[2]	Oxidic[3]	Metallic[4]	Insoluble[5]
A	12	68.9	0.98	4.6	1.8	90	1.3	6.0	2.4	10
B	11	8.7	1.4	2.0	1.6	64	10	15	12	36

1: Estimated as SO/(SO+SU+O+M). 2: Estimated as SU/(SO+SU+O+M); 3: Estimated as O/(SO+SU+O+M); 4: Estimated as M/(SO+SU+O+M); 5: Estimated as (SU+O+M)/(SO+SU+O+M)

Table 4.1.1.2.3.2.B: Nickel speciation data for aerosols collected in Finnish electroplating shops (Kiilunen et al., 1997b)

Job	N	Type of sampler	Aerosol fraction	Concentration of 'total' Ni (µg/m^3)	Soluble Ni (%)
Plating tank workers	NA [1]	Personal [2]	'Total'	0.5	30 - ~100
Plating tank area	1	Static [3]	'Total'	0.05	60
Plating tank area	1	Static [3]	'Total'	0.2	25
'Near' a Ni-bath	1	Static [3]	'Total'	26	~ 100
Maintenance	1	Personal [2]	'Total'	0.7	80
Electroplaters	6	Personal [2]	'Total'	5.6-78.3	18 – 90
'Near' nickel baths	NA	Static [3]	'Total'	73.3	~ 90
Plating tank area	NA	Static [3]	'Total'	12-18	~ 90

1: Not available. 2: 37-mm filter cassette (presumably closed face). 3: 37-mm filter cassette (presumably closed face) operated at 20 l/min.

For the assessment a typical aerosol composition in terms of nickel species was estimated as given in Table 4.1.1.2.3.2.C. The data from Zatka et al. (1992) and Bolt et al. (2002) shows that basic nickel carbonate occurs primarily in the oxidic fraction. As it is unlikely that other potential components of the oxidic fraction (e.g. nickel oxides, silicates) would be present, exposure to oxidic nickel was considered as exposure to nickel hydroxycarbonate (worst-case). The median of the aerosol composition of shop A and B was considered the typical composition and the aerosol composition of shop B was considered a reasonable worst-case.

Table 4.1.1.2.3.2.C: Estimation of typical and reasonable worst-case nickel speciation of aerosols collected in electroplating. The data are given as a percentage of 'total' airborne nickel.

Ref.	Comment	Soluble	Insoluble	Metal	Oxidic	Sulfidic
Tsai *et al.*, 1996a	Shop A	90	~10*	2.4	6.0	1.3
	Shop B	64	~36*	12	15	10
	'Typical' nickel speciation (the median of shop A and B)	~77**	~23**	(2.4+12)/2~7	(6.0+15)/2~10	(1.3+10)/2~6
	Reasonable worst-case speciation***	64	36	12	15	10

* Estimated as 'Metal'+'Oxidic'+'Sulfidic'. **Estimated as the median of the tabulated data for shop A and B. ***In terms of exposure to oxidic nickel the speciation data for shop B were considered a reasonable worst-case for plating tank workers.

4.1.1.2.3.2.2 Exposure by inhalation – measured exposure levels

The risk assessment report for nickel sulphate has a scenario for electroplating. The scenario includes comprehensive data on exposure by inhalation of aerosols and all the data were considered useful for the present scenario. The data are tabulated in Table 4.1.1.2.3.2.D-E. 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. Some data sets are characterized in terms of detailed sub-groups of workers with similar tasks, while other sets have less information on the tasks characterized by the data. The majority of the data sets were collected by an approach of personal or personal/static sampling, but the tabulated data also include data from static sampling. Exposure measured in terms of the 'total' aerosol fraction was converted to the inhalable fraction by factors of 3.0 (37-mm/25-mm open or closed face cassettes) and 1.17 (25-mm seven hole sampler).

For the scenario it appears that current exposure to 'total' nickel ('total' aerosol fraction) ranged from a median or mean level of 0.4 μg/m^3 (perhaps even less) to 120 μg/m^3 as measured by an approach of personal or personal/static sampling. The high median of 120 μg/m^3 was reported for a sub-group of workers with the task of electroless plating. The sampling strategy for this group included an approach of personal/static sampling. It has to be emphasized that data from static sampling may not be valid for estimates of personal exposure. In terms of the inhalable aerosol fraction current exposure ranged from a median or mean level of 1.2 μg/m^3 to 350 μg/m^3. Including data sets obtained by an approach of personal or personal/static sampling the median of the median or mean levels was 25 μg/m^3 (typical exposure level). Such an exposure level was observed for a sub-group of jiggers.

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=18; more than 348 observations) was ≈480 μg/m^3 . Three data sets had an upper limit at or above this concentration. An upper limit of exposure at 480 μg/m^3 was observed for a sub-group of plating tank workers. The data set for this group of workers was rather large (20 observations). The median of the data set was 240 μg/m^3 and the 95th percentile was 420 μg/m^3. Another large data set (102 observations) for a group of electroplaters reported an upper limit of exposure at a level of 2400 μg/m^3 as measured by personal sampling. The median of the data set was at or below 240 μg/m^3. An even higher upper limit (5400 μg/m^3) was reported for a group of electroplaters, but the data set did not specify the number of observations and the data were obtained by personal/static sampling. The median o the data set was not given. Taking the quality of the three data sets into consideration, it appears prudent to estimate the worst-case exposure at a level of 2400 μg/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 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 2×2400=4800 μg/m^3.

For the scenario no data were available on the size distribution of aerosols in the workroom air. Perhaps electroplating and electrowinning operations may be similar in terms of the size distribution of the aerosols in workroom air. If so the aerosols in electroplating are rather coarse as most particles have a diameter (by count) above >5 μm (Kiilunen *et al*., 1997a). The extrathoracic aerosol fraction was reported (Thomassen *et al*., 1999) to be responsible for the nickel exposure experienced by the electrowinning workers at the Monchegorsk refinery in Russia. In contrast Werner *et al*. (1999) reported that approx. 40% of the inhalable nickel exposure in electrowinning was fine aerosols (thoracic and respirable fraction).

Table 4.1.1.2.3.2.D: Electroplating - current exposure by inhalation of 'total' nickel.

Ref.	Process	N	Year	Type of Sampler	Aerosol Fraction	Exposure to 'total' nickel µg/m^3					
						'Total' aerosol fraction			Inhalable aerosol fraction		
						Range	Median	95th perc.	Range	Median	95th perc.
Tola *et al*., 1979	Plating tank workers	20	NA	Personal [1]	'Total'	30-160	80 [7,8]	140 [8]	90-480	240 [7,8]	420 [8]
Bernacki *et al*., 1978	Electroplaters; intermittent exposure	11	~1978	Personal [1]	'Total'	0.04-2	0.8 [9]	NA	0.12-6	2.4 [9]	NA
Bernacki *et al*., 1980	Electroplaters	15	~1979	Personal [1]	'Total'	0.5-21	9.3 [9]	19	1.5-63	28 [9]	57
Ghezzi *et al*., 1989	Plating tank workers	23	~1988	Personal [2]	'Total'	NA	4.2-19 [7,10]	NA	NA	13-57 [7,10]	NA
UM Data*[A]	Electroless plating	29	1993-1994	Personal [3]	Inhalable	-	-	-	1-37	10	NA
UM, 1995	Electroless plating	26	1993-1994	Personal [3]	Inhalable	-	-	-	8-180	59	NA
Stamm *et al*., 1998	Electroplaters	340	1989-1992	NA [4]	'Total'	NA	2.0	10[12]	-	-	-
Oliveira *et al*., 2000	Electroplaters	NA	~1998	Personal [1]	'Total'	NA	2.8-117 [7,10]	NA	NA	8-350 [7,10]	NA
Kiilunen *et al*.	Plating tank workers	NA	~1995	Personal [2]	'Total'	NA	0.5 [11]	NA	NA	1.5 [11]	NA
1997b	Plating tank area	2	~1995	Static [5]	'Total'	0.05-0.2	0.1 [11]	-	-	-	-
	'Near' a Ni-bath	1	~1995	Static [5]	'Total'	-	26	-	-	-	-
	Maintenance	1	~1995	Personal [2]	'Total'	-	0.7	-	-	2.1	-
	Plating tank workers	6	~1995	Personal [2]	'Total'	5.6-78	NA	NA	17-230	NA	NA
	'Near' the Ni-baths	NA	~1995	Static [5]	'Total'	NA	73 [11]	NA	-	-	-
	Plating tank area	NA	~1995	Static [5]	'Total'	12-18	NA	NA	-	-	-
Bavazzano *et al*., 1994	Electroplaters	41	~1993	Personal [1]	'Total'	0.1-42	2.3 [7]	19.8	0.3-130	6.9 [7]	59
Bright *et al*., 1997	Bath operators	34	~1994	Personal [6]	'Total'	5-93	26.5 [9]	NA	5.9-110	31 [9]	NA
	Jiggers	22	~1994	Personal [6]	'Total'	0.5-83	21.2 [9]	NA	0.6-97	25 [9]	NA
	Managers	4	~1994	Personal [6]	'Total'	0.5-6	2.6 [9]	NA	0.6-7.0	3.0 [9]	NA

*: Data tabulated by NIPERA (1996). A: Including the data reported by Tsai *et al*. (1996a).

1: 37-mm closed face filter cassette. 2: 37-mm filer cassette (presumably closed face) operated at a flow rate of 3 l/min. 3: IOM-sampler. 4: unknown type of sampler. 5: 37-mm filter cassette (presumably closed face) operated at 20 l/min 6: 25-mm filter seven-hole cassette. 7: geometric mean; 8: data estimated from graphs given by Tola *et al*. (1979). 9: arithmetic mean; 10: range. 11: presumably the arithmetic mean. 12: 90^{th} percentile.

Table 4.1.1.2.3.2.E: Electroplating - current exposure by inhalation of 'total' nickel.

Ref.	Process	N	Year	Type of Sampler	Aerosol Fraction	Exposure to 'total' nickel μg/m^3					
						'Total' aerosol fraction			Inhalable aerosol fraction		
						Range	Median	95th perc.	Range	Median	95th perc.
Hery *et al*., 1990	Electroplating	102	Pre-1990	Personal [1]	'Total'	0.1-800	0.4-79 [5,7]	NA	0.3-2400	1.2-240 [5,7]	NA
Mahieu *et al*., 1990	Electroplating	NA	1990	Personal/Static [2]	'Total'	1-1800	NA	NA	3-5400	-	-
EIS Data*	Electroless plating	4	1991-1993	Personal/Static [3]	'Total'	10-50	<23 [6]	NA	-	-	-
EIS-05, 1993	Electrolytic plating	4	1991-1993	Personal/Static [3]	'Total'	20-190	100	NA	-	-	-
HSE Data* HSE-02	Electroplating	6	1985	Personal/Static [4]	'Total'	NA	Trace	NA	-	-	-
HSE Data* HSE-03	Electroplating	10	1985	Personal/Static [4]	'Total'	NA	10 [6]	NA	-	-	-
HSE Data* HSE-15	Electroless plating	15$^+$	1985	Personal/Static [4]	'Total'	51-360	120 [6]	NA	-	-	-
	Ancillary operations	3$^+$	1985	Personal/Static [4]	'Total'	4-15	10 [6]	NA	-	-	-
HSE Data* HSE-17	Electro-arming	NA	1985	Personal/Static [4]	'Total'	NA	<100 [6]	NA	-	-	-
HSE Data* HSE-28	Electroplating	78$^+$	1985	Personal/Static [4]	'Total'	1-100	10 [6]	NA	-	-	-
HSE Data* HSE-52	Electroforming	10$^+$	1985	Personal/Static [4]	'Total'	1-70	20 [6,8]	NA	-	60 [6,8]	-
HSE Data* HSE-53	Electroforming	2	1985	Personal/Static [4]	'Total'	13-19	16 [6]	NA	-	-	-
Bicknell *et al*. 1989	NA	9	1987-1988	Personal [1]	'Total'	3-51	18 [6]	NA	9-150	54 [6]	NA
Daniels & Gunter 1987	NA	7	1986	Personal/Static [1]	'Total'	<1-4.5	2.5 [5]	NA	<3-13	7.5 [5]	NA
Daniels *et al*., 1988	NA	10	1987	Personal/Static [1]	'Total'	<1-39	6 [6]	NA	<3-120	18 [6]	NA
Mortimer, 1982	NA	4	1982	Personal [1]	'Total'	3-6	4 [6]	NA	9-18	12 [6]	NA
HSE Data**[A]	Electroplating	50	1989-1999	Personal/static [3]	'Total'	1-80	8.6 [5]	50	-	-	-
HEDSET, Data from 40 different German shops [A]	Electroplaters	60	NA	Personal [3]	'Total'	-38	2.5 [5]	13	-	-	-
HEDSET, Comp #1 [A]	Electroplaters	6	1991-1996	Personal [1]	'Total'	9-30	22 [5]	NA	27-90	66 [5]	NA

HEDSET, Comp #2 [A]	Electroplaters	2	1976	Personal [1]	'Total'	3-45	24 [5]	-	9-140	72 [5]	-

*: Data tabulated by NIPERA (1996). **UK HSE's NEDB (National Exposure Database). A: Data tabulated in the Risk Assessment Report on nickel metal. +: The number of observations was estimated from the arithmetic mean and the range using the approach given by Vincent and Werner (2003).
1: 37-mm closed face filter cassette. 2: 37-mm filer cassette (open and closed face). 3: unknown type of sampler. 4: 25-mm closed face filter cassette (personal sampling) and unknown type of static sampler. 5: geometric mean. 6: arithmetic mean; 7: range. 8: mean based upon personal sampling.

4.1.1.2.3.2.3 Exposure by inhalation – modelled data (EASE 2.0)

If the electrolyte is agitated vigorously by air bubbles nickel hydroxycarbonate in the form of mist is generated from bursting bubbles. At present stage EASE does not allow modelling of exposure to mist generated from bursting bubbles. The task of plating tank workers may include many specific operations such as the preparation of solutions. The preparation may involve short-term exposure during manipulation of dry nickel hydroxycarbonate and such an operation was considered useful for modelling. 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 hydroxycarbonate 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 hydroxycarbonate
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 hydroxycarbonate 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 hydroxycarbonate is 5-50 mg/m^3.

The predicted exposure level was high by contrast to the measured data as tabulated in Table 4.1.1.2.3.2.D-E. 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 4.1.1.2.3.2.C) current exposure to groups of nickel species is estimated as tabulated below (Table 4.1.1.2.3.2.F).

Table 4.1.1.2.3.2.F: Estimated exposure by inhalation of groups of nickel species in electroplating.

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 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)	
O	10	0.025	0.0025	15	2.4	0.36	0.72
M	7	0.025	0.0018	12	2.4	0.29	0.58
S	6	0.025	0.0015	10	2.4	0.24	0.48
SO	77	0.025	0.019	63	2.4	1.5	3.0

1: O = Oxidic nickel considered being all nickel hydroxycarbonate (worst-case); M = nickel metal; S = Sulfidic nickel; SO = Soluble nickel salts.

4.1.1.2.3.2.4 Dermal exposure – measured exposure levels

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%. The data provided by Bavazzano *et al*. (1994) are tabulated in Table 4.1.1.2.3.2.G.

Table 4.1.1.2.3.2.G: 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

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

4.1.1.2.3.2.5 Dermal exposure - modelled data (EASE 2.0)

The drag-out of articles from the baths is a common task in electroplating. 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 hydroxycarbonate
The temperature of the process is 20
The physical-state is solid
Dust-inhalation is false
Mobile-solid is true
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 hydroxycarbonate 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 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 hydroxycarbonate 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.

The predicted exposure level is high by contrast to the measured data as tabulated in Table 4.1.1.2.3.2.G. 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. 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. On condition the contaminants deposited on the skin has a content of nickel species similar to the airborne dust (Table 4.1.1.2.3.2.C) the typical (50th percentile) and worst-case (95th percentile) dermal exposure of the hands to nickel salts is estimated as given below. These levels can be used in risk characterization comparison with acute toxicity data.

Nickel species (1)	**Typical exposure**			**Reasonable 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)**
O	10	39	4	15	370	56
M	7	39	2.7	12	370	44
S	6	39	2.3	10	370	37
SO	77	39	30	63	370	230

1: O = Oxidic nickel considered being all nickel hydroxycarbonate (worst-case); M = nickel metal; S = Sulfidic nickel; SO = Soluble nickel salts.

4.1.1.2.3.2.6 Discussion and conclusions

Rather solid data in terms of the 'total' aerosol fraction were available for the assessment of exposure by inhalation of 'total' nickel in electroplating operations. 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. An emphasis was made to assess exposure in terms of inhalable aerosols. However, a few data sets did not specify sufficient details on sampling methods to allow 'total' aerosols to be converted to inhalable aerosols. The reasonable worst-case exposure level (0.48 mg/m^3 'total' nickel) was observed for a sub-group of plating tank workers, while the typical exposure level (0.025 mg/m^3 'total' nickel) was observed for a sub-group of workers with the task of jiggers. The data available on groups of nickel species in workroom indicated that nickel species are not uniform among electroplating shops. Nevertheless an estimate was made for a typical and a worst-case nickel speciation, but the validity of the estimated data remains unknown. The estimated exposure to oxidic nickel was as a worst-case considered exposure to nickel hydroxycarbonate.

Some measured data specific for dermal exposure in electroplating operations were available. Compared to the modelled (EASE) exposure the measured data were low by several orders of magnitude. It is recognized that the measured data are biased at unknown extent towards low exposure levels. The EASE model is only intended to give generalized exposure data while the measured data were specific for electroplating. Thus the measured data are taken forward to the risk characterization. As a first approximation nickel speciation of contaminants deposited on the skin was assumed to be similar to speciation of the aerosols in workroom air, but it has to be

emphasized that no data were available for validation of such an approach. Personal protective equipment is a common approach to reduce dermal exposure in electroplating operations. However, contamination of the protective gear is almost impossible to avoid (Wall & Calnan, 1980). Thus an additional risk of exposure caused by contaminated personal protective equipment cannot be excluded. In conclusion the estimated levels of exposure to groups of nickel species are summarized below.

Nickel species (1)	Exposure by inhalation (µg/m³)			Dermal exposure (µg/day)	
	Typical	Reasonable worst-case	Short term	Typical	Reasonable worst-case
O	2.5	360	720	4.0	56
M	1.8	290	580	2.7	49
S	1.5	240	480	2.3	37
SO	19	1500	3000	30	230

1: O = Oxidic nickel considered being all nickel hydroxycarbonate (worst-case); M = nickel metal; S = Sulfidic nickel; SO = Soluble nickel salts.

4.1.1.2.3.3 Scenario B3 – Nickel hydroxycarbonate used in the synthesis of other nickel containing chemicals.

4.1.1.2.3.3.1 Exposure by inhalation – nickel species

Nickel carbonate 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 carbonate from nickel matte. The production of nickel carbonate involves exposure to insoluble nickel during the production process. The use of nickel carbonate as an intermediate in the production of chemicals involves exposure to insoluble 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 insoluble nickel ranging from 35% to 41%. The median of the data (≈40%) is considered a typical content while a content of 100% is considered a worst-case situation. It is noted that the data are combined exposure to nickel sulphate and nickel carbonate. Thus the data are not useful for an estimate of the content of insoluble nickel in a worst-case exposure situation. For the exposure assessment insoluble nickel is considered being all nickel carbonate (worst-case).

Process[1]	N	Exposure			Content of total Ni as % of dust	Content of insoluble 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)	35 (27-50)
Packing of Ni carbonate	4	0.4 (0.3-5.9)	6 (1-41)	3 (1-20)	1 (0.5-4.7)	41 (29-50)

1: 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. 2: Median. 3: Range

4.1.1.2.3.3.2 Exposure by inhalation – measured exposure levels

No data on personal exposure by inhalation are available for the assessment. 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 4.1.1.2.3.3.A) are considered useful for the present scenario.

Table 4.1.1.2.3.3.A. Scenario B3: 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, 2004	Packing Ni Carbonate	4	2003-2004	Personal	Inhalable	1-41	SO[1]	6	SO	41	SO
						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. 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/m³ to 450 µg/m³, while the worst-case exposure was estimated to be 7000 µg/m³. The data reported by Hughson (2004) indicates an exposure 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.

4.1.1.2.3.3.3 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 carbonate
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 carbonate is 0-1 mg/m³

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 carbonate is 5-50 mg/m³.

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 4.1.1.2.3.3.B).

Table 4.1.1.2.3.3.B: Estimated exposure by inhalation of nickel in the production of chemicals.

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 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)**	
SO	60	0.006-0.45	0.004-0.27	0	7.0	0	0
U	40	0.006-0.45	0.002-0.18	100	7.0	7.0	14

1: SO = Soluble nickel. U = Other nickel species than soluble nickel.

4.1.1.2.3.3.4 Dermal exposure – measured and modelled exposure levels

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. Since nickel carbonate is used as feedstock for the production of chemicals, nickel carbonate packing data is considered useful for an exposure assessment in the production of chemicals. 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).

4.1.1.2.3.3.5 Discussion and conclusion

Industry has supplied little information about this method of production. The RAR on nickel metal has a scenario for nickel metal in the production of other nickel-containing chemicals. By analogy the data for that scenario was considered useful as a rough estimate of exposure to nickel chloride in the production of chemicals. The estimated exposure is tabulated below. For the assessment insoluble nickel was considered being all nickel carbonate (worst-case). It has to be emphasized that the validity of the estimated exposure remains unknown.

Dermal exposure to nickel carbonate was estimated by two approaches, (i) by measured dermal exposure in the packing of nickel sulphate and nickel carbonate and (ii) by modelling. The predicted exposure level was much higher than the levels estimated from 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 chemicals the highest exposure to nickel carbonate is expected to be during packing of the chemicals. Thus it appears prudent to take the measured exposure 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**
U	0.002-0.18	7.0	14	0.4	0.8
SO	0.004-0.27	≈0	≈0	0.8	1.4

1): U = Other nickel species than soluble nickel salts; SO = Soluble nickel salts.

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 some scenarios 'total' airborne nickel was considered being all nickel hydroxycarbonate (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 sub-groups of workers at high risk of exposure.

Measured data for dermal exposure to nickel were available for scenario A1 (the production of nickel hydroxycarbonate) and scenario B2 (nickel hydroxycarbonate used in electroplating). For other scenarios (B1 and B3) no measured data were available. Based on expected similarities in the tasks performed by the workers data from scenario A1 was extrapolated to scenario B1 and B3. Scenario A1 is for the production of nickel hydroxycarbonate while scenario B1 or B3 is for the use of the chemical as feedstock for the production of catalysts or nickel containing chemicals. The handling of nickel carbonate is expected to be more intensive in the production than in the use of the chemical. Thus the estimated exposure is considered biased towards high levels for scenario B1 and B3.

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 (hr/day)	Frequency (day/year)	Full shift (8 hour time weighted average)				Short-term			Typical level		Reasonable worst-case level	
				Typical level	Method	Reasonable worst-case level	Method	Level		Method				
A1	Nickel hydroxycarbonate production from soluble nickel salts	6-8	200	0.10 U[1] 0.15 SO	Meas.[2]	0.9 U ≈0 SO	Meas.	1.8 U ≈0		Exp.[3]	0.4[4] U 0.8[4] SO		0.8[4] U 1.4[4] SO	
B1	Nickel hydroxycarbonate used in the production of catalysts	6-8	200	0.09 U 0.003 SO	Meas.	4.4 U 0.04 SO	Meas.	8.8 U 0.1 SO		Exp.	0.4[4] U 0.8[4] SO		0.8[4] U 1.4[4] SO	
B2	Nickel hydroxycarbonate used in electroplating	6-8	200	0.0025 O 0.0018 M 0.0015 S 0.019 SO	Meas.	0.36 O 0.29 M 0.24 S 1.5 SO	Meas.	0.72 O 0.58 M 0.48 S 3.0 SO		Exp.	0.004 O 0.003 M 0.002 S 0.03 SO		0.06 O 0.05 M 0.04 S 0.23 SO	
B3	Nickel hydroxycarbonate used in the synthesis of other nickel containing chemicals	6-8	200	0.002-0.18 U 0.004-0.27 SO	Ana.[5]	7.0 U ≈0 SO	Ana.[5]	14 U ≈0 SO		Ana.[5]	0.4[4] U 0.8[4] SO		0.8[4] U 1.4[4] SO	

1: U= Other nickel species than soluble nickel - considered to be all nickel hydroxycarbonate (worst-case); SO = Soluble nickel salts. O = oxidic nickel (considered to be all nickel hydroxycarbonate - worst-case). M = metallic 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 packing nickel hydroxycarbonate and nickel sulphate
5: 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 carbonate.

4.1.1.4 Exposure of man via the environment

4.1.1.5 *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".

4.1.2 Human health effects assessment

This section deals with the health effect assessment of nickel hydroxycarbonate. As it is not always clear which substance has actually been studied, studies performed with either nickel carbonate or nickel hydroxycarbonate are described here. Other nickel compounds now under review under EU Regulation 793/93 are nickel metal, nickel sulphate, nickel chloride, and nickel nitrate. The results of studies carried out on other nickel compounds may have relevance for the effect assessment of nickel carbonate. 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 carbonate.

Very little information on the health effects of specifically nickel hydroxycarbonate has been provided by Industry. A lot of data on nickel and nickel compounds has 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, metabolisn and distribution

4.1.2.1.1 Absorption

No data regarding absorption and retention of nickel in experimental animals or in humans following inhalation, oral administration, or dermal contact to nickel carbonate have been located.

4.1.2.1.2 Distribution and elimination

4.1.2.1.2.1 Animal studies

4.1.2.1.2.1.1 Inhalation

Following intratracheal instillation of nickel carbonate in mice (0.05 mg/animal), most of the nickel was eliminated after 12 days (Furst & Al-Mahrouq 1981 - quoted from IPCS 1991).

4.1.2.1.2.1.2 Oral

Metabolic data from nickel-balance studies carried out by Phatak & Padwardhan (1950 - quoted from IPCS 1991) who fed rats nickel carbonate (250, 500, or 1000 mg/kg in the diet for 2 months) demonstrated that appreciable quantities of nickel from the nickel-containing diets were retained and tissue accumulation was significant (bones > heart > kidney > blood > spleen > intestine > testes > skin > liver at 1000 mg/kg diet). According to the authors, this was attributed to ready solubility of the compound in the stomach and the easier absorption from the intestine.

O’Dell et al. (1971 – quoted from IPCS 1991) fed calves a basal diet supplemented with nickel (as the carbonate) at levels of 62.5, 250, or 1000 mg/kg for 8 weeks and found pronounced increases in nickel levels in the tissues at the highest dietary level (serum > kidney > vitreous humour > lung > testis > bile > tongue > pancreas > rib > spleen > brain > liver > heart). According to the citation in IPCS (1991), the results of this study showed that the absorption and tissue retention of dietary nickel can be increased and that the increase is related to the rate of nickel intake as well as to the total nickel intake.

4.1.2.1.2.2 Human studies

No data regarding distribution and elimination of nickel in humans following exposure to nickel carbonate have been located.

4.1.2.1.3 Transplacental transfer

The newborn offspring of rats fed nickel carbonate in the diet showed whole-body levels of 12-17 or 22-30 mg/kg bw/day, when dams received 500 or 1000 mg nickel/kg diet, respectively (Phatak & Padwardhan 1950 - quoted from IPCS 1991).

Transplacental transfer has also 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*.

4.1.2.1.4 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*.

4.1.2.1.5 Discussion and conclusions

4.1.2.1.5.1 Absorption

4.1.2.1.5.1.1 Inhalation

No data regarding the absorbed fraction of nickel in humans or experimental animals following inhalation of nickel carbonate 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 are absorbed from the respiratory tract, while slightly soluble nickel compounds are expected only to be absorbed from the respiratory tract following inhalation exposure to a very limited extent. For the slightly soluble compounds the particles are expected to be retained in the airways and/or to be removed by the mucociliary action and translocated into the gastrointestinal tract, depending on the particle size.

The Industry derogation statement (Laine, 2003d) indicates that in the absence of relevant data derogation to either soluble or insoluble nickel compounds, whichever is worst-case, is appropriate. In this case derogation to soluble nickel compounds represent the worst-case.

Therefore, 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 hydroxycarbonate 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 *Risk Assessment Reports on nickel sulphate and nickel chloride* as well as to the *Background document in support of the individual Risk Assessment Reports*.

4.1.2.1.5.1.2 Oral

No studies providing specific information about the absorbed fraction of nickel in humans or experimental animals following oral administration of nickel carbonate have been located.

Slightly soluble nickel compounds, such as nickel carbonate, are expected to be absorbed from the gastrointestinal tract following oral exposure to a limited extent. However, some nickel compounds such as nickel carbonate may be more soluble in the acidic gastric fluid than in water thus facilitating absorption from the gastrointestinal tract. This is supported by one study in rats (Phatak & Padwardhan 1950 - quoted from IPCS 1991), which demonstrated that appreciable quantities of nickel from diets containing nickel carbonate were retained and tissue accumulation was significant; according to the authors, this was attributed to ready solubility of the compound in the stomach and the easier absorption from the intestine.

For the purpose of risk characterisation, the same value of 30% as is used for the three soluble nickel compounds will be taken forward to the risk characterisation for the absorbed fraction of nickel from the gastrointestinal tract following oral exposure to nickel carbonate in the exposure scenarios where fasting individuals might be exposed to nickel carbonate. 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.*

4.1.2.1.5.1.3 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* or *in vitro* studies providing information about the absorbed fraction of nickel in humans or experimental animals following dermal contact to nickel carbonate have been located.

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 carbonate. An *in vitro* study of soluble nickel compounds (nickel sulphate, nickel chloride, nickel nitrate, and nickel acetate) using human skin (Tanojo *et al*. 2001, for details are referred to the respective reports) 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 carbonate.

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

4.1.2.1.5.2 Distribution and elimination

The information on distribution and elimination of nickel following exposure to nickel carbonate is very limited. Nickel from diets containing nickel carbonate has been reported to accumulate in tissues of rats (Phatak & Padwardhan 1950 - quoted from IPCS 1991) and of calves (O'Dell et al. 1971 – quoted from IPCS 1991). One study in mice (Furst & Al-Mahrouq 1981 - quoted from IPCS 1991) indicates that most of the nickel was eliminated 12 days after intratracheal instillation of nickel carbonate.

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 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 insoluble nickel compounds. In the UK HSE (1987) review a number of single dose studies are mentioned.

4.1.2.2.1 Animal studies

4.1.2.2.1.1 Inhalation

No data have been found.

4.1.2.2.1.2 Oral

An acute oral toxicity study in rats with nickel carbonate has been performed (FDRL, 1983). An LD_{50} value of 625 mg Ni/kg for males and 402 mg Ni/kg for females was reported, corresponding to (625/0,495) 1263 mg nickel carbonate for males and (402/0,495) 812 mg nickel carbonate for females. Animals receiving 192 mg Ni/kg and above had diarrhoea, decreased activity, and ataxia. Deaths occurred at 3-7 days post-dose. At necropsy, some animals had blood in the intestinal lumen.

The study was performed according to a method resembling EU method B1 and according to GLP, and is therefore considered relevant for the risk assessment.

Nickel carbonate fulfils the Annex VI criteria for classification as Harmful with R22 (Harmful if swallowed).

4.1.2.2.1.3 Dermal

No data have been found.

4.1.2.2.2 Human studies

No data 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 carbonate via this route have been found. Thus, it is not possible to reach a conclusion for nickel carbonate alone.

From the *Background document in support of the individual Risk Assessment Reports* 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. Absorbtion of soluble nickel salts following inhalation is considerably greater than after oral administration. The absorbtion of less soluble salts is less. A value of 100% absorbtion has been agreed for the risk assessment, based on the Industry derogation statement to a "worst-case" comparison. Based on the acute oral toxicity, the TC C&L has agreed to classify nickel carbonate as Harmful with Xn; R20(Harmful by inhalation). This classification is included in the Annex I entry in the 30th ATP.

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

4.1.2.2.3.2 Oral

An acute oral rat study has been found, which shows that nickel carbonate is harmful via this route. The LD_{50} value of 402 mg Ni/kg (females, FDRL, 1983)) will be taken forward to the risk characterisation.

The existing classification of nickel carbonate as Harmful with Xn; R22 (Harmful if swallowed) remains unchanged in the 30th ATP.

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 carbonate via this route have been found.

From the *Background document in support of the individual Risk Assessment Reports* 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 NIPERA (1997) review, or the TERA (1999) review, skin or eye irritation of insoluble nickel compounds is not discussed. In the UK HSE (1987) review it is mentioned that no data were found on the skin and eye irritancy of insoluble nickel compounds.

4.1.2.3.1 Animal studies

No studies have been found.

4.1.2.3.2 Human data

No studies have been found.

4.1.2.3.3 Other data

Information on the pH of nickel (hydroxy)carbonate solutions is available from the main EU producers. One litre of pure water was added to 100 g samples of the commercially available product. The pH of the resulting solutions varied between 7.8 and 8.9 (Königswarter & Ebell, 2004; Laine, 2004a, PCF, 2004).

4.1.2.3.4 Conclusion

No skin or eye irritation data on nickel carbonate have been found. Thus, it is not possible to reach a conclusion for irritation based on data for nickel carbonate alone.

Data on eye irritation is available for nickel sulphate and nickel nitrate. Nickel sulphate was not eye irritating in an animal study, whilst nickel nitrate was a severe eye irritant (Xi; R41) as the effects are not reversible at the end of the test period. Considering that nickel carbonate has no oxidising potential as nickel nitrate and considering that the solubility of the substance is limited compared to nickel sulphate, there is no reason to believe that the eye irritating potential of nickel hydroxy carbonate will exceed that of nickel sulphate. The TC C&L has agreed not to classify nickel hydroxycarbonate as an eye irritant.

Similarly, for skin irritation, information on nickel sulphate is available, which shows that nickel sulphate was not irritant to animals. However, human data show skin irritation for both nickel sulphate and nickel chloride, and classification is considered relevant. Animal data for nickel nitrate show that this soluble nickel compound is also a skin irritant. Based on the data for these soluble nickel compounds, nickel carbonate is classified as Xi; R38 with a specific concentration limit of 20% in the 30th ATP.

Regarding respiratory irritation the available data on nickel carbonate do not allow a conclusion for this endpoint. The criteria for classification for respiratory irritation are mainly based on human experience, which is lacking. There is a concern for respiratory irritation. However, this concern is considered to be more appropriately covered by the proposed classification for chronic effects (T; R48/23).

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 in support of the individual Risk Assessment Reports* it appears that it is the nickel ion that causes skin sensitisation. It can therefore be assumed that nickel carbonate under conditions where the nickel ion can be released 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

No data regarding skin sensitisation or elicitation in humans have been located.

4.1.2.4.2.1.1 Conclusion, human data, skin sensitisation

No data regarding skin sensitisation or elicitation in humans have been located.

From the *Background document in support of the individual Risk Assessment Reports* it appears that it is the nickel ion that causes skin sensitisation. It can therefore be assumed that nickel carbonate under conditions where the nickel ion can be released is a skin sensitiser in humans.

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 carbonate. From the *Background document in support of the individual Risk Assessment Reports* 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

No data regarding skin sensitisation or elicitation in humans have been located. Based on data from other nickel compounds, nickel carbonate may cause sensitisation under conditions where the nickel ion is released. The current classification of nickel carbonate with R43 has been confirmed in the 30th ATP.

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.

No data regarding respiratory sensitisation in humans have been located. Based on data for other nickel compounds it is concluded that nickel carbonate is a respiratory sensitiser. Nickel carbonate is classified as R42 in the 30th ATP.

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

4.1.2.5 Repeated dose toxicity

In the NIPERA (1997) review, or the TERA (1999) review, the repeated dose toxicity of nickel carbonate is not discussed. In the UK HSE (1987) review two studies are mentioned, one in calves, the other in monkeys.

4.1.2.5.1 Animal studies

4.1.2.5.1.1 Inhalation

No studies have been found.

4.1.2.5.1.2 Oral

Twenty-three male dairy calves were fed 0, 62.5, 250 or 1000 ppm elemental Ni as Ni CO_3 in the total diet (experimental basal diet, containing 0.9 ppm Ni, plus added nickel) from 13 to 21 weeks of age (O'Dell *et al*., 1970). The amount of nickel ingested per kg and day is not given in the publication. Three animals per group were killed for histopathological studies immediately after the 8-week dosing period, while the remaining animals were returned to the basal diet for a 6-week recovery period before sacrifice. Administration of 1000 ppm Ni drastically reduced feed intake and resulted in weight loss by every animal, but the animals appeared

normal, only younger-looking. In the animals receiving 250 ppm Ni a non-significant reduced weight gain of 11% was observed; 62.5 ppm Ni had no effect. The growth suppression did not persist when the calves were restored to a normal (basal) diet. Histopathological examination revealed various kidney abnormalities in the control and Ni-dosed groups, no other consistent effects were found. The study is well reported. Because of the small group size (3-4 animals), the sensitivity is limited. Consequently the study is not considered useful for the setting of a LOAEL/NOAEL.

No effects on body weight or haematology were seen in monkeys (*Macaca sinicus*) given from 250 to 1000 ppm Ni as nickel carbonate in the diet for 4 months (Phatak & Patwardham, 1950, quoted from UK HSE, 1987). In the same study using 8 male and female rats/group, body weight was found to be less in the high dose group but this was not statistically significant. As no further details on this study is given, it is not possible to assess the quality and relevance. However, given the fact that the study was published half a century ago, it seems reasonable to assume that present-day test requirements are not met.

4.1.2.5.1.3 Dermal

No studies have been found.

4.1.2.5.2 Human data

No data have been found.

4.1.2.5.3 Conclusion

4.1.2.5.3.1 Inhalation

No data on repeated dose toxicity of nickel carbonate via inhalation have been found.

From the *Background document in support of the individual Risk Assessment Reports* it appears that long-term inhalation of insoluble as well as soluble nickel compounds results in adverse effects on the lungs including chronic inflammation and fibrosis. Chronic lung inflammation and lung fibrosis are serious and potentially irreversible effects. Based on data from other nickel compounds, nickel carbonate is classified as T; R48/23 in the 30th ATP.

Whilst there is evidence of potency differences between the different nickel compounds (see *Background document in support of the individual Risk Assessment Reports*), a LOAEC of 0.056 mg Ni/m^3 will be used based on the 2-year rat study of nickel sulphate by NTP (1996a).

4.1.2.5.3.2 Oral

The calf study shows that nickel carbonate incorporated in the feed at 1000 ppm causes reduced feed intake and growth inhibition. The small group size means that possible effects at lower concentrations could easily have been missed, and therefore it is not possible to deduct a NOAEL from this study.

From the *Background document in support of the individual Risk Assessment Reports* 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 not in conflict with the database on nickel carbonate, and are considered relevant for the risk assessment of nickel carbonate.

The effects following repeated oral administration of nickel compounds in general do not lead to a need for classification. Mortality was observed in the study with nickel chloride by American Biogenics Corporation (1988), however, this is believed to be a result of the particular way of administration (gavage), because studies using the routes which are more relevant in relation to human exposure, via feed or drinking water, indicate that severe toxicity is not a problem following repeated oral exposure.

4.1.2.5.3.3 Dermal

For the dermal route, no data on nickel carbonate have been found.
From the *Background document in support of the individual Risk Assessment Reports* 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 carbonate 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)[2] 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 carbonate. 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.

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

4.1.2.6.1.2 Gene mutations

There is no data available on the effects of nickel carbonate on gene mutation *in vitro*.

4.1.2.6.1.3 Chromosomal effects

The studies on nickel carbonate on chromosomal effects *in vitro* are summarised in table 4.1.2.6.1.A.

Nickel carbonate has been tested for sister chromatid exchanges (SCE) in two studies, both carried out by Montaldi *et al*. (1985, 1987 - reviewed by NiPERA and TERA). Positive effects were seen in both studies.

In the Montaldi *et al*. (1987) study referred to above, chromosome aberrations were also studied, with a positive result.

Table 4.1.2.6.1.A: In vitro studies with nickel carbonate in mammalian cells.

Species (Test system).	Endpoint	Result	Reference	Review
Hamster CHO	SCE	Positive	Montaldi *et al.* (1985, 1987)	NiPERA, TERA
Hamster CHO	CA	Positive	Montaldi *et al.* (1987)	NiPERA, TERA

4.1.2.6.1.4 Discussion and conclusion, in vitro studies.

The data on *in vitro* genotoxicity of nickel carbonate is very limited. The positive results seen for chromosomal aberrations and SCE in hamster CHO cells *in vitro* are consistent with effects seen for other nickel compounds.

4.1.2.6.2 *In vivo* studies

4.1.2.6.2.1 DNA Damage and Repair.

Nickel carbonate has been tested in two *in vivo* studies for effects on DNA strand breaks, X links and alkaline elution in rats at doses from 5 – 40 mg Ni/kg intraperitoneally. The two studies by Ciccarelli *et al*. (1981, 1982) which were reviewed by IPCS, IARC, NiPERA, 1996) showed single strand breaks in lung and kidney nuclei. The damage correlated with the nickel concentration (quoted from NiPERA 1996). Whilst not direct evidence of mutagenicity, these studies indicate that effects seen with nickel salts *in vitro* can also be seen *in vivo*. NiPERA (2003) regards the meaning of these studies for *in vivo* mutagenicity as unclear.

4.1.2.6.2.2 Gene mutations

There is no *in vivo* data available on the effects of nickel carbonate on gene mutation *in vivo*.

[2] 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.

4.1.2.6.2.3 Chromosomal effects.

There is no *in vivo* data available on the effects of nickel carbonate on chromosomal aberrations or sister chromatid exchange.

4.1.2.6.2.4 Discussion and conclusion, in vitro studies.

There is practically no data on the *in vivo* genotoxicity of nickel carbonate. The two Ciccarelli studies provide evidence that effects similar to those seen with other nickel compounds can also occur *in vivo*.

4.1.2.6.3 Conclusions

The data on the *in vitro* and *in vivo* genotoxicity of nickel carbonate is very limited indeed. The two studies showing effects *in vitro* on chromosome aberrations and sister chromatid exchanges with nickel carbonate are consistent with the effects seen with other better studied nickel compounds. *In vivo* studies on DNA damage suggest that effects can also be seen *in vivo*. The genotoxicity of nickel compounds has been reviewed by NiPERA (1996) and TERA (1998). 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."

There is no evidence concerning possible hereditable effects on germ cells.

The opinion of the Specialised Experts has being sought with regard to the classification of nickel sulphate, nickel chloride, nickel nitrate and nickel carbonate 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 concluded that there was insufficient evidence for classification of nickel carbonate. The Specialised Experts did not consider that further testing of effects on germ cells was practicable (European Commission, 2004).

NiPERA (2003) considers that the mutagenicity assessment for nickel carbonate could be derogated to the overall mutagenicity assessment for either soluble or insoluble nickel compounds (worst-case). The evidence for significant absorption of nickel carbonate after oral administration (see 4.1.2.1.5.1.2), and the acute toxicity (see 4.1.2.2.3.2) also indicates that the possibility that the germ cells are affected cannot be excluded.

The TC C&L has agreed to classify nickel carbonate as Muta. Cat. 3; R68, and this classification has been included in the 30th ATP.

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.

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 carbonate 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 carbonate 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 carbonate in experimental animals have been located.

4.1.2.7.1.4 Other routes of administration

Studies on the carcinogenicity of nickel carbonate following intramuscular implants or intraperitoneal injections have been performed in rats; these studies are summarised in Table 4.1.2.7.1.A. Tumours were observed following both routes of administration.

Table 4.1.2.7.1.A: Summary of carcinogenicity studies of nickel carbonate in experimental animals by other routes of administration than inhalation, oral administration, and dermal contact.

Route of administration	**Species, group size and sex**	**Concentration, exposure duration**	**Results**	**Reference**
Intramuscular implants (in sheep fat pellets)	NIH black rats, 35 animals per group Vehicle controls	3 implants (interval unspecified) of 7 mg of nickel carbonate Observation for 18 months	Implantation-site sarcomas in 6/35 rats No tumours in controls (0/35)	Payne (1964 – quoted from IARC 1990, TERA 1999). Reported as an abstract.
Intraperitoneal injections	Wistar rats 35 females Controls: 1 ml saline x 3 1 ml saline x 50 2 ml saline x 4	25 or 50 injections of 1 mg nickel as nickel carbonate twice weekly Observation for 132 weeks	Abdominal tumours in 1/35 (1 sarcoma) or 3/33 (2 mesothelioma, 1 sarcomas) 1/33 (sarcoma) 0/34 3/66 (1 mesothelioma, 2 sarcomas)	Pott *et al*. (1989, 1992) (Pott *et al*. 1992 cited in IARC 1990 and TERA 1999 as Pott *et al*. 1990)

4.1.2.7.1.5 Promoter studies

No data regarding the promoting effect of nickel carbonate 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 carbonate 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 carbonate 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 carbonate in experimental animals following inhalation.

4.1.2.7.1.6.2 Oral

No data regarding carcinogenicity of nickel carbonate 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 tumourogenic 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 carbonate.

4.1.2.7.1.6.3 Dermal

No data regarding carcinogenicity following dermal contact to nickel carbonate 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 carbonate.

4.1.2.7.1.6.4 Other routes of administration

Studies on the carcinogenicity of nickel carbonate following intramuscular implants or intraperitoneal injections have been performed in rats; tumours were observed following both administration routes.

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 carbonate. 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 carbonate to human beings.

4.1.2.7.1.6.5 Promoter studies

No data regarding the promoting effect of nickel carbonate 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, based on the available studies, it is not possible to draw any conclusion regarding a promoting potential of the five prioritised nickel compounds (nickel sulphate, nickel chloride, nickel nitrate, nickel carbonate, and nickel metal). Furthermore, such information is difficult to use with respect to evaluating the carcinogenic potential of nickel carbonate.

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 carbonate 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 carbonate 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 carbonate. However, as oral exposure to nickel carbonate 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 carbonate is generally considered to form part of the oxidic fraction (NiPERA, 1996). For further details of the behaviour of nickel hydroxycarbonate in this leaching process, see Chapter 4.1.1.2.1.2.

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

A single case of nasal cancer has been reported among nickel-refinery workers engaged in a high-temperature process where nickel carbonate was decomposed to nickel oxide (Enterline *et al.*, 1982). Results from the same refinery cohort were included in the report of the International Committee on Nickel Carcinogenesis in Man (Doll *et al*., 1990), but there was no strong evidence for nickel related increased risk of respiratory cancer.

In the report from the International Committee on Nickel Carcinogenesis in Man (Doll *et al*., 1990), nickel carbonate was classified as an insoluble form of nickel for most of the nickel refineries, while for the Norwegian one it was classified as water-soluble. The contribution from nickel carbonate to the inhalation exposure in these cohorts was probably rather low compared to the other forms of nickel.

An evaluation of the carcinogenicity to humans of nickel carbonate could possibly be based on the toxico-kinetic properties of nickel carbonate compared to other nickel compounds such as nickel sulphides and nickel oxides.

4.1.2.7.2.1 Overall conclusion for carcinogenicity

The Industry derogation statement (Laine, 2003d) indicates that the carcinogenicity should be evaluated using the worst-case comparison with data for soluble and insoluble nickel compounds.

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). They also agreed that nickel carbonate should be classified as Carc. Cat. 1. Since both the water-soluble nickel compounds considered at this meeting and the insoluble inorganic nickel compounds already classified in Annex I are considered as human carcinogens consequently also the nickel carbonate was considered to be a human carcinogen (European Commission, 2004).

The TC C&L has agreed to classify nickel carbonate as Carc. Cat. 1; R49 (May cause cancer by inhalation), as there is no concern for carcinogenic potential with other routes of administration. This classification is included in the Annex I entry in the 30th ATP.

4.1.2.8 Toxicity for reproduction

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

From the *Background document in support of the individual Risk Assessment Reports* 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 carbonate) 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 limited studies after oral, inhalation or subcutaneous administration of nickel chloride or nickel sulphate. The NOAEC for effects on male sex organs of 0.45 mg Ni /m^3 for inhalation exposure and the NOAEL of 2.2 mg Ni/kg bw/day for oral administration 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. There is evidence for significant absorption of nickel carbonate after oral administration (see 4.1.2.1.5.1.2), supported by the acute toxicity data (see 4.1.2.2.3.2). The C&L has agreed to classify nickel carbonate as Repr. Cat. 2; R61and this classification is included in the 30th ATP.

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.

4.1.3 Risk characterisation.[3]

4.1.3.1 General aspects

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

There is no known consumer exposure to nickel hydroxycarbonate.

Table 4.1.3.1.A. Scenarios for the risk characterisation.

Scenario		**Occupational exposure**	**Consumer exposure**	**Indirect exposure**
A1	Nickel hydroxycarbonate production from soluble nickel salts	Yes	No	yes
B1	Nickel hydroxycarbonate used in catalyst production	Yes	No	yes
B2	Nickel hydroxycarbonate used in electroplating	Yes	No	yes
B3	Nickel hydroxycarbonate used in synthesis of other nickel containing chemicals	Yes	No	yes

[3] 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.

4.1.3.1.1 Exposure assessment summary

Occupational exposure to nickel hydroxycarbonate is described in chapter 4.1.1.2. Occupational exposure to nickel hydroxycarbonate 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 hydroxycarbonate.

The occupational exposures in the industrial production and use of nickel hydroxycarbonate 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 hydroxycarbonate 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 hydroxycarbonate production from soluble nickel salts	U	0.10	0.9	Meas.	1.8	Exp.
		SO	0.15	≈0		≈0	
B1	Nickel hydroxycarbonate used in catalyst production	U	0.09	4.4	Meas.	8.8	Exp.
		SO	0.003	0.04		0.1	
B2	Nickel hydroxycarbonate used in electroplating	O	0.0025	0.36	Meas.	0.72	Exp.
		M	0.0018	0.29		0.58	
		S	0.0015	0.24		0.48	
		SO	0.019	1.5		3.0	
B3	Nickel hydroxycarbonate used in synthesis of other nickel containing chemicals	U	0.002-0.18	7.0	Ana.	14	Ana.
		SO	0.004-0.27	≈0		≈0	

1: U= insoluble nickel (considered being all nickel hydroxycarbonate - worst-case); SO = Soluble nickel salts; O = oxidic nickel (considered to be all nickel hydroxycarbonate - worst-case); M = metallic nickel; S = sulphidic 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 three of the five processes (A1, B1, B2) are based on measured data. The typical exposure levels for nickel hydroxycarbonate are based on measurements of the total nickel exposures, taking into account available speciation information. In scenario A1, B1 and B3 speciation is expressed as soluble and insoluble nickel species. Here all the "insoluble nickel" is considered to be nickel hydroxycarbonate. In scenario B2, more detail speciation data is available. Here all the "oxidic" nickel is assumed to be nickel hydroxycarbonate. For scenario B3, where little data is available, estimates have been made by analogy to the production of chemicals using metallic nickel (see nickel metal risk assessment report).

"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/m³ in force in a number of European countries[4] for two of the use scenarios (B1 and B2). For some processes in scenario B3 the typical exposure is below the OEL. The OEL is exceeded in the other "typical" levels and in all the "worst-case" scenarios.

[4] There is a range of OELs for nickel carbonate. The OEL in Belgium is 1 mg Ni/m³, in Austria and Germany is 0.5 mg Ni/m³, and either 0.01 or 0.05 mg Ni/m³ depending on whether the compound is considered as soluble or insoluble.

As discussed in the toxicokinetics summary below, nickel in air 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 hydroxycarbonate.

Scenario		**Dermal exposure**						
		Speciation (1)	**Typical**			**Worst-case**		
			mg/day	**µg/cm²**	**method (2)**	**mg/day**	**µg/cm²**	**method (2)**
A1	Nickel hydroxycarbonate production from soluble nickel salts	U SO	0.4 0.8	0.2(5) 0.4(5)	Meas.	0.8 1.4	0.4(5) 0.7(5)	Meas.
B1	Nickel hydroxycarbonate used in catalyst production	U SO	0.4(3) 0.8(3)	0.2(5) 0.4(5)	Ana.	0.8(3) 1.4(3)	0.4(5) 0.7(5)	Ana.
B2	Nickel hydroxycarbonate used in electroplating	O M S SO	0.004 (4) 0.003 0.002 0.03	0.005 (6)	Meas.	0.06 (4) 0.05 0.04 0.23	0.07 (6)	Meas.
B3	Nickel hydroxycarbonate used in synthesis of other nickel containing chemicals	U SO	0.4(3) 0.8(3)	0.2(5) 0.4(5)	Ana.	0.8(3) 1.4(3)	0.4(5) 0.7(5)	Ana.

1: U= Other nickel species than soluble nickel - considered being all nickel hydroxycarbonate – (worst-case); SO = Soluble nickel salts; O = oxidic nickel (considered to be all nickel hydroxycarbonate - worst-case); M = metallic nickel; S = sulphidic nickel.
2: Meas. = Measured data. Ana: = Analogy to other scenarios.
3: Analogy to measured data for operators packing nickel hydroxycarbonate or nickel sulphate (scenario A1)
4: The mass of dust deposited on the skin was estimated from 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

Some measured data were available for the exposure assessment. The sampling strategy in measuring the dermal exposure was designed to allow an estimation of the typical exposure in operating a given task. Thus personal protective equipment was used when required. Workers involved in the production of nickel carbonate from soluble nickel salts (scenario A1) wore cotton overalls and rigger type gloves. There is no measured data available for scenario B1 and B3, and for both scenarios exposure was estimated by analogy to measured data for operators in the packing of nickel hydroxycarbonate and nickel sulphate hexahydrate (scenario A1). The handling of nickel hydroxycarbonate in the production of catalysts (scenario B1) or chemicals (scenario B3) is expected to be less intensive than in the packing of nickel hydroxycarbonate. Thus the exposure estimated by the analogy is considered biased towards high levels. No information on the use of personal protective equipment was available for nickel-plating operators (scenario B2). For plating operators the nickel species deposited on the skin are assumed to be similar to the airborne contaminants.

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 hydroxycarbonate 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, nickel in air is exhaled or leads 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 available for nickel hydroxycarbonate, and much of the data used in this risk characterisation are based on data from studies carried out using nickel sulphate and should be considered as a conservative starting point as solubility data and acute oral toxicity indicate a lower bioavailability.

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} = 402 mg Ni/kg bw Xn; R22
Irritation / corrosivity	Inconclusive with regard to respiratory tract irritation	Skin irritant, Xi; R38 Not classified as an eye irritant	
Sensitisation	Respiratory sensitiser: R42	Skin sensitiser: 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 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 hydroxycarbonate. 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 hydroxycarbonate 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 hydroxycarbonate in the exposure scenarios where fasting individuals might be exposed to nickel hydroxycarbonate. 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 hydroxycarbonate.

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 (non-retained fraction of particles), by absorption in the respiratory tract, or by removal due to mucociliary elimination.

4.1.3.1.2.2 Acute toxicity

An LD_{50} for acute oral toxicity of 402 mg Ni/kg for nickel carbonate is used for this risk characterisation. Nickel carbonate is classified as Xn; R22.

No data for acute inhalational toxicity of nickel hydroxycarbonate 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 carbonate 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.

There is no data on irritation or corrosivity for nickel hydroxycarbonate.

The effects on skin irritation are evaluated on the basis of data for nickel sulphate, where there is human data that indicate that nickel sulphate in concentrations above 20% can induce skin irritation. There is also animal data to show that nickel nitrate is also a skin irritant. Nickel carbonate is classified as Xi; R38.
The animal data for nickel sulphate do not support classification as an eye irritant, whilst there is evidence of serious eye irritation for nickel nitrate. Considering that nickel carbonate has no oxidising potential as nickel nitrate and considering that the solubility of the substance is limited compared to nickel sulphate, there is no reason to believe that the eye irritating potential of nickel carbonate will exceed that of nickel sulphate.

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 hydroxycarbonate is a skin and respiratory sensitiser. The evidence for both skin and respiratory sensitisation is based on analogy with other nickel compounds. Nickel carbonate is classified as R42/43.

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 $\mu g/cm^2$ 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 very limited data on repeated dose toxicity of nickel hydroxycarbonate. Nickel carbonate is classified as T; R48/23 as results from a number of nickel compounds show that serious effects are induced in the form of chronic lung inflammation and fibrosis.

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 carbonate. 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 no concern for systemic effects from the dermal route of exposure.

4.1.3.1.2.6 Mutagenicity

There is limited evidence on the genotoxicity of nickel hydroxycarbonate. The Specialised Experts have concluded at their meeting in April 2004 that there was insufficient evidence for classification as Muta. Cat. 3; R68. On the basis of the derogation proposed by Industry (NiPERA, 2003), the TC C&L have agreed that nickel

carbonate should be classified as Muta. Cat. 3; R68. The evidence for significant absorption of nickel carbonate after oral administration and the acute toxicity also indicates that the possibility that the germ cells are affected cannot be excluded.

As there is concern for the genotoxic effects of nickel hydroxycarbonate 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 carbonate 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.

There is no data on the carcinogenicity of nickel hydroxycarbonate. Based on the opinion of the Specialised Experts and on the derogation statement from Industry (Laine, 2003), nickel carbonate is classified as Carc. Cat. 1; R49.

As nickel carbonate 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 x 10^{-4} / μg/m^3	298
US EPA, nickel subsulfide; high	9.2 x 10^{-4}/ μg/m^3	78
WHO unit risk	3.8 x 10^{-4}/ μg/m^3	188
CEPN	2.5 x 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 most scenarios involve varying degrees of mixed exposure to different nickel species. Since the effects seen are due to the total nickel exposure rather than to nickel hydroxycarbonate 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.

4.1.3.1.2.8 Reproductive toxicity.

There is no data on the developmental toxicity of nickel hydroxycarbonate. 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. There is evidence for significant absorption of nickel carbonate after oral administration supported by the acute toxicity data. The TC C&L have agreed to classify nickel carbonate as Repr. Cat. 2; R61.

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 hydroxycarbonate.

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 carbonate, data is available from nickel sulphate and nickel chloride, as well as from other insoluble nickel compounds.

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 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 carbonate in Category 2 for developmental toxicity has been agreed. The potential for effects of nickel carbonate 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 and not nickel hydroxycarbonate, the Rapporteur considers that this data is an adequate basis for the risk characterisation apart from the above mentioned effect endpoints, 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 hydroxycarbonate may occur by inhalation of aerosols containing nickel hydroxycarbonate or by skin contact.

Occupational exposure to nickel hydroxycarbonate 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 hydroxycarbonate 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 hydroxycarbonate 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 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 carbonate 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).

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

Scenario		**Short term**		
		mg Ni/m^3	**MOS (1)**	**Conclusion**
A1	Nickel hydroxycarbonate production from soluble nickel salts	1.8	0.4	**iii**
B1	Nickel hydroxycarbonate used in catalyst production	8.8	0.08	**iii**
B2	Nickel hydroxycarbonate used in electroplating	0.72	1	**iii**
B3	Nickel hydroxycarbonate used in synthesis of other nickel containing chemicals	14	0.05	**iii**

1): 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 nickel hydroxycarbonate. 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 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 concern for all scenarios, **Conclusion (iii)**.

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 carbonate as a skin irritant. There is concern for this effect, whilst 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 no data on eye irritation for nickel carbonate. Data on eye irritation is available for nickel sulphate and nickel nitrate. Nickel sulphate was not eye irritating in an animal study, whilst nickel nitrate was a severe eye irritant (Xi; R41) as the effects are not reversible at the end of the test period. Considering that nickel carbonate has no oxidising potential as nickel nitrate and considering that the solubility of the substance is limited compared to nickel sulphate, there is no reason to believe that the eye irritating potential of nickel hydroxy carbonate will exceed that of nickel sulphate. The TC C&L has agreed not to classify nickel hydroxycarbonate as an eye irritant, and **conclusion (ii)** applies to all workplace situations.

There is some concern for respiratory irritation. However, these concerns are better addressed under repeated dose toxicity, requiring the use of appropriate protective equipment.

4.1.3.2.3 Sensitisation

Nickel hydroxycarbonate is a skin and respiratory sensitiser, and the substance is classified 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 μg/cm^2 has been defined. This effect concentration can be used as a starting point for a quantitative risk characterisation for the working population.

Scenario B2 (nickel hydroxycarbonate used in plating) has the lowest typical dermal exposure of 0.004 mg/day for exposure to oxidic nickel compounds. This corresponds to 0.005 μg/cm^2/day. The worst-case exposure calculated for this scenario is 0.07 μg/cm^2. Scenarios A1, B1 and B3 have a typical dermal exposure of 0.4 mg/day for exposure to other nickel species than soluble nickel salts. This corresponds to 0.2 μg/cm^2. The worst-case exposure calculated for these scenarios is 0.4 μg/cm^2. Whilst the worst-case exposure for scenario A1, B1 and B3 is slightly above the empirical threshold of 0.3 μg/cm^2, all the estimated typical and worst-case exposure levels are considered to be acceptable as the empirical threshold of 0.3 μg/cm^2 is based on evidence from human studies (**conclusion (ii)**) involving prolonged (48 h) and close occlusive contact to nickel sulphate.

4.1.3.2.3.2 Respiratory tract

Nickel hydroxycarbonate 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 sulphate. Further, considerations should be given to inter- and intra species variations in susceptibility and to the use of a LOAEC value as a starting point. At the LOAEC rather severe effects on the respiratory tract were observed and data indicated 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 [2)]**	**Conclusion**	**mg Ni/m^3**	**MOS [2)]**	**Conclusion**
A1	Nickel hydroxycarbonate production from soluble nickel salts	0.10	0.56	**iii**	0.9	0.06	**iii**
B1	Nickel hydroxycarbonate used in catalyst production	0.09	0.6	**iii**	4.4	0.01	**iii**
B2	Nickel hydroxycarbonate used in electroplating	0.0025	22	**iii**	0.36	0.16	**iii**
B3	Nickel hydroxycarbonate used in synthesis of other nickel containing chemicals	0.002-0.18	0.3-28	**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).

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 carbonate 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 carbonate 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 $\mu g/m^3$ (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 hydroxycarbonate 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 hydroxycarbonate production from soluble nickel salts	U SO	0.10 0.15	24(2)	**iii**
B1	Nickel hydroxycarbonate used in catalyst production	U SO	0.09 0.003	8.8 (2)	**iii**
B2	Nickel hydroxycarbonate used in electroplating	O M S SO	0.0025 0.0018 0.0015 0.019	2.4 (2)	**iii**
B3	Nickel hydroxycarbonate used in synthesis of other nickel containing chemicals	U SO	0.002-0.18 0.004-0.27	0.6-43(2)	**iii**

1: U= insoluble nickel (considered being all nickel hydroxycarbonate - worst-case); SO = Soluble nickel salts; O = oxidic nickel (considered to be all nickel hydroxycarbonate - worst-case); M = metallic nickel; S = sulphidic nickel.
2: The different nickel species have been added and the risk calculated from the sum.

The WHO unit risk estimate of 3.8 x 10^{-4} used for calculation 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 hydroxycarbonate, 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 of this risk characterisation.

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 sulphate. Considerations to inter- and intraspecies 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 [2)]	Conclusion	mg Ni/m^3	MOS [2)]	Conclusion
A1	Nickel hydroxycarbonate production from soluble nickel salts	0.10	4.58	**iii**	0.9	0.5	**iii**
B1	Nickel hydroxycarbonate used in catalyst production	0.09	5.0	**iii**	4.4	0.10	**iii**
B2	Nickel hydroxycarbonate used in electroplating	0.0025	180	**ii**	0.36	1.25	**iii**
B3	Nickel hydroxycarbonate used in synthesis of other nickel containing chemicals	0.002-0.18	2.5-225	**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 and 180. Scenario B3 has a MOS value of 1. 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 B3 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 most 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 hydroxycarbonate, 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 nickel hydroxycarbonate 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 MOS values < 50 are 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 2)**	**Conclusion**	**mg Ni/m^3**	**MOS 2)**	**Conclusion**
A1	Nickel hydroxycarbonate production from soluble nickel salts	0.10	2.8	**iii**	0.9	0.3	**iii**
B1	Nickel hydroxycarbonate used in catalyst production	0.09	3.1	**iii**	4.4	0.063	**iii**
B2	Nickel hydroxycarbonate used in electroplating	0.0025	111	**ii**	0.36	0.77	**iii**
B3	Nickel hydroxycarbonate used in synthesis of other nickel containing chemicals	0.002-0.18	1.5-140	**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 0.62 and 111. Scenario B3 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 B3 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 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 for skin and eye irritation, and to all workplace scenarios for skin sensitisation (induction and elicitation)
Conclusion (iii) applies to all other 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 hydroxycarbonate production from soluble nickel salts	**iii**	**ii**	**iii**	**iii**	**ii**	**iii**	**ii**	**iii**	**iii**	**ii**	**iii**	**iii**	**ii**
B1: Nickel hydroxycarbonate used in catalyst production	**iii**	**ii**	**iii**	**iii**	**ii**	**iii**	**ii**	**iii**	**iii**	**ii**	**iii**	**iii**	**ii**
B2: Nickel hydroxycarbonate used in electroplating	**iii**	**ii**	**iii**	**iii**	**ii**	**iii**	**ii**	**ii**	**iii**	**ii**	**ii**	**iii**	**ii**
B3: Nickel hydroxycarbonate used in synthesis of other nickel containing chemicals	**iii**	**ii**	**iii**	**iii**	**ii**	**iii**	**ii**	**ii-iii** [1]	**iii**	**ii**	**ii-iii** [1]	**iii**	**ii**

1) It is noted that scenario B3 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 hydroxycarbonate.

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 hydroxycarbonate is not explosive.

4.2.2.2 Flammability.

Nickel hydroxycarbonate is not flammable.

4.2.2.3 Oxidising potential.

Nickel hydroxycarbonate is not oxidising.

4.2.3 Risk characterisation.

There is no concern for the physical-chemical effects of nickel hydroxycarbonate (**conclusion (ii)**).

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 carbonate 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 hydroxycarbonate production from soluble nickel salts	iii	iii	iii	iii	Iii	iii	iii	iii	iii
B1: Nickel hydroxycarbonate used in catalyst production	iii	iii	iii	iii	Iii	iii	iii	iii	iii
B2: Nickel hydroxycarbonate used in electroplating	iii	iii	iii	iii	Iii		iii		iii
B3: Nickel hydroxycarbonate used in synthesis of other nickel containing chemicals	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 typical inhalational exposure for effects on 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 carbonate.

5.2.3 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".

5.2.4 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".

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:

- There is no reason for concern with respect to the physico-chemical properties of nickel carbonate.

6. REFERENCES

- ACGIH [American Conference of Government Industrial Hygienists] (1998): Threshold Limit Values (TLVs) for Chemical Substances and Biological Exposure Indices (BEIs). ACGIH, Cincinnati, Ohio, USA.
- Aitken RJ, Baldwin PEJ, Beaumont GC, Kenny LC, Maynard AD (1999): Aerosol inhalability in low air movement environments. J Aerosol Sci **30**: 613-626.
- Andersen I, Berge SR, Resmann F (1998): Speciation of airborne dust from a nickel refinery roasting operation. Analyst **123**: 687-689.
- Almaguer D (1987): Health hazard evaluation report HETA 86-251-1842, American Cyanamid, Michigan City, Indiana. Cincinnati, OH: Nat Inst Occ Safety and Health, report No. HETA 86-251-1842.
- Antonsen DH (1981): Nickel compounds. In: Kirk-Othmer Encyclopaedia of Chemical Technology, 3rd. Edition, Vol. 15, Mark HF, Othmer DF, Overberger CG, Seaborg GT, Grayson M. (Eds.), John Wiley & Sons, New York, 801-809.
- Antonsen DH (1996): Nickel compounds. In: Kirk-Othmer Encyclopaedia of Chemical Technology, 4th. Edition, Vol. 17. Kroschwitz JI (Exec. Ed.), John Wiley. New York, Chichester, Brisbane, Toronto, Singapore.
- Arbejdstilsynet (2000): At-vejledning C.):1 Grænseværdier for stoffer og materialer. Arbejdstilsynet, København. October, 2000. (In Danish).
- Atlas of Thermoanalytical Curves (1975): Ed. Liptay, G., Heyden & Son Ltd.
- BauA [German Federal Institute for Occupational Safety and Health] (2003): German National legislative controls for nickel and nickel compounds. Letter to Danish Rapporteur from Raimund Weiß, 16 July, 2003.
- Bavazzano P, Bolognesi R, Cassinelli C, Gori R, Li Donni V, Martellini F, Oliva G, Riccucci S (1994) Skin contamination and low airborne nickel exposure of electroplaters. Sci Total Env 155: 83-86.
- Benson JM, Chang IY, Cheng YS, Hahn FF, Kennedy CH, Barr EB, Maples KR, Snipes MB (1995): Particle clearance and histopathology in lungs of F344/N rats and B6C3F1 mice inhaling nickel oxide or nickel sulfate. Fundam. Appl Toxicol. **28:** 232-244.
- Bernacki EJ, Parsons GE, Roy BR, Mikac-Devic M, Kennedy CD, Sunderman FW (1978): Urine nickel concentrations in nickel-exposed workers. Ann Clin Lab Sci **8**: 184-189.
- Bicknell R, McManus KP, Kaiser EA, Koenig J, Fidler AT (1989): Health hazard evaluation report HETA 87-075-1988, American Cyanamid, Wallingford, Connecticut. Cincinnati, OH: U.S. Department of Health and Human Services, National Institute of Occupational Safety and Health; report No. HETA 87-075-1988.
- Boiano JM, Lipscomb JA, Liss GM (1983): Health hazard evaluation report HETA 80-187-1395, Saft America Inc., St. Paul, Minnesota. Cincinnati, OH: Nat Inst Occ Safety and Health, report No. HETA 80-187-1395.
- Bright P, Burge PS, O'Hickey SP, Gannon PFG, Robertson AS, Boran A (1997): Occupational asthma due to chrome and nickel electroplating. Thorax **52**: 28-32.
- Carlsen L (2001): Aqueous Solubilities and Complex Stabilities of Ni(II) Species. Part 1: Inorganic Ligands. Draft report to the Danish EPA.
- CEN [Comité Européen de Normalisation] (1993): Workplace Atmospheres: Size fraction definitions for measurement
- CEPA [Canadian Environmental Protection Act] (1994): Priority Substance list Assessment Report. Nickel and its compounds. Canada.
- Chemical Information Services Ltd. (1988): Directory of World Chemical Producers 1989/90 Edition, Oceanside, NY pp. 49, 287, 426-427, 489-490 (Quoted in IARC, 1990).
- Ciccarelli RB, Hampton TH, Jennette KW (1981): Nickel carbonate induces DNA-protein crosslinks and DNA strand breaks in rat kidney. Cancer Lett. **12(4)**: 349-354.
- Ciccarelli RB, Wetterhahn KE (1982): Nickel distribution and DNA lesions induced in rat tissues by the carcinogen nickel carbonate. Cancer Res. **42**: 3544-3549.
- CRC (2000). Handbook of Chemistry and Physics, 81th ed., CRC Press
- CSTEE [Commission Scientific Committee on Toxicology, Ecotoxicology and the Environment] (2001): Opinion on: Position Paper on Ambient Air Pollution by Nickel Compounds. Final Version October 2000. Opinion expressed at the 22nd. CSTEE plenary meeting, Brussels, 6/7 March, 2001.
- Daniels W, Orris P, Kramkowski R, Almaguer D (1988): Health hazard evaluation report HETA 86-121-1923, Modern Plating Corporation, Freeport, Illinois. Cincinnati, OH: U.S. Department of Health and Human Services, National Institute of Occupational Safety and Health; report No. HETA 86-121-1923.
- Daniels W, Gunter B (1987): Health hazard evaluation report HETA 86-063-1843, Olson Industries, Denver, Colorado. Cincinnati, OH: U.S. Department of Health and Human Services, National Institute of Occupational Safety and Health; report No. HETA 86-063-1843.
- Danish EPA [Miljøstyrelsen] (2000): List of undesirable substances 2000. An advisory list of chemicals, the use of

which should be reduced or stopped in the long term. Environmental Review Nr. 9 2000. København.
- Danish Product Registry (2001): Data from Registry for 3333-67-3 nickel carbonate. February 1998.
- Dean JA (1973): Lange's Handbook of Chemistry. 11th. Edn. McGraw-Hill, New York.
- Delabarre P (1989): Occupational exposures during the production of catalysts containing inorganic nickel compounds. Polish J Occ Med **2**:357-366.
- Donaldson HM, Cassady M, Jones JH (1978) Environmental exposure to airborne contaminants in the nickel industry, 1976-1977. National Institute for Occupational Safety and Health, DHEW (NIOSH) Pub. No. 78-178, Cincinnati, OH.
- Doll R, Andersen A, Cooper WC, Cosmatos I, Cragle DL, Easton D *et al*. (1990): Report of the International Committee on Nickel Carcinogenesis in Man. Scand J Work Environ Health **16**, 1-82.
- EC (1994a): Commission Regulation (EC) 1488/94 of 28 June 1994 laying down the principles for the assessment of risks to man and the environment of existing substances in accordance with Council Regulation (EEC) No 793/93. OJ. L 161, 29.06.1994 p. 3 – 11
- EC (1994b): Council Directive 94/33/EC of 22 June 1994 on the protection of young people at work. OJ. L216, 20.8.1994, p. 12
- EC (1996): Council Directive 96/61/EC of 24 September 1996 concerning integrated pollution prevention and control. OJ. L257, 10.10.1996, p.26 – 40
- EC (1998a): Council Directive 98/24/EC of 7 April 1998 on the protection of the health and safety of workers from the risks related to chemical agents at work (fourteenth individual Directive within the meaning of Article 16(1) of Directive 89/391/EEC). OJ L131, 5.5.1998, p. 11.
- EC (1998b): Commission Directive 98/98/EC of 15 December 1998 adapting to technical progress for the 25 time Council Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances. O.J. L355, 30.12.1998, p. 1.
- EC (1999): Directive 1999/45/EC of the European Parliament and of the Council of 31 May 1999 concerning the approximation of the laws, regulations and administrative provisions of the Member States relating to the classification, packaging and labelling of dangerous preparations. O.J. L200, 30.7.1999, p. 1.
- EC (2000a): Directive 2000/60/EC of the European Parliament and of the Council of 23 October 2000 establishing a framework for Community action in the field of water policy. OJ. L 327, 22.12.2000, p. 1 – 73.
- EC (2000b): Commission Regulation (EC) No 2364/2000 of 25 October 2000 concerning the fourth list of priority substances as foreseen under Council Regulation (EEC) No 793/93. OJ L273, 26.10.2000, p. 5 - 7.
- EC (2000c): Directive 2000/76/EC of the European Parliament and of the Council of 4 December 2000 on the incineration of waste. OJ. L 332, 28.12.2000, p. 91 – 111
- EC (2001a): Commission Decision 2001/118/EC of 16 January 2001 amending Decision 2000/532/EC as regards the list of wastes. OJ. L47, 16.2.2001, p. 1 – 31
- EC (2001b): Commission Decision 2001/119/EC of 22 January 2001 amending Decision 2000/532/EC replacing Decision 94/3/EC establishing a list of wastes pursuant to Article 1(a) of Council Directive 75/442/EEC on waste and Council Decision 94/904/EC establishing a list of hazardous waste pursuant to Article 1(4) of Council Directive 91/689/EEC on hazardous waste. OJ. L 47, 16.2.2001, p. 32.
- EC (2001c): Commission Directive 2001/58/EC of 27 July 2001 amending for the second time Commission Directive 91/155/EEC defining and laying down the detailed arrangements for the system of specific information relating to dangerous preparations in implementation of Article 14 of European Parliament and Council Directive 1999/45/EC and relating to substances in implementation of Article 27 of Council Directive 67/548/EEC (safety data sheets)OJ. L212, 7.8.2001, p. 24 – 33.
- EC (2001d): Decision of the European Parliament and of the Council of 20 November 2001 establishing the list of priority substances in the field of water policy and amending Directive 2000/60/EC. OJ. L331, 15.12.2001, p. 1
- EC (2002a): Commission Communication 2002/C12/04: Adoption of eight reference documents for the purpose of Council Directive 96/61/EC concerning integrated pollution prevention and control. OJ C12, 16.1.2002. p.5.
- ECETOC, (1989): Technical Report N° 33, Nickel and Nickel compounds : Review of Toxicology and Epidemiology with Special reference to Carcinogenesis
- ECIS [European Customs Inventory of Chemical Substances] (1997): European Customs Inventory of Chemical Substances – A guide to the classification of chemicals in the Combined Nomenclature. Volume 1 – Alphabetical list of chemical products. Volume 2 – Numerical list (by CUS-Number) Correlation between CAS- and CUS-Numbers. Office for Official Publications of the European Communities. ISBN 92-828-0637-5. Also available online at http://europa.eu.int/comm./taxation_customs/databases/ecis_en.htm.
- ECMA, [European Catalyst Manufacturers Association] (2002): Confidential information on the catalyst industry submitted by individual companies in response to letter from Poul Anselme, CEFIC ECMA Manager, of 29. April, 2002.
- EEC (1976): Council Directive 76/464/EEC of 4 May 1976 on pollution caused by certain dangerous substances discharged into the aquatic environment of the Community. OJ. L129, 18.05.1976, p. 23 – 29

- EEC (1980): Council Directive 80/68/EEC of 17 December 1979 on the protection of groundwater against pollution caused by certain dangerous substances. OJ. L20, 26.1.1980, p. 43 – 48.
- EEC (1988): Council Directive 88/379/EEC of 7 June 1988 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the classification, packaging and labelling of dangerous preparations. OJ. L187, 16.7.1988, p. 14.
- EEC (1989): Council Directive 89/656/EEC of 30 November 1989 on the minimum health and safety requirements for the use by workers of personal protective equipment at the workplace (third individual directive within the meaning of Article 16 (1) of Directive 89/391/EEC). OJ. L393, 30.12.1989, p. 18 – 28.
- EEC (1990): Council Directive 90/394/EEC of 28 June 1990 on the protection of workers from the risks related to exposure to carcinogens at work (Sixth individual Directive within the meaning of Article 16 (1) of Directive 89/391/EEC). OJ. L196, 26.7.1990, p. 1.
- EEC (1991a): Commission Directive 91/632/EEC of 28. October 1991 adapting to technical progress for the fifteenth time Council Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances. OJ. L 338, 10.12.1991 p. 23 – 24; OJ. L338A, 10.12.1991, p. 1.
- EEC (1991b): Council Directive 91/689/EEC of 12 December 1991 on hazardous waste. OJ. L377, 31.12.1991, p. 20 – 27
- EEC (1992a): Council Directive 92/32/EEC of 30 April 1992 amending for the seventh time Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances. O.J. L154, 5.6.1992, p. 1.
- EEC (1992b): Council Directive 92/85/EEC of 19 October 1992 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 (tenth individual Directive within the meaning of Article 16 (1) of Directive 89/391/EEC). OJ. L348, 28.11.1992, p. 1.
- EEC (1993) Council Regulation (EEC) 793/93 of 23 March 1993 on the evaluation and control of the risks of existing substances. OJ. L 84, 05.04.1993 p.1 -75
- Enterline PE, Marsh GM (1982): Mortality among workers in a nickel refinery and alloy manufacturing plant in West Virginia. J. Natl. Cancer Inst., **68**: 925-933.
- Eramet (2002): Eramet Comments and proposals to working draft of nickel chloride risk assessment. Christian Plazanet, Eramet. 14. October, 2002.
- ERAMET-SLN [Entreprise de Recherches et d'Activités Métaux – Société le Nickel] (1989): Nickel sulphate. Nickel Chloride. Estimated Quantity of product per year, Paris. (quoted in IARC, 1990).
- Eurocolour (2002): Letter and document from Eurocolour to Danish Rapporteur, 1. August, 2002.
- European Commission (1996): Technical Guidance Document in support of Commission Directive 93/67/EEC on Risk Assessment for New Notified Substances and Commission Regulation (EC) No. 1488/94 on Risk Assessment for Existing Substances. 1996. Luxembourg: Office for Official Publications of the European Communities. Part I: General Introduction and Risk Assessment for Human Health, CR-48-96-001-EN-C, ISBN 92-827-8011-2. Part II: Environmental Risk Assessment, CR-48-96-002-EN-C, ISBN 92-827-8012-0. Part III: Use of QSAR, Use Categories, Risk Assessment Format, CR-48-96-003-EN-C, ISBN 92-827-8013-9. Part IV: Emission Scenario Documents. CR-48-96-004-EN-C, ISBN 92-827-8014-7.
- European Commission (1997): Corrigendum: Technical Guidance Document in support of Commission Directive 93/67/EEC on risk assessment for new notified substances and Commission Regulation (EC) 1488/94 on risk assessment for existing substances. 1997. Luxembourg, Office for Official Publications of the European Communities. Part II. EC Catalogue No. CR-48-96-002-EN-C.
- European Commission (1998): Technical Guidance Document on development of risk reduction strategies. January 1998. Luxembourg, Office for Official Publications of the European Communities. ISBN 92-828-3296-1.
- European Commission (2000): Ambient Air Pollution by As, Cd and Ni Compounds. Position paper Final Version October 2000. Working Group on Arsenic, Cadmium and Nickel Compounds. Luxembourg, Office for Official Publications of the European Communities. ISBN 92-894-2054-5. 2001.
- European Commission (2002a): List of EU High production volume chemicals. ESIS (Existing Substances Information Service) (http://ecb.jrc.it/ESIS). European Chemicals Bureau, IHCP, JRC Ispra.
- European Commission (2002b): List of EU Low production volume chemicals. ESIS (Existing Substances Information Service) (http://ecb.jrc.it/ESIS). European Chemicals Bureau, IHCP, JRC Ispra.
- European Commission (2004): Summary Record, Commission Group of Specialised Experts in the fields of Carcinogenicity, Mutagenicity and Reproductive Toxicity, Meeting at Arona, 20-21 April 2004. ECBI/74/04 Rev. 2, 2.8.2004
- FDRL (1983):. Acute oral LD50 study in rats. Study N° 7702E submitted to NiPERA 1983. Food and Drug Research Laboratories. Inc. POB 107, Rt 17C, Waverly, N.Y., U.S.A., 14892-0107,
- Finland (2000): Ministry of the Environment Legislation No. 2000/86.

- Ghezzi I, Baldasseroni A, Sesana G, Boni C, Cortona G, Alessio L (1989): Behavior of urinary nickel in low-level occupational exposure. Med Lav **80**: 244-250.
- Gmelin (1966). Gmelins Handbuch der Anorganischen Chemie, 8te Aufl. Nickel (System-Nummer 57), Teil B – Lieferung 3, Verlag Chemie, Weinheim
- Grandjean P (1986): Health Effects Document on Nickel, Odense, Department of Environmental Medicine, Odense University.
- Heiskanen J (2003): Information supplied by the Finnish Environment Institute, Chemicals Division to Danish Rapporteur, 27. February, 2003.
- Hostynek JJ; Dreher F; Nakada T; Schwindt D; Anigbogu A; Maibach HI (2001a): Human Stratum Corneum Adsorption of Nickel Salts: Investigation of Depth Profiles by Tape Stripping in vivo. Acta Derm Venereol **S212**: 11-18.
- Hostynek JJ; Dreher F; Pelosi A; Anigbogu A; Maibach HI (2001b): Human Stratum Corneum Penetration by Nickel: In vivo Study of Depth Distribution after Occlusive Application of the Metal as Powder. Acta Derm Venereol **S212**: 5-10.
- Hughson, GW (2004): An occupational hygiene assessment of dermal nickel exposures in primary production industries. A research project carried out for Nickel Producers Environmental Research Association (NiPERA). Institute of Occupational Medicine, Edinburgh, November2004.
- IARC (1990): IARC Monographs on the evaluation of carcinogenic risks to humans, Volume 49, Chromium, nickel and welding. IARC, Lyon, France, 1990. p.257-446.
- Inco (1981-1982): INCOMOND, Nickel Plating Chemicals, The International Nickel Company, New York.
- InfoMil (2003): Letter from Linda van Berkel to J. Hart, 18. April 2003.
- INSG [International Nickel Study Group] (2001): INSG World Nickel Statistics, No. 11, November 2001.
- IPCS (1991): Environmental Health Criteria 108: Nickel. World Health Organisation, Geneva. 383 p.
- ISO [International Standards Organization] (1992): Air quality - particle size fraction definitions for health-related sampling. Technical report ISO/TR/7708-1983, ISO, Geneva, 1983 (revised 1992).
- IUCLID (2002): IUCLID Data set for nickel carbonate. Prepared by Parametrix Inc. for NiPERA. Last revised|: 05.04.2002.
- Kemi [Swedish National Chemicals Inspectorate] (2002): Information from the Swedish Product Register. Letter from Bent-Ove Lund to Danish Rapporteur of 15. January 2002
- Kenny LC, Aitken R, Chalmers C, Fabriès, Gonzalez-Fernandez E, Kromhout H, Liden G, Mark D, Riediger G, Prodi V (1997): A collaborative European study of personal inhalable aerosol sampler performance. Ann Occup Hyg **41**: 135-153.
- Kiilunen M, Utela J, Rantanen T, Norppa H, Tossavainen A, Koponen M, Paakkulainen H, Aitio A (1997a): Exposure to soluble nickel in electrolytic nickel refining. Ann Occup Hyg **41**: 167-188.
- Kiilunen M, Aitio A, Tossavainen A (1997b): Occupational exposure to nickel salts in electrolytic plating. Ann Occup Hyg **41**: 189-200.
- Königswarter & Ebell (2003): Letter from Thomas Hindenburg to Danish Rapporteur, 31. July, 2003.
- Königswarter & Ebell (2004): pH of nickel(hydroxy)carbonate solution. Letter from Thomas Hindenburg to Danish Rapporteur, 28. May 2004.
- Laget S (2003): Umicore Information on import and export of nickelhydroxy carbonate. Letter to J. Hart, 16. April, 2003.
- Laine L (2001): Description of nickel carbonate. Letter to Sally Williams, June 11, 2001.
- Laine L (2002a): Details of CAS numbers for nickel carbonate substances. Letter to Sally Williams, 24. October, 2002.
- Laine L (2002b): Comments on draft risk assessment, Chapters 1 & 2, of November 2002. Letter to J. Hart, 28. November, 2002.
- Laine L (2003a): Import and export statistics for nickel salts. Information on nickel (hydroxy)carbonate. Letter to S. Williams, 8. April, 2003.
- Laine L (2003b): Comments on draft risk assessment. Letter to J. Hart, 9. April, 2003.
- Laine L (2003c): Information for draft risk assessment. Letter to J. Hart, 17. April, 2003.
- Laine L (2003d): Nickel Carbonate Derogation Statement, 29.04.2003.
- Laine L (2004a): pH of nickel(hydroxy)carbonate solution. Letter to Danish Rapporteur. 6. May 2004.
- Laine L (2004b): Derogation statement for physical-chemical data of nickel hydroxycarbonate, 30.07.2004.
- Lascelles K, Morgan L, Nicholls D (1991): Nickel Compounds. In: Ullmann's Encyclopaedia of Industrial Chemistry. 5. Edition. Volume A.17. Elves B, Hawkins S, Schulz G. (Eds.) VCH, Weinheim. 1991.
- Leidell NA, Busch KA, Lynch JR (1977): Occupational exposure sampling strategy manual. DHEW (NIOSH) Pub No 77-173, National Institute for Occupational Safety and Health, Cincinnati, Ohio, USA.
- Lepicard S, Schneider T, Fritsch P, Maximilien R, Deloraine A (1997): Risk Assessment for Nickel and Nickel

Compounds in the Ambient Air from Exposure by Inhalation. Fontenay aux roses Cedex: CEPN Centre d`etude sur l`Evaluation de la Protection dans le domaine Nucléaire.

- Li SN, Lundgren DA, Rovell-Rixx D (2000): Evaluation of six inhalable aerosol samplers. Am Ind Hyg Assoc J **61**: 506-516.
- Lichtenwalner CP (1992): Evaluation of wipe sampling procedures and elemental surface contamination. Am Ind Hyg Assoc J **53**: 657-659.
- McArthur B (1992): Dermal measurement and wipe sampling methods: a review. Appl Occup Environ Hyg **7**: 599-606.
- Mahieu JC, Oury B, Boulet a (1990): Caratèristiques de l'èmission d'aërosols des bains de nickelage. Cah. Notes Doc., **139**, 313-322.
- Mark D, Vincent JH (1986): A new personal sampler for airborne total dust in workplaces. Ann Occup Hyg **30**: 89-102.
- Mark D, Lyons CP, Upton SL, Kenny LC (1994): Wind tunnel testing of the sampling efficiency of personal inhalable aerosol samplers. J Aerosol Sci **25** (suppl 1): S339-S340.
- Meyer-Wulf C (2002): Comments on draft nickel sulphate risk assessment report March 2002
- Montaldi A, Zentalin L, Vernier P, Gola I, Bianchi V, Paglialunga S, Levis AG (1985): Interaction of nitrilotriacetic acid with heavy metals in the induction of sister chromatid exchanges in cultured mammalian cells. Environ. Mutagen. **7**: 381-390.
- Montaldi A, Zentalin L, Zordan M, Bianchi V, Levis AG, Clonfero E, Paglialunga S (1987): Chromosomal effects of heavy metals (Cd, Cr, Hg, Ni and Pb) on cultured mammalian cells in the presence of nitrilotriacetic acid (NTA). Toxicol. Environ. Chem. **14**: 183-200.
- Netherlands (1974): Uitvoeringsbesluit artikel 1, derde lid, Wet verontreiniging oppervlakte wateren (Wvo) of 28. November, 1974.
- Netherlands (1997): Lozingbesluit bodembescherming of 8. December, 1997.
- Netherlands (2001): Nedenlandse emissionsrichtlinjen lucht (NeR) [Netherlands Emissions Guidelines for Air]. November 2001. http://www.infomil.nl.
- Netherlands Rapporteur (2003): Risk Assessment, Zinc Oxide. Part 2: Human Health. Draft of May 2003.
- Netherlands RIVM (2002): From concentration to dose: factors influencing airborne particulate matter deposition in humans and rats. Winter-Sorkina R & Cassee FR. RIVM report 650010031/2002.
- Nielsen GD, Søderberg U, Jørgensen PJ, Templeton DM, Rasmussen SN, Andersen KE, Grandjean P (1999): Absorption and retention of nickel from drinking water in relation to food intake and nickel sensitivity. Toxicol Appl Pharmacol **154**, 67-75.
- NiPERA (1996) (in collaboration with Eurométaux for DG V): Occupational exposure limits: Criteria Document for nickel and nickel compounds. Volume I: Summary, Conclusions and Recommendations; Volume II: Assessment of Occupational Exposures; Volume III: Health Assessment of various species of Nickel. Prepared by NiPERA in collaboration with Eurométaux for the European Commission, Directorate General V. Public health and Safety at Work Directorate. Batiment Jean Monnet, Plateau du Kirchberg. L-2920 Luxembourg.
- NiPERA (2003): Review of nickel mutagenicity studies in vivo and their implications for risk assessment. January 31. 2003. Circulated by ECB as: COM311+312+419+420+424_hh_IND1.
- NMR [Nordic Council of Ministers] (2002): Overview of some important Directives relating to Community level risk reduction of chemicals. http://www.norden.org/miljoe/sk/ January02 version.pdf
- NTP [National Toxicology Program] (1996a): Technical Report on the toxicology and carcinogenesis studies of nickel sulfate hexahydrate (CAS NO. 10101-97-0) in F344/N rats and B6C3F1 mice. (Inhalation studies). National Institutes of Health, Springfield (VA). National Toxicology Program Technical Report Series 454 (NIH Publication No. 96-3370): 376 p.
- NTP [National Toxicology Program] (1996b). Technical Report on the toxicology and carcinogenesis studies of nickel oxide (CAS NO. 1313-99-1) in F344/N rats and B6C3F1 mice. (Inhalation studies). National Institutes of Health, Springfield (VA). National Toxicology Program Technical Report Series 451 (NIH Publication No. 96-3370): 376 p.
- NTP [National Toxicology Program] (1996c). Technical Report on the toxicology and carcinogenesis studies of nickel subsulphide (CAS NO. 12035-72-2) in F344/N rats and B6C3F1 mice. (Inhalation studies). National Institutes of Health, Springfield (VA). National Toxicology Program Technical Report Series 453 (NIH Publication No. 96-3370).
- O'Dell GD, Miller WJ, King WA, Moore SL, Blackmon DM (1970): Nickel toxicity in the young bovine. J. Nutrition, **100(12)**: 1447-54.
- Oliveira JP, Pereira Bastos de Siqueira ME, Sergio da Silva C (2000): Urinary nickel as bioindicator of workers' Ni exposure in a galvanizing plant in Brazil. Int Arch Occup Environ Health **73**:65-68.
- OMG Harjavalta Nickel Oy (2003): Comments on draft risk assessment. Letter to J. Hart, 9. April, 2003.
- OMG Harjavalta Nickel Oy (2004): Water octanol distribution coefficient Kow for nickel hydroxyl carbonate.

Report of 29.11.2004
- Payne WW (1964): Carcinogenicity of nickel compounds in experimental animals (Abstract No. 197). Proc. Am. Assoc. Cancer Res., **5**:50.
- PCF (2003): Letter from Jaques-Antoine Rondeau to Danish Rapporteur, 29. July, 2003.
- PCF (2004): Letter from Laurence Vey to Danish Rapporteur, 3. June 2004.
- Pharmacie Centrale (1988): Nickel carbonate. Paris. (Quoted from IARC, 1990).
- Phatak SS, Patwardham VN (1950): Toxicity of nickel. J. Sci. Ind. Res. **9B**: 70-76.
- Pott F, Rippe RM, Roller M, Csicsaky M, Rosenbruch M, Huth F. (1989): Tumours in the abdominal cavity of rats after intraperitoneal injection of nickel compounds. In: Proceedings of the International Conference on heavy Metals in the Environment. Geneva, 12-15 September, 1989. Vol. 2. Ed.: Vernet JP. World Health Organisation, Geneva. p. 127-129.
- Pott F, Rippe RM, Roller M, Csicsaky M, Rosenbruch M, Huth F. (1992): Carcinogenicity of nickel compounds and nickel alloys in rats by intraperitoneal injection. In Nickel in Human Health: Current Perspectives. Nieboer E, Nriagu IO, Eds., Wiley New York. pp. 491-502. (Cited in IARC 1990 as Pott *et al.*, 1990: In press.).
- Sanner T (2002): Draft quantitative risk assessment for nickel and nickel compounds. Document supplied to Danish Rapporteur. 22. February, 2002.
- Sanner T, Dybing E, Willems MI, Dinant Kroese ED (2001): A simple method for quantitative risk assessment of non-threshold carcinogens based on the dose descriptor T25. Pharmacol Toxicol. **88**: 331-341.
- Sibley SF (1985): Nickel. In: Mineral facts and Problems, 1985 ed. (Preprint from Bulletin 675). Washington DC. Bureau of Mines, pp. 1-17.
- Skeaff J, King P (2002): Transformation Tests of nickel carbonate hydroxide in aqueous media OECD 203 for hazard identification. Work performed for NiPERA/ Project 602341. Report MMSL 01-051(CR). CANMET-MMSL.
- SLI (1999): A dermal irritation/corrosivity study in rabbits with nickel sulphate hexahydrate. Final report 3472.1. December 16, 1999. Springborn Laboratories, Inc. Spencerville, Ohio, USA.
- SLI (1999): A dermal irritation/corrosivity study in rabbits with Inco© Type 123 nickel powder. Final report 3472.5. December 16, 1999. Springborn Laboratories, Inc. Spencerville, Ohio, USA.
- SLI (1999): A primary eye irritation study in rabbits with nickel sulphate hexahydrate. Amended Final report 3472.2. November 23, 1999. Springborn Laboratories, Inc. Spencerville, Ohio, USA.
- Stamm R, Bock W, Breuer D, Hahn JU, Kleine H, Pfeiffer W, Pflaumbaum W, Stückrath M, Blome H (1998):Zur Expositionssituation krebserzeugender Gefahrstoffe am Arbeitsplatz. BIA-Report 2/96. Hauptverband der gewerblichen Berufsgenossenschaften, Sankt Augustin, Germany.
- Symanski E, Chang CC, Chan W (2000): Long-term trends in exposures to nickel aerosols. Am Ind Hyg Assoc J **61**: 324-333.
- Symanski E, Chan W, Chang CC (2001): Mixed-effects models for the evaluation of long-term trends in exposure levels with an example from the nickel industry. Ann Occup Hyg **45**: 71-81.
- TA Luft (2002): Bundesministerium für Umwelt, Naturschutz und Reaktorsicherheit. Erste Allgemeine Verwaltungsvorschrift zum Bundes-Immisionsschutzgesetz (Technische Anleitung zur Reinhaltung der Luft – TA Luft) Vom 24. Juli, 2002. GMBl. 2002, Heft 25 - 29, p. 511 - 605. (In German).
- TERA (1999): Toxicological review of soluble nickel salts. Prepared for: Metal Finishing Association of Southern California, Inc., US Environmental Protection Agency and Health Canada. Prepared by Toxicology Excellence for Risk Assessment (TERA) under subcontract in part with Science Applications International Corporation (SAIC). EPA Contract #68-C7-0011. March 1999.
- Thomassen I, Niebor E, Ellingsen D, Hetland S, Norseth T, Odland JØ, Romanova N, Chernova V, Tchachtchine VP (1999): Characterisation of workers' exposure in a Russian nickel refinery. J Environ Monit **1**: 15-22.
- Tola S, Kilpiö J, Virtamo M (1979): Urinary and plasma concentrations of nickel as indicators of exposure to nickel in an electroplating shop. J Occ Med **21**: 184-188.
- TRGS 900 (2000): Technische Regeln für Gefahrstoffe TRGS 900 Grenzwerte in der Luft am Arbeidsplatz "Luftgrenzewerte". Ausgabe Oktober 2000, BarbBl. 2000-10 p. 34, zuletzt geändert BarbBl. 2002-10 s. 76.
- TRGS 905 (2002): Technische Regeln für Gefahrstoffe TRGS 905. Verzeichnis krebserzeugender, erbutverändernder oder fortpflanzungsgefährdender Stoffe. Ausgabe: März, 2001, zuletzt geändert BarbBl. Heft 3-2003.
- Tsai PJ, Vincent JH, Wahl G, Maldonado G (1995): Occupational exposure to inhalable and total aerosol in the primary nickel production industry. Occ Env Med **52**: 793-799.
- Tsai PJ, Werner MA, Vincent JH, Maldonado G (1996a): Worker exposure to nickel-containing aerosol in two electroplating shops: Comparison between inhalable and total aerosol. Appl Occ Env Hyg **11**: 484-492.
- Tsai PJ, Vincent JH, Wahl G, Maldonado G (1996b): Worker exposures to inhalable and total aerosol during nickel alloy production. Ann Occ Hyg **40**:651-659.
- Tsai PJ, Vincent JH.(2001): A study of workers' exposures to the inhalable and total aerosol fractions in the

primary nickel production industry using mannequins to simulate personal sampling. Ann Occ Hyg **45**: 385-394.

- UK EGVM [Expert Group on Vitamins and Minerals] (2003): Safe Upper Levels for Vitamins and Minerals. Food Standards Agency, May 2003. ISBN 1-904026-11-7. Available at: http://www.foodstandards.gov.uk/multimedia /pdfs/evm_nickel.pdf
- UK HSE [Health & Safety Executive] (1987): Toxicity Review 19. The toxicity of nickel and its organic compounds. Health and Safety Executive. HMSO. ISBN 0 11 883961 6
- UK HSE [Health & Safety Executive] (2000): Occupational Health Limits 2000. Report EH40.
- UN (2001): Recommendations on the Transport of dangerous Goods. Model Regulations. Twelfth revised Edition. ST/SG/AC.10/1/Rev.12. United Nations, New York & Geneva, 2001.
- UN ECE [Economic Commission for Europe] (2001a): European Agreement concerning the international carriage of dangerous goods by inland waterways. ECE/TRANS/150. United Nations, New York & Geneva, 2001.
- UN ECE [Economic Commission for Europe] (2001b): Restructured ADR applicable as from 1 July 2001. European Agreement concerning the international carriage of dangerous goods by road. ECE/TRANS/140 (Vols. I & II). United Nations, New York & Geneva, 2001.
- US ATSDR [Agency for Toxic Substances and Diseases Registry] (1997): Toxicological Profile for Nickel. September 1997. US Department of Health and Human Services, Public Health Service.
- US EPA [Environmental Protection Agency] (1991a): Integrated Risk Information System (IRIS). Reference concentration (RfC) for inhalation exposure for nickel refinery dust (http://www.epa.gov/iris/subst/0272.htm) Cincinnati, OH, (revised 01/01/1991).
- US EPA [Environmental Protection Agency] (1991b): Integrated Risk Information System (IRIS). Reference concentration (RfC) for inhalation exposure for nickel subsulfide (http://www.epa.gov/iris/subst/0273.htm). Cincinnati, OH. (revised 01/01/1991).
- Uter W, Fuchs T, Hausser M, Ippen H (1995): Patch test results with serial dilutions of nickel sulfate (with and without detergent), palladium chloride, and nickel and palladium metal plates. Contact Dermatitis **32**, 135-42.
- Vincent JH, Mark D (1990): Entry characteristics of practical workplace aerosol samplers in relation to the ISO recommendations. Ann Occup Hyg **34**: 249-262.
- Vincent JH, Werner MA (2003): Critical evaluation of historical occupational aerosol exposure records: Applications to nickel and lead. Ann Occup Hyg **47**: 49-59.
- Wall LM, Calnan CD (1980): Occupational nickel dermatitis in the electroforming industry. Contact Derm **6**: 414-420.
- Warner JS. (1984): Occupational exposure to airborne nickel in producing and using primary nickel products. In: Nickel in the human environment. Proceedings of a joint symposium held at IARC, Lyon, France, 8-11 March 1983. Sunderman FW (Editor in chief). International Agency for Research on Cancer (IARC), Lyon: IARC scientific publications No. 53, pp. 419-37.
- Werner MA, Spear TM, Vincent JH (1996): Investigation into the impact of introducing workplace aerosol standards based on the inhalable fraction. Analyst **121**:1207-1214.
- Werner MA, Vincent JH, Thomassen Y, Hetland S, Berge S (1999): Inhalable and 'total' metal and metal compound aerosol exposures for nickel refinery workers. Occ Hyg **5**: 93-109.
- WHO [World Health Organisation]: (1999): Nickel. In: Air Quality Guidelines for Europe. WHO Regional Publication Copenhagen. pp. 162-165.
- Zatka VJ, Warner JS, Maskery D (1992): Chemical speciation of nickel in airborne dusts: analytical methods and results of an interlaboratory test program. Env Sci Tech **26**,138-144.

7. APPENDICES

7.1 EUSES RISK CHARACTERISATION RESULT TABLE

7.2 EUSES SUMMARY REPORT

7.3 IUCLID DATA SET

7.4 REVISED 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
028-010-00-0	nickel carbonate; basic nickel carbonate; carbonic acid, nickel (2+) salt; [1] carbonic acid, nickel salt; [2] [μ-[carbonato(2-)-*O*:*O*']] dihydroxy trinickel; [3] [carbonato(2-)] tetrahydroxytrinickel [4]	E	222-068-2 [1] 240-408-8 [2] 265-748-4 [3] 235-715-9 [4]	3333-67-3 [1] 16337-84-1 [2] 65405-96-1 [3] 12607-70-4 [4]	Carc Cat 1; R49 Muta. Cat. 3; R68 Repr. Cat. 2; R61 Xn; R20/22 T; 48/23 Xi; R38 R42/43 N; R50-53.	T; N R: 49-61-20/22-38-42/43-48/23-50/53 S: 53-45-60-61		

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