SIDS INITIAL ASSESSMENT PROFILE

CAS No.	CAS-No.: 7440-02-0, 7786-81-4, 3333-67-3 (12122-15-5, 12607-70-4), 7718-54-9, 13138-45-9
Chemical Name	Nickel (metal), Nickel Sulphate, Nickel Carbonate (2:3 basic nickel carbonate, 1:2 basic nickel carbonate), Nickel Chloride, Nickel Dinitrate
Structural Formula	Ni , $NiSO_4$, $NiCO_3$, $Ni(OH)_2$, $NiCl_2$, $Ni(NO_3)_2$

SUMMARY CONCLUSIONS OF THE SIAR

READ ACROSS JUSTIFICATION FOR HUMAN HEALTH

This group of five nickel chemicals, nickel, nickel sulphate, nickel chloride, nickel dinitrate and nickel carbonate are presented in this SIAP together as read across has been done in a number cases where available test data alone did not fulfill the SIDS requirements. Data from other nickel compounds than the five nickel substances covered by this SIAP have been used where relevant to support the conclusions concerning the hazard identification of the five selected nickel substances. It is expected that the nickel cation is the determining factor for systemic toxicity and toxicity to environmental organisms.

The conclusions of the SIAR for nickel chloride (CAS No. 7718-54-9) do not apply to a second compound, nickel chloride, (CAS No. 37211-05-5) as this substance is a Ni1+ compound.

The conclusions of the SIAR for nickel dinitrate also apply to a second compound, nitric acid, nickel salt (CAS No. 14216-75-2).

CATEGORY JUSTIFICATION FOR ENVIRONMENT

Nickel and the four nickel salts are HPV chemicals prioritized for comprehensive risk assessment within the EU Existing Substances Regulation. Apart from the administrative and legal purpose, the main reason for providing a background SIAP and SIAR on all of these nickel compounds are that they release the biologically active form, i.e. ionic Ni^{2+} in the environment and in the tissues of organisms. Therefore, ecotoxicological effects and systemic effects in organisms can be considered together for these substances.

BACKGROUND

A large amount of information was provided by industry for the compilation of the data presented in the SIAR. Additional data on nickel from published literature 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) [See reference list in full SIAR]. The effects of nickel on the skin have also been reviewed (Maibach & Menné, eds. 1989, Hostýnek and Maibach, 2002). 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 health reviews plus (where considered relevant) the primary literature, have been used widely in assembling the SIAR as it was determined 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 the SIAR have been checked and studies have often been described in a summary form. To ensure transparency in the SIAR, when information was cited from reviews, the primary source was given with the notation “quoted from”.

The ecotoxicological data in this report were derived from comprehensive new research activities and from

original papers on the subject, published in international journals. Databases searched for literature included NiPERA CAB abstracts (1972-2006), Current Contents, Science Direct, IS Web of Science, and AGRICOLA. Review articles covering nickel in the environment were also searched for data sources, as were draft Effects Assessments for Water, Sediment, and Soil that were prepared by the Danish Rapporteur in 2004. Only original literature was quoted.

This document provides relevant hazard information for all nickel substances which release Ni^{2+} and where the effects can be attributed to this nickel ion.

Nickel metal is commonly divided into two product categories. Class I nickel products are metallic nickel with a nickel content of 99% or more. Class II nickel products include metallic nickel of lower purity as well as nickel oxides and ferronickel. The conclusions of the SIAR covers metallic nickel (CAS No.: 7440-02-0) of both Class I and II.

The CAS numbers shown above for the four nickel salts refer to the anhydrous compounds, and follow the EU convention in relation to EINECS numbers of including both the anhydrous and hydrated forms of the compound under the same number. The conclusions of the SIARs apply to all the hydrated forms of the four salts.

The identity of the nickel carbonates covered by the SIAR is particularly complex. The name "nickel carbonate" is most often used as a common class name rather than to identify the simple salt $NiCO_3$, and most of the commercial "nickel carbonates" are described more appropriately as basic nickel carbonates with a general formula $xNiCO_3.yNi(OH)_2.zH_2O$. The SIAR refers to "nickel carbonate" throughout, although this also covers both the 2:3 basic carbonate (CAS No. 12122-15-5) and the 1:2 basic carbonate (CAS No. 12607-70-4) which are regarded as the commercial product.

PHYSICAL-CHEMICAL PROPERTIES

Nickel chloride: exists as a hydrated crystalline powder. The solubility of nickel chloride hexahydrate at 20°C is 2540 g/L. Vapour pressure for nickel chloride is 1 mm Hg at 671°C. Octanol-water partition coefficients for nickel sulphate are not relevant.

Nickel dinitrate: exists as a hydrated crystalline powder. The solubility of nickel dinitrate at 0°C is 2385 g/L. No data are available on the vapour pressure for nickel dinitrate. Octanol-water partition coefficients for nickel dinitrate are not relevant.

Nickel hydroxycarbonate: exists as a hydrated crystalline powder. The solubility of nickel oxycarbonate in water is rather low, with the solubility product KSP ranging from 10-7 to 10-8. No data are available on the vapour pressure for nickel oxycarbonate. Octanol-water partition coefficients for nickel oxycarbonate are not relevant.

Nickel sulphate: exists as a hydrated crystalline powder. The solubility of nickel sulphate hexahydrate at 0°C is 625 to 655 g/L. No data are available on the vapour pressure of nickel sulphate. Octanol-water partition coefficients for nickel sulphate are not relevant.

Nickel metal: exists in virtually all forms, shapes and particle sizes. Nickel metal can be regarded as insoluble in water. Vapour pressure for nickel metal is 133 Pa at 1810°C.

The Octanol-water partition coefficients are not relevant for inorganic substances.

HUMAN HEALTH

The following Table shows the availability of human health effect data for the five nickel compounds.

Nickel compound	Human Health effects Table of data availability						
	Acute	Irritation	Sensi-tisation	Repeated dose	Muta-genicity	Carcino-genicity	Repro ductive toxicity
nickel metal	□	□	□	□	(□)	(□)	-

nickel sulfate	□	□	□	□	□	□	□
nickel chloride	□	(□)	□	□	□	□	□
nickel dinitrate	□	□	(□)-	-	□	-	-
"nickel carbonate"	□	(□)	-	(-)	(□)	-	-

Key: "□" denotes sufficient data were available for the substance/endpoint. "(□)" indicates that there was some data, but not enough to draw a direct conclusion "(-)" indicates only very limited data from which no conclusions can be drawn. "-" denotes no data available.

In all cases except for "□" read across has been performed to varying extents as described in more detail in the SIARs

Toxicokinetics

The available data on nickel sulfate and nickel chloride indicate that the absorption of nickel following inhalation of the respirable fraction (particulates with an aerodynamic diameter below 5 µm) might be as high as up to 97-99% in experimental animals. No human data were available. The fraction absorbed apparently depends on the concentration of the nickel compound in the inhaled air as well as on the duration of exposure. No data regarding the absorbed fraction of nickel in humans or experimental animals following inhalation of nickel dinitrate or nickel carbonate have been located.

The absorbed fraction of nickel from the respiratory tract following exposure by inhalation of nickel sulfate, nickel chloride, nickel dinitrate and nickel carbonate for the respirable fraction is considered to be 100%.

No data regarding the absorbed fraction of metallic nickel in humans following inhalation of nickel metal have been located. Data from a 13-week inhalation study in rats exposed to nickel powder with a mean particle size of 1.2 µm showed pulmonary accumulation of nickel particles. The particles were found to be slowly eliminated following pulmonary absorption, as decreases in nickel lung burden and increases in nickel blood level were found in the animals throughout a 90-day exposure free recovery period. As a rough upper estimate, an absorbed fraction of 6% (pulmonary + gastrointestinal absorption) has been calculated based on data from repeated inhalation exposure of 1 mg/m^3 of nickel powder in the 13-week study in rats.

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 thus absorbed according to the absorption rate for oral exposure.

Other data on nickel oxide indicate that the absorption of nickel from the respiratory tract following inhalation of insoluble nickel compounds is very limited.

The absorbed fraction of nickel following oral ingestion can be as high as 27% when nickel sulfate is administered in drinking water to fasting individuals while the absorbed fraction seems to be around 1 to 5% when nickel sulfate is administered together with food and to non-fasting individuals based on studies with human volunteers. The absorbed fraction of nickel following oral ingestion of nickel chloride was up to about 10% and for nickel dinitrate up to 34% in studies in rats. No human data were available. The fasting status of these animals was not reported but the compounds were administered in a 5 % starch saline solution by gavage. No data were available for nickel carbonate, although there was a study in rats which demonstrated that appreciable quantities of nickel from diets containing nickel carbonate were retained and tissue accumulation was significant. Based on human data for nickel sulfate, the absorbed fraction of nickel following oral ingestion of nickel sulfate, nickel chloride, nickel dinitrate and nickel carbonate is considered to be 30% for fasting individuals and 5% in all other situations.

The absorbed fraction of nickel following oral administration of nickel metal in 5% starch saline solution by gavage was about 0.09% in a study in rats. No human data were available. Based on

this study in rats, which indicates a 100-fold lower absorption of nickel following administration of nickel metal than for soluble nickel compounds (by direct comparisons of the absorbed fractions), the absorbed fraction of nickel following oral ingestion of nickel metal is considered to be 0.3% for fasting individuals and 0.05% in all other situations.

Other data on insoluble nickel compounds (nickel oxides and nickel sulphides) indicate that absorption of nickel from the gastrointestinal tract may occur following oral exposure; however, the data were too limited for an evaluation of the absorbed fraction of nickel.

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 were too limited for an evaluation of the absorbed fraction of nickel following dermal contact to the five nickel compounds. A recent *in vitro* study with human stratum corneum indicated an absorbed fraction of about 1-1.5% for nickel sulfate, nickel chloride and nickel dinitrate. Thus, the absorbed fraction of nickel following dermal contact to nickel sulfate, nickel chloride, nickel dinitrate, and nickel carbonate is considered to be 2%. A recent human *in vivo* study with nickel metal showed that around 0.2% remained in the stratum corneum. The absorbed fraction of nickel following dermal contact to nickel metal is therefore considered to be 0.2%.

Upon entry into the bloodstream, the nickel ion is bound to specific serum components and rapidly distributed throughout the body. In serum, nickel is present in three forms: 1) as a complex associated with albumin; 2) as a complex associated with a nickel-metalloprotein (nickeloplasmin); and 3) as ultrafiltrable material. In human serum, 40% of the nickel is present as ultrafiltrable material, 34% is associated with albumin, and 26% is associated with nickeloplasmin. Absorbed nickel is widely distributed in the body with tissue levels generally below 1 ppm; elevated tissue levels of nickel have been observed in the kidney, liver and lung. Generally, nickel tends to deposit in the lungs of workers occupationally exposed to nickel compounds and in experimental animals following inhalation or intratracheal instillation.

Nickel has been shown to cross the human placenta. Transplacental transfer has also been demonstrated in rats administered nickel carbonate or nickel metal catalyst in the diet, in mice following administration of nickel chloride by intraperitoneal injection, and in rats following administration of nickel by intramuscular injection.

The cellular uptake of soluble and insoluble nickel compounds are different as insoluble nickel compounds enter the cell via phagocytosis, while soluble nickel compounds are not phagocytised, but enter the cell via metal ion transport systems, particularly the magnesium transport system or through membrane diffusion. The latter two processes are much less efficient implicating that the same extracellular levels of soluble and insoluble nickel compounds lead to lower nickel levels intracellularly for soluble nickel compounds. Soluble forms of nickel interact with the cell in a way that maximises cytotoxicity and minimises nickel delivery to the nucleus, while insoluble forms of nickel interact with cells in a way that decreases the cytotoxic potential while increasing the delivery of nickel to the nucleus.

Absorbed nickel is excreted in the urine, regardless of the route of exposure; the half-life for urinary excretion in humans has been reported to range from 17 – 29 hours. 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 soluble nickel compounds accounts for 20-30% of a dose when the nickel compound is 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. Small amounts of absorbed nickel can also be excreted through other routes, including hair, saliva, sweat, tears, and milk. Inhaled nickel particles that are deposited in the respiratory tract can be eliminated from the airway by absorption from the lung or by removal via the mucociliary action. This latter fraction may subsequently be swallowed and enter the gastrointestinal tract. An elimination half-life of 30-60 days has been estimated for metallic nickel particles accumulated in lung tissue. The elimination is dependent on dissolution of the accumulated nickel particles followed by absorption and elimination of nickel from the blood.

Acute toxicity

There were no data for acute inhalation toxicity from properly conducted Guideline inhalation tests for any of the nickel compounds. Considering the acute oral toxicity of the soluble nickel

compounds (see below), the potential for an almost complete absorption via the respiratory tract of nickel from respirable nickel particulates, and observed lethality in rats in a 16-day inhalation study with nickel sulfate, there is a concern for acute inhalation toxicity. In the absence of acute inhalation toxicity data, data from repeated dose inhalation studies is used for the evaluation of acute inhalation toxicity. These data do not indicate a solubility-related difference in toxicity. A LOAEC of 0.7 mg Ni/m^3 for reduced body weight and adverse local effects in the respiratory tract (atrophy and inflammation) is determined for acute inhalation toxicity of nickel sulfate, nickel chloride, nickel dinitrate, and nickel carbonate from the 16-day rat inhalation study with nickel sulfate. The use of results from the repeated dose study is considered to be a conservative approach, since greater toxicity is expected from repeated exposure compared to a single 4-hour exposure as in the Guideline acute inhalation test. Data from an acute inhalation study in rats with nickel metal indicate a low order of toxicity via inhalation, however an acute inhalation LC_{50} value cannot be estimated from that study. For metallic nickel a NOAEC for acute inhalation toxicity of 10200 mg Ni/m^3 based on a 1-hour exposure duration is determined for mortality and signs of toxicity.

The five nickel compounds have been tested in acute oral toxicity tests.

	nickel sulfate	nickel chloride	nickel dinitrate	nickel carbonate	nickel metal
LD50 mg Ni/kg bw	61-72 to 112	43-51 to 105-130	330	402 - 625	> 9000
LD50 mg salt (hydrate) /kg bw	275-325 to 500 mg nickel sulfate hexahydrate /kg bw	175-210 to 432-535 mg nickel chloride hexahydrate /kg bw	1620 mg nickel dinitrate hexahydrate /kg bw	812 - 1263 mg nickel carbonate/kg bw	
Acute toxic class			range between 200 and 2000 mg/kg bw		

The results show that soluble nickel compounds are more toxic by the oral route than the insoluble salts. However, the very soluble nickel dinitrate appears to be less toxic than the other two soluble nickel compounds, with an LD_{50} value (1620 mg/kg bw) comparable to that for nickel carbonate. The nickel dinitrate LD_{50} study was reported in 1969 and may not be comparable to more recent studies, as the study was carried out in non-fasted animals and is probably an underestimate of the acute toxicity. However, a more recent toxic class method study with nickel dinitrate showed no mortality or signs of toxic symptoms at 200 mg nickel nitrate hexahydrate/kg bw.

Other data for nickel acetate show LD_{50} values of 350-360 mg /kg bw (115-118 mg Ni/kg bw) and for nickel hydroxide LD_{50} values of 1500-1700 mg /kg bw (915-1037 mg Ni/kg bw). The insoluble oxides and sulphides show LD_{50} values above 5000 mg /kg bw.

No data for acute dermal toxicity of the five nickel compounds were available. There is no concern for acute systemic effects following dermal exposure to nickel compounds due to poor absorption of nickel by this route.

Irritation/Corrosivity

The available data for skin irritation produced by the nickel salts indicate that they are skin irritants, although the data were not entirely consistent. Nickel sulfate caused only a slight degree of skin irritation in a Guideline study, whilst skin irritation was seen in humans following dermal exposure in concentrations above 20%. There is some evidence that nickel chloride is also an irritant in humans, possibly at lower concentrations. Nickel dinitrate was a skin irritant in an Guideline animal study. No data were available for nickel carbonate. On the basis of the human data for nickel sulphate, nickel carbonate is also considered a skin irritant.

The insoluble nickel metal did not cause skin irritation in a Guideline study and nickel metal is not

considered as a skin irritant.

The more limited data for eye irritation produced by the nickel salts were not consistent. Nickel sulfate caused only a slight degree of eye irritation in a Guideline study, whilst nickel dinitrate was a severe eye irritant in a Guideline study as irritation persisted at the end of the observation period. No data were available for nickel chloride, nickel carbonate or nickel metal. Based on the animal data nickel dinitrate is considered as a severe eye irritant whereas the other nickel compounds (nickel sulfate, nickel chloride, nickel carbonate, nickel metal) are not considered as eye irritants. However, mechanical irritation of the eye from nickel metal powder might occur.

Short-term repeated inhalation of soluble as well as insoluble nickel compounds is associated with lesions in the olfactory and lung epithelium. No data were found regarding respiratory irritation following a single inhalation exposure for any of the five nickel compounds. Based on the repeated dose toxicity data, there is a concern for respiratory irritation of nickel compounds although the available data do not allow a firm conclusion on acute respiratory irritation.

Sensitisation

All five compounds are regarded as skin sensitisers in humans. Nickel sulfate is a skin sensitiser in humans and in experimental animals. Nickel chloride is a skin sensitiser in experimental animals and can elicit an allergic reaction in nickel sensitive humans. Nickel dinitrate can elicit an allergic reaction in nickel sensitive humans. Nickel metal is a skin sensitiser in humans. No data were available for nickel carbonate. The Ni^{2+} ion is considered exclusively responsible for the immunological effects of nickel.

For nickel metal, the experience in Denmark following the introduction of legislation with a cut-off release rate of 0.5 µg Ni/cm^2/week suggests that limiting the release to this level is sufficient to protect against sensitisation of non-sensitised individuals in a substantial part of the population exposed to direct and prolonged contact with nickel and nickel alloys. The release rate of 0.5 µg Ni/cm^2/week after direct and prolonged contact is also considered sufficient to protect against elicitation in a significant proportion of nickel sensitized individuals. There were no data from skin exposure to nickel sulfate, nickel chloride, nickel carbonate or nickel dinitrate to allow an estimate of the dose of these salts that may cause skin sensitisation. Based on elicitation testing of nickel sensitised patients an empirical elicitation threshold of 0.3 µg Ni/cm^2 for nickel sulfate is suggested as the best estimate of a threshold for sensitisation. As sensitisation is assumed to require higher doses than elicitation, this estimate for sensitisation is more conservative than the estimate for elicitation.

It was not possible to establish a NOAEL for oral challenge in patients with nickel dermatitis. The LOAEL established after provocation of patients on an empty stomach is 12 µg Ni/kg bw. It should be noted that the dose of 12 µg Ni/kg bw is the acute LOAEL in fasting patients on a 48-hour diet with reduced nickel content. A LOAEL after repeated exposure may be lower and a LOAEL in non-fasting patients is probably higher because of reduced absorption of nickel ions when mixed in food.

Nickel sulfate is considered to be a respiratory sensitiser in humans, based on a limited number of cases. There were no data for nickel chloride, nickel dinitrate or nickel carbonate. The Ni^{2+} ion is considered exclusively responsible for the immunological effects of nickel. As nickel sulfate is considered to induce respiratory sensitisation it must be assumed that nickel chloride, nickel dinitrate and nickel carbonate also may have the potential to induce respiratory sensitisation and thus, should be regarded as respiratory sensitisers. Metallic nickel has also been reported to cause respiratory sensitisation, but the available data do not allow a firm conclusion. It is not possible to set a threshold for sensitisation or elicitation.

Repeated exposure

Following repeated exposure by inhalation of nickel sulfate and nickel chloride the main target is the respiratory tract (both the lungs and the nose) in experimental animals. For nickel sulfate, lung inflammation and fibrosis were observed, while for nickel chloride apparently less severe effects were seen. A LOAEC of 0.056 mg Ni/m^3 (0.25 mg nickel sulfate hexahydrate/m^3 with a mean particle diameter of 1.8–3.1 µm for lung inflammation and fibrosis is determined from a 2-year study in F344 rats. It should be noted that data from this study indicate that adverse effects possibly occur at lower exposure levels. With nickel chloride, the LOAEC for local lung effects

(adverse effects on lung macrophages) in rabbits exposed for up to 8 months was 0.2 mg Ni/m^3 (0.8 mg nickel chloride hexahydrate/m^3). There were no data on repeated dose toxicity of nickel dinitrate or nickel carbonate following inhalation.

Following repeated exposure by inhalation of nickel metal, the main target is the lung where serious effects were induced in the form of chronic inflammation and fibrosis in experimental animals. A LOAEC of 1 mg Ni/m^3 (nickel powder, mean particle diameter of 1.2 µm) for changes in lung weight and relative lung weight, alveolar proteinosis and granulomatous inflammation, accumulation of nickel particles in the lung and increased nickel blood levels is determined from a 13-week study in rats.

Other data on insoluble nickel compounds show that repeated exposure by inhalation also results in lung inflammation and fibrosis. For the two insoluble compounds nickel subsulphide and nickel oxide, inflammatory lung lesions were observed at all concentration levels in two-year studies in rats.

Thus it appears that the effects following repeated inhalation exposure to nickel compounds do not depend on the solubility characteristics. Chronic lung inflammation and lung fibrosis were serious and potentially irreversible effects.

Since nickel sulfate and nickel chloride have not been tested in a parallel manner, it is not possible to carry out a direct comparison of the potency. For the three compounds tested by NTP in a similar protocol, the following order of toxic potency, based on mg Ni/m^3, could be determined: Nickel sulfate hexahydrate > nickel subsulphide > nickel oxide.

In the absence of adequate repeated inhalation toxicity data for nickel chloride, and no data for nickel dinitrate and nickel carbonate, the LOAEC of 0.056 mg Ni/m^3 for lung inflammation and fibrosis in the 2-year rat study for nickel sulfate hexahydrate is determined as a LOAEC for repeated dose toxicity via inhalation for nickel chloride, nickel dinitrate and nickel carbonate.

For metallic nickel, a LOAEC of 1 mg Ni/m^3 (for changes in lung weight and relative lung weight, alveolar proteinosis and granulomatous inflammation, accumulation of nickel particles in the lung and increased nickel blood levels) is determined from a 13-week study in rats.

Sufficient oral repeated dose toxicity data were only available for nickel sulfate and nickel chloride. In experimental animals administration of nickel sulfate via feed or drinking water was mainly associated with non-specific indications of toxicity, such as decreased survival and decreased body weight. In addition, increased urinary albumin (indicator of diminished kidney function), mild tubular nephrosis, as well as immuno-suppressive effects were observed. A NOAEL of 2.2 mg Ni/kg bw/day for reduced body weight and increased mortality is determined for nickel sulfate from a 2-year carcinogenicity study (OECD TG 451) in rats. Reduced survival was also found with gavage administration of nickel chloride; however, when nickel chloride was administered in feed or drinking water at comparable doses no effects were found. There were no adequate data on repeated dose toxicity of nickel carbonate following oral administration and no data for nickel dinitrate and nickel metal as well as no data on effects following repeated oral exposure with insoluble nickel compounds.

In the absence of data for nickel compounds other than nickel sulfate as well as for insoluble nickel compounds, the values for nickel sulfate (oral LOAEL of 6.7 mg Ni/kg bw/day based on reduced body weight and increased mortality and NOAEL of 2.2 mg Ni/kg bw/day) is determined for repeated dose oral toxicity for nickel compounds. Uncertainties remain whether this actually should be considered as a NOAEL as reduced body weight gain (both sexes) and increased mortality (females) occurred to a statistically non-significant extent in the 2-year carcinogenicity study in rats.

When using this NOAEL for nickel metal, consideration should be given to differences in bioavailability between nickel sulfate and metallic nickel.

Dermal repeated dose toxicity data were lacking for soluble as well as for insoluble nickel compounds. There is no concern for systemic effects following dermal exposure to nickel compounds, due to poor absorption of nickel by this route.

Genotoxicity

There is considerable evidence for the *in vitro* genotoxicity of nickel compounds. Positive effects

were generally seen in studies of chromosomal effects (chromosomal aberrations, sister chromatid exchanges), cell transformation tests and tests for DNA damage and repair. Whilst there were positive results for gene mutations, particularly with nickel chloride, the positive results in at least some of these assays could possibly be due to genetic events other than point mutations.

Interpretation of the results of *in vivo* studies is more complicated. Most of the reviewed studies were carried out with nickel chloride, nickel sulfate and nickel dinitrate. There were little *in vivo* data on other soluble compounds, and *in vivo* data on sparingly soluble nickel compounds such as nickel carbonate, insoluble compounds such as nickel oxide and nickel sulphides as well as nickel metal were also very limited.

Of the individual compounds, the genotoxicity of nickel chloride has been the most extensively studied. In a recent and well-performed Comet assay (mice), there was clear evidence that nickel chloride induces DNA strand breaks *in vivo* in leukocytes after a single oral dose. Four studies showed chromosomal aberrations in somatic cells *in vivo* (three in mice and one in hamsters, three with intraperitoneal (ip) administration and one with oral administration). Data from four *in vivo* micronucleus studies in mice were conflicting. One of three i.p. studies was regarded as positive whilst two other studies were negative; the oral study was regarded as positive. There is no obvious explanation for the differences in the conclusions of the different studies. Some studies were carried out to see whether there are effects on germ cells. One bone marrow micronucleus test found morphological changes in spermatozoa after oral administration. There were two dominant lethal tests, one in mice and one in rats. In a dominant lethal test (mice), treatment decreased significantly the incidence of pregnant females and the mean number of implanted embryos, but did not increase the post-implantation loss. Pre-implantation losses have also been recorded in a dominant lethal test in rats. Studies in man indicate that nickel exposure might induce chromosomal aberrations in the exposed workers studied. Taken together, the evidence for an *in vivo* clastogenic effect of nickel chloride is convincing. There were no definitive studies on germ cells, and little evidence concerning hereditable effects on germ cells. Evidence from human studies was limited.

The *in vivo* data on nickel sulfate were rather more limited than for nickel chloride. An *in vivo* inhalation study in rats showed that nickel sulfate seemed to induce DNA damage and inflammation in lung cells at approximately the same concentrations. The results from other *in vivo* studies (oral and intraperitoneal) were conflicting. One i.p. study for chromosomal aberrations was negative whereas one oral study was regarded as positive. Of the three micronucleus studies, one oral study was positive whilst two more recent studies an ip study and oral guideline study were both negative. Studies in man indicate that nickel exposure might induce chromosomal aberrations in the exposed workers studied. Taken together, there was evidence for an *in vivo* clastogenic effect of nickel sulfate in somatic cells. There were no definitive studies on germ cells, and little evidence concerning hereditable effects on germ cells. Evidence from human studies was limited.

The evidence for nickel dinitrate was even more limited, and added little new information, as many of the studies included either nickel sulfate and/or nickel chloride, and were the same as the studies discussed above.

An *in vivo* inhalation study in rats showed that nickel subsulfide induced DNA damage in lung cells at lower concentrations than with nickel sulfate.

Overall, the soluble nickel compounds (nickel sulfate, nickel chloride, nickel dinitrate) as well as nickel carbonate, based on available information are regarded as being genotoxic in somatic cells *in vivo*; hence the possibility that the germ cells are affected cannot be excluded .

The available data on nickel metal were inadequate in order to draw any direct conclusion on the *in vivo* genotoxicity of nickel metal.

Carcinogenicity

There was no evidence of carcinogenicity in rats and mice following inhalation of nickel sulfate hexahydrate (mass median aerodynamic diameter of 1.8-3.1 $\pm$ 1.6-2.9 µm) in concentrations up to 0.11 mg Ni/m^3 or 0.22 mg Ni/m^3, respectively for 2 years. No studies regarding carcinogenicity following inhalation exposure or intratracheal instillation of nickel chloride, nickel dinitrate, and nickel carbonate in experimental animals have been located.

The studies in experimental animals on the carcinogenicity of nickel metal following inhalation or intratracheal instillation suffer from inadequacies and were considered inadequate for an evaluation of the carcinogenic activity of nickel metal following inhalation.

Other inhalation studies on nickel oxide and nickel subsulphide 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.

The epidemiological data for nickel sulfate and nickel chloride were considered to be sufficient to establish a causal association between the human exposure to the substances and the development of lung cancer. There was supporting evidence for this conclusion from more limited data on nasal cancer. No epidemiological data were available for nickel dinitrate and nickel carbonate.

Epidemiological evidence for carcinogenicity in humans exposed to nickel metal and nickel-containing alloys alone has not been found. However, epidemiological studies have shown elevated risks of cancer in workers that were known or supposed to be exposed to nickel metal together with other nickel compounds. Further, there was epidemiological evidence to regard both nickel oxide and nickel sulfide as human carcinogens.

Overall, the four nickel salts are considered as human carcinogens by inhalation.

The available data on nickel metal do not provide evidence on which to draw a firm conclusion about the carcinogenicity following inhalation. A study to evaluate the inhalation carcinogenicity of nickel metal has been initiated.

There were sufficient oral carcinogenicity data, including a well-conducted OECD TG 451 study in rats, to show that nickel sulfate does not have any carcinogenic potential in experimental animals following oral administration. No data regarding carcinogenicity of nickel chloride, nickel dinitrate, nickel carbonate, and nickel metal in experimental animals following oral administration have been located. No human data were available.

Overall, there was evidence for lack of a carcinogenic potential following oral administration based on the OECD TG 451 study with oral administration of nickel sulfate to rats. Based on the data on nickel sulfate, the other nickel compounds are considered to be without carcinogenic concern by the oral route.

No data regarding carcinogenicity following dermal contact to nickel sulfate, nickel chloride, nickel dinitrate, nickel carbonate, and nickel metal in experimental animals or in humans have been located. No tumours developed in the buccal pouch, oral cavity, or intestinal tract of male hamsters painted on the mucosa of the buccal pouches with α-nickel subsulphide.

Overall, although the available data were sparse, the lack of a carcinogenic potential after oral exposure to nickel sulfate indicate that carcinogenic effects are very unlikely to occur systemically following dermal exposure to nickel sulfate, nickel chloride, nickel dinitrate, nickel carbonate, and nickel metal. However, data were too limited for an evaluation of local carcinogenicity following dermal contact to nickel compounds.

Reproductive toxicity

Experimental animal data on nickel chloride and nickel sulfate were used for the evaluation of the reproductive toxicity of nickel compounds. The basic assumption is that that it is the nickel ion that is the determining factor for the reproductive and developmental toxicity.

No effects on fertility were seen in animal studies following oral administration of nickel sulfate or nickel chloride. The most reliable NOAEL for effects on fertility for nickel sulfate is 2.2 mg Ni/kg bw/day (the highest dose in a recent OECD TG 416 two-generation study in rats); it should be noted that the NOAEL for fertility is possibly higher. Based on the available studies on nickel chloride, it was not possible to consider a NOAEL for effects on fertility for nickel chloride.

Additional data on the effects on male reproductive organs in experimental animals have been reported in other studies on nickel sulfate following oral or inhalation exposure. A NOAEC for effects on male reproductive organs of 0.45 mg Ni /m^3 is determined for inhalation exposure and a NOAEL of 2.2 mg Ni/kg bw/day for oral administration. Based on the available studies on nickel chloride, it was not possible to reach a conclusion for effects on reproductive organs. The potential for effects on reproductive organs has not been sufficiently investigated, as sperm quality and

oestrus cyclicity either were 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 reproductive organs further studies using higher dose levels and including these end-points would be relevant.

No standard prenatal developmental toxicity studies via either the oral or inhalation routes were located. The available studies on nickel sulfate, nickel chloride and an unspecified nickel salt provide consistent evidence of increased postimplantation / perinatal lethality in rats after oral exposure. Based on increased postimplantation / perinatal lethality in F1 generation in an OECD TG 416 two-generation study at 2.2 mg Ni/kg bw/day a NOAEL of 1.1 mg Ni/kg bw/day for nickel sulfate was determined in rats. For nickel chloride, a definite NOAEL could not be determined.

No data regarding reproductive effects in experimental animals of nickel carbonate, nickel dinitrate, metallic nickel or other nickel compounds have been found.

There were no conclusive studies regarding reproductive toxicity in humans.

Overall, based on the recent oral OECD TG 416 two-generation study in rats with nickel sulfate, a NOAEL of 2.2 mg Ni/kg bw/day is determined for effects on fertility and on male reproductive organs and a NOAEL of 1.1 mg Ni/kg bw/day for developmental toxicity following oral ingestion of nickel sulfate, nickel chloride, nickel dinitrate, nickel carbonate as well as for nickel metal. It should be noted that the NOAEL for fertility is possibly higher. When applying this oral NOAEL for nickel metal, consideration should be given to the lower bioavailability of metal compared to nickel sulphate.

For inhalation, a NOAEC for effects on male reproductive organs of 0.45 mg Ni/m^3 is determined for nickel sulfate, nickel chloride, nickel dinitrate, nickel carbonate as well as for nickel metal based on the data for nickel sulfate. No data on fertility and developmental toxicity following inhalation were available; a NOAEC of 0.55 mg Ni/m^3 for fertility and of 0.277 mg Ni/m^3 for developmental toxicity was estimated from the oral NOAELs for nickel sulfate.

For dermal contact, no data were available, but there is no concern for reproductive effects following dermal contact to nickel compounds, due to poor absorption of nickel by this route.

ENVIRONMENT

The Effects Assessments for the Aquatic, Terrestrial, Sediment, and Marine compartments, and the Secondary Poisoning (accumulation though the food chains), and Indirect Human Exposure Assessments are comprised of an Effects Database, Implementation of Bioavailability, and determination of Predicted No Effects Concentrations (PNECs).

Environmental Fate:

All five nickel compounds (nickel chloride, nickel dinitrate, nickel hydroxycarbonate, nickel sulphate, nickel metal) release Ni^{2+} into the environment, and partitioning coefficients for this ionic form are therefore relevant for all five substances. Ni^{2+} partitioning coefficient for solid-water in suspended matter (Kp susp) is 26,303 (log Kp susp = 4.42). Ni^{2+} partitioning coefficient for sediment-porewater (Kp sed) is 7,079 (log Kp sediment = 3.85). Ni^{2+} partitioning coefficient for soil-water (Kp soil) is 726 (log Kp soil = 2.86). Ni^{2+} partitioning coefficients were based on 50^{th} percentiles of distributions of values from available high quality data.

Common effects assessment basis: The ecotoxicity databases on the effects of soluble nickel compounds to aquatic, soil- and sediment-dwelling organisms are in general extensive. It should be noted that the effects assessments of Ni metal and for Ni compounds is based on the assumption that adverse effects to aquatic, soil- and sediment-dwelling organisms are a consequence of exposure to the (bio)available Ni-ion, as opposed to the parent substances. The result of this assumption is that the ecotoxicology will be similar for the five priority nickel substances (i.e., nickel metal, nickel sulfate, nickel chloride, nickel carbonate, and nickel dinitrate). Therefore, data from soluble nickel salts are used in the derivation of chronic ecotoxicological NOEC and $L(E)C_{10}$ values. If both NOEC and $L(E)C_{10}$ data are available, the $L(E)C_{10}$ value was used in the effects assessment. The soil database includes data on Nickel acetate (a soluble nickel substance) as the inclusion of these data increase the breadth of the database that will be applied to all soluble and sparingly soluble nickel substances.

Application of metal-specific risk assessment methodologies: Recognition of metal-specific ecotoxicological and geochemical characteristics led to several modifications of risk assessment approaches for

metals which have been employed in the past. These modifications are related to the treatment of extensive data sets also used in the past (cf. SIARs of Zn and Cd), but furthermore also includes further advancements of approaches to incorporate bioavailability corrections, and implementation of the Ecoregion Approach to derive PNECs at the regional scale. Extensive sensitivity analyses were conducted to justify the selection of approaches, methods and critical parameters.

Aquatic

One generic goal of the nickel risk assessment is to express the chronic toxicity of Ni in the bioavailable form. Bioavailability models were subsequently used to normalize the ecotoxicity data to sets of standard physicochemical conditions for important abiotic factors (i.e., pH, hardness, and dissolved organic carbon (DOC)). This approach allows for the comparison of intrinsic toxicity among organisms on an equal basis.

For the aquatic compartment, Biotic Ligand Models (BLMs; cf. SIAR for Zn) were used to normalize the ecotoxicity data. BLMs were developed and validated for two invertebrates (*Ceriodaphnia dubia* and *Daphnia magna*), an alga (*Pseudokirchneriella subcapitata*), and a fish (*Oncorhynchus mykiss*). Appropriate use of this bioavailability normalization necessitates that the geochemical boundaries of the BLMs are defined relative to the environmental conditions considered. In general, the BLMs cover between 10 and 90% of the pH, hardness, and DOC observed in EU surface waters (Table 1). Only reliable ecotoxicity data from tests conducted within the boundaries of the BLMs have been used for establishment of the PNEC. Definition of the relevant environmental conditions and the exclusion of otherwise reliable ecotoxicity data relative to these conditions may need to be adapted for other regions.

Table 1: Ranges of pH and hardness used for data selection

Test organism	**pH range**	**Hardness range (mg/l $CaCO_3$)**
Algae – *P. subcapitata*	5.7-8.2	(20-480)
Higher plants – *H. vulgare*	4.1-7.5	NA
Invertebrates – *D. magna*	5.9-8.2	6-320
Invertebrates – *C. dubia*	6.5-8.2	6-320
Fish – *O. mykiss*	5.4-8.5	20-310

Effects data sets selected: More than 250 individual NOEC/EC_{10} values were collected and screened for quality and relevancy, which yielded 193 individual high quality data covering 30 different species. The selected data set covers 16 different families, different trophic levels and feeding patterns and is so far the largest data set on a metal. It should be noted that some reliable aquatic ecotoxicity data that passed the relevancy criteria were set aside because they were obtained from tests in which the geochemical parameters were outside of the BLM boundaries. These otherwise high quality data were listed in separate tables in the SIAR, some of which will be used in a special scenario to assess risk of Ni exposure in particular alkaline waters (i.e., pH = 8.3 – 9.0) that are outside of the BLM boundary.

For algae, EC_{10} values of Ni for chronic exposures conducted with *Pseudokirchneriella subcapitata* ranged from 25.3 to 425 µg Ni L^{-1}, with a median value of 88.2 µg Ni L^{-1} (n = 47). Chronic growth inhibition data (EC_{10}) were available for nine additional ***freshwater algae species***. These EC_{10} values ranged from 12.3 µg Ni/L for *Scenedesmus accumulates* to 51.8 µg Ni/L for *Coelastrum microporum*. For higher aquatic plants, chronic effects to *Lemna gibba* and *Lemna minor* ranged between 8.2 and 80 µg Ni L^{-1}.

Chronic nickel toxicity data were available for fifteen ***invertebrate species***. The large majority of data were from crustaceans, but data from insects, hydrozoans, and molluscs were also available. The NOEC/L(E)C_{10} varied between 2.8 µg/l for *Ceriodaphnia dubia* and 1193.3 µg/l for *Chironomus tentans* .

Chronic nickel toxicity data were available for three species of **fish,** with NOEC/LC_{10} values ranging from 40 µg Ni L^{-1} for *Brachydanio rerio* to 1,100 µg Ni L^{-1} for *Oncorhynchus mykiss*. NOEC/L(E)C_{10} data were available for three species of amphibians, with values ranging from 84.5 µg Ni L^{-1} to 13,147 µg Ni L^{-1}, both values from *Xenopus laevis*.

In summary, NOEC/L(E)C_{10} values for chronic nickel toxicity to aquatic organisms ranged from 2.8 µg Ni L^{-1} (*C. dubia*) to 13,147 µg Ni L^{-1} (*X. laevis*).

Bioavailability correction: Many of the aquatic toxicity data were obtained from experiments designed to determine effects of water quality parameters on nickel toxicity. Factors identified to affect nickel toxicity included pH, hardness, and dissolved organic carbon (DOC). The use of the BLM performs two principal functions. First, it removes the influence of variable geochemical conditions when calculating species mean values from individual toxicity tests, which may have been performed using different combinations of pH, hardness, and DOC. Geochemical normalization is accomplished by the chemical speciation software within the BLM (WHAM VI, in the case of the nickel BLM), and ensures that all data within a given Species Sensitivity Distribution (SSD) are evaluated on an equivalent free nickel ion basis. Second, the BLM takes into account the competitive effects of positively-charged constituents of freshwater, such as Ca^{2+}, Mg^{2+}, and H^{+}, on the uptake of Ni^{2+} at the assumed site of action on the organisms.

Biotic Ligand Models have been developed for the three standard trophic levels for bioavailability correction covering the algae *Pseudokirchneriella subcapitata*, the invertebrate *Daphnia magna*, and the fish *Oncorhynchus mykiss*. An additional BLM was developed for *Ceriodaphnia dubia* because intraspecies variability for this particular sensitive species could not be explained by the *D. magna* BLM. Recalibrating the speciation model to accurately estimate nickel speciation at the low nickel concentrations (e.g., < 5 µg Ni/L) that are relevant to *C. dubia* was required for the development of an accurate *C. dubia* BLM. Effects of DOC were evaluated in toxicity tests using natural waters that represented ranges of natural DOC type (e.g., streams and ponds) and quantity (low to high DOC concentration). Therefore, the effect of varying DOC quality on Ni toxicity was implicitly addressed in the BLM development. An additional BLM was developed under hydroponic conditions for the plant *Hordeum vulgaris*, and this may be useful for normalizing nickel toxicity to aquatic vascular plants. Because the intra- and interspecies variability that are present among the data are largely influenced by the water quality parameters that were used in the toxicity tests, it is critical for the PNEC derivation to include a step that normalizes the NOECs/L(E)C10 values to a set of standard water quality parameters, e.g., pH, hardness, and DOC. All individual toxicity data were normalized using BLMs. In most cases, BLMs from taxonomically similar group of organisms were used to normalize the NOEC/L(E)C_{10} data, i.e., all fish and amphibian toxicity data were normalized by the *O. mykiss* BLM, invertebrate data were normalized by the more stringent of the either the *C. dubia* or *D. magna* BLM, and algae were normalized by the more stringent of either the *P. subcapitata* or *H. vulgaris* BLM. For certain groups of organisms with no BLM, the most stringent BLM was used even if it was not obvious that this BLM originated from the taxonomically most similar organism. For example, L(E)C_{10} data for *Lemna minor*, a vascular plant, were normalized using the *D. magna* BLM because the *D. magna* BLM was shown to result in the most cautious predictions. Support for the cross-species extrapolation was provided by examples from the literature for phytoplankton and fish, and from a spot-check study for invertebrates and vascular plants. The spot check study was performed on three non-crustacean invertebrates (the midge larvae *Chironomus tentans*, the rotifer *Brachionus calicyflorus*, and the snail *Lymnaea stagnalis*) and one higher plant (duck weed, *L. minor*). The results of the spot check study indicated that the available BLMs were capable of predicting toxicity to the test species used in the spot testing exercise, within a factor of 2. It was based on this concluded that "full cross-species extrapolation" as described above was the preferred approach which was therefore taken forward as the basis for normalizing the SSD according to the abiotic factors hardness, pH and DOC concentration in freshwaters.

Ecoregion Approach: The use of statistically based scenarios to represent a "reasonable worst case" was not applied to the Ni case as the combination of water quality parameters used to define these scenarios very often do not occur in actual natural surface waters. The Ecoregion approach was developed as an alternative to calculate regional hazard concentration at the 5th percentile (HC5) and PNECs for a series of typical freshwater systems that cover at least 90 % of abiotic conditions ranges in EU freshwaters. The Ecoregion approach was developed for conditions typically found in EU freshwaters and its applicability for use in other jurisdictions should be evaluated on a case by case basis. Seven systems were chosen, and they include frequently occurring existing river/lake types of typical surface waters (i.e., "Ecoregions") (Table 2). The systems ranged in pH from 6.7 to 8.2, in hardness from 28 to 273 mg $CaCO_3$/L, and in DOC from 2.5 to 12.0 mg/L (Table 2). The HC5s ranged from 7.1 µg Ni L^{-1} (for a system with pH = 7.9, hardness = 48.3 mg $CaCO_3$ L^{-1} and DOC = 2.5 mg L^{-1}) to 43.6 µg Ni L^{-1} (for a system with pH = 6.9, hardness = 260 mg $CaCO_3$ L^{-1}, and DOC = 12.0 mg L^{-1}). The combination of high hardness and DOC together with low pH is *equivalent to low bioavailability (low sensitivity)*, as exemplified by the scenario represented by the Small River scenario (Table 2). On the other hand, the combination of low hardness and DOC together with high pH is *equivalent to high bioavailability (high sensitivity)*, as exemplified by the Lake (1) scenario (Table 2).

HC5 and PNEC derivation: For PNEC derivation, data for the most sensitive endpoint for a given species were aggregated to derive a species geometric mean ecotoxicity value. Species geometric mean values were

used to establish a species sensitivity distribution (SSD), from which an HC_5 was derived. The Predicted No Effects Concentration (PNEC) was derived as a function of the HC_5 and an assessment factor covering residual uncertainty (PNEC = HC5/Assessment Factor).

For each Ecoregion scenario, the HC_5 was determined by the full cross-species normalization approach, which resulted in HC_5 values ranging from 7.1 µg/l for the high pH low DOC scenario (Lake 1), to 43.6 µg/l for the low pH high DOC and hardness scenario (Small River) (Table 2).

Table 2. Physico-chemical characteristics for seven typical freshwater systems to which the nickel BLMs were applied. HC5 values represent the 5th percentile of the Species Sensitivity Distribution based on BLM-normalized data assuming lognormal distributions.

Selected example of typical surface water (ecoregion) Name	**Bioavail-ability**	**pH**	**Hardness (mg/l $CaCO_3$)**	**DOC (mg/l)**	**HC5 at 50th % confidence limit (µg/l) using Log normal distribution**
Small River	Low	6.9	260	12.0	43.6
Medium River (1)	Medium	8.1	165	3.2	8.1
Medium River (2)	Medium	7.6	159	8.0	19.0
Large River (1)	Medium	7.8	217	2.8	10.8
Large River (2)	Medium/High	8.2	273	3.7	8.7
Lake (1)	High	7.7	48.3	2.5	7.1
Lake (2)	Medium	6.7	27.8	3.8	12.1

Based on the remaining uncertainty, consideration of the amount, type and nature of available chronic data on aquatic species an Assessment Factor was chosen for the aquatic effects data set on nickel in its present status.

Summary: A semi-probabilistic approach was used to characterize the risk of nickel to aquatic organisms at the regional scale. Bioavailability-normalized PNECs were compared with distributions of PECs that were based on measured dissolved nickel data obtained from monitoring programs for the selected ecoregions identified in Table 2.

The most senstitive aquatic environment identified was represented by the Medium River (1) Scenario (low DOC/high pH/medium hardness implying high sensitivity). However, data on the distribution of nickel and the relevant abiotic factors (pH, hardness, and DOC) was insufficient in the Lake (1) scenario to perform the semi-probabilistic approach. The relative bioavailability of this system is high (Table 2), which would indicate a sensitive environment. In generic terms, therefore, sensitive aquatic environments to nickel exposure at the regional scale occur in systems with combinations of high pH and low DOC.

Sediment

The classical Equilibrium Partitioning - Kp approach to derive the PNEC sediment failed to deliver reliable values. A comprehensive sediment testing program was therefore initiated in support of the EU Risk Assessment of Nickel, and included testing for six species of benthic invertebrates in a range of sediment types.

The chronic data generated by this program in combination with additional data collected from open literature formed the basis for the PNEC sediment derivation using a Species Sensitivity Distribution (SSD). However, the results of the laboratory experiments were confounded by the diffusion of nickel from the spiked sediments into the overlying water. In fact, it was shown that the concentration of nickel in the overlying water in the

semi-static test system generally correlated better with the observed effect concentrations on the sediment organisms than the nickel concentrations measured in the bulk sediment. Therefore, extensive calculations were necessary to extrapolate from overlying water nickel concentrations to sediment concentrations using the equilibrium partitioning approach. The very cautious assumptions that were necessarily taken in this extrapolation implied a high degree of scientific uncertainty. As a consequence, a high assessment factor was deemed appropriate when calculating the PNEC from the estimated HC5(50%) (55 mg Ni/kg based on 5% sediment organic carbon) based on the above mentioned approach. The scientific uncertainty of the described approach yielded a PNECsed of 18.3 mg Ni/kg, which is close to or below nickel background concentrations in many sediments of EU countries.

Based on the results of the draft Sediment Effects Assessment and the impact of this PNECsed on risk characterization for the sediment compartment it was determined that all local sites would be estimated to be at risk, and that risk would be concluded at the regional scale as well. Because of this and because the PNECsed was also shown to be below a generic natural background concentration of 29 mg Ni/kg for EU countries, it was concluded that the current sediment data set should not be used to derive a PNEC sediment and that additional research was warranted for generation of scientifically justified nickel sediment toxicity test data in order to derive a reliable PNEC for the sediment compartment.

To this end, a subsequent sediment testing program has been initiated, with the goal of performing tests in a way that limits the release of dissolved Ni from sediments to the overlying water similar to those of relevant natural systems. The results of this research will be reported post-SIAM as soon as it has been completed and the results analysed.

Marine

Effect data sets: The marine chronic ecotoxicity database is represented by 15 species of marine organisms from 14 families, and includes a wide range of taxonomic groups, including unicellular algae, macroalgae, crustaceans, molluscs, echinoderms, and fish.

EC_{10} values for four species of ***marine algae*** are reported, ranging from 97 µg Ni/L for growth of giant kelp (*Macrocystis pyrifera*) to 17891 µg Ni/L for growth of the dinoflagellate, *Dunaliella tertiolecta.*

EC_{10} values are reported for nine species of ***marine invertebrates***, ranging from 22.5 µg Ni/L for reproduction of the polychaete, *Neanthes arenaceodentata*, to 335 µg Ni/L for development of the echinoderm, *Strongylocentrotus purpuratus*.

EC_{10} values are reported for two species of ***marine fish***, ranging from 3599 µg Ni/L for growth of the topsmelt, *Atherinops affinis*, to 20,760 µg Ni/L for growth of the sheepshead minnow, *Cyprinodon variegatus.*

In summary, the chronic EC_{10} data used in the derivation of the HC5 (50%) for the marine compartment ranged from 22.5 µg Ni/L for *Neanthes arenaceodentata* to 20,760 µg Ni/L for *Cyprinodon variegates*.

Bioavailability: No incorporation of the potential modifying effect of abiotic factors was included in this analysis. Most of the factors known to affect Ni bioavailability and toxicity in freshwater, e.g., Ca^{2+}, Mg^{2+}, and H^{+}, are relatively constant in marine waters, and therefore the utility of bioavailability correction is limited. Dissolved organic carbon (DOC) can vary considerably in coastal marine waters, and has been shown to be an important factor controlling the toxicity of nickel in the freshwater environment. Therefore, DOC may also be important in the marine environment. However, the range of DOC concentrations present in the natural seawaters tested as part of this program (0.22 to-2.7 mg/L) was probably too narrow with the obtained precision and accuracy of the EC_x results to accurately quantify any variation of effect concentrations attributable to DOC.

HC5 and PNEC derivation: A range of statistical options were explored for determining the HC5(50%) from the marine ecotoxicity data using the SSD approach. Alternatives to the preferred approach of using the lognormal distribution were required because this distribution was rejected based on Goodness of Fit tests. The alternative approaches included

1) alternative non-rejected parametric frequency distributions (all data points)

2) log-normal distribution using a reduced data base (with exclusion of fish and dinoflaggelate data based on a mechanistically based hypothesis) ; and,

3) a non-parametric approach called “flexible kernel density estimation” (all data points).

It was concluded that each of the above approaches had advantages and disadvantages (pros and cons) and that

no approach could be said to be scientifically and indisputably superior. A weight-of-evidence approach was used to evaluate the options, and it was agreed to take the mean from the most cautious approach of option 1 (i.e. the arithmetic mean HC5 (50%) value of 19.9 µg/L for all statistically valid parametric distributions) and the outcome of option 3 (i.e. the HC5 (50%) of 14.5 µg/L of the Kernel Density Estimation approach with optimal band width). Therefore an HC5 (50%) value of 17.2 µg/L is taken forward for the $PNEC_{marine}$ determination.

Based on the amount, type and nature of chronic data on marine organisms and remaining uncertainty an Assessment Factor was chosen.

STP

An assessment of effects of nickel exposure on microbial activity in STPs will be completed under the same regulatory framework as the Sediment Effects Assessment. A PNECmicroorganism will be derived, and local scale risk characterization for the EU will be completed and afterwards reported post-SIAM.

Soil

As for the aquatic compartment, bioavailability models were used to normalize ecotoxicity data to sets of standard physicochemical conditions. For the soil compartment, relationships between cation exchange capacity (CEC[1]) and chronic nickel toxicity were used to normalize the ecotoxicity data. Appropriate use of normalization of chronic toxicity to soil organisms necessitates that the CEC boundaries of the experimentally derived relationships are defined relative to the environmental conditions considered. Hence data from studies that passed the reliability and relevance criteria in general, but that were conducted on soils that fell outside of this CEC range were not maintained for PNEC derivation. Data from studies that did not report CEC or additional information enabling an estimation of CEC were rejected. Data that were not maintained for PNEC derivation were, however, listed in separate tables. Definition of the relevant environmental conditions and the exclusion of otherwise reliable ecotoxicity data relative to these conditions may need to be adapted for other regions.

Effect data sets: Extensive chronic soil toxicity data sets exist for soil microbial processes, plants, and invertebrates. More than 250 individual $NOEC/EC_{10}$ values were screened for quality and relevancy, which resulted in a data set of 173 individual high quality data that covered 42 different species. The selected data set covers 8 different families, different trophic levels and feeding patterns for invertebrates, and microbial activities. Chronic toxicity data for individual species were generated in 16 different soils, enabling a toxicity comparison between soils and the establishment of toxicity soil-type models. This data set is, to date, the largest data set on a metal for soil.

Data for 12 ***microbial processes*** were available, with $NOEC/EC_{10}$ values range from 28 mg Ni kg^{-1} for nitrification to 2,491 mg kg^{-1} for respiration. Additional data were available for enzyme activity measured in soil, with $NOEC/EC_{10}$ values ranging from 7.9 mg Ni/kg^{-1} for dehydrogenase to 7,084 mg Ni kg^{-1} for arylsulfatase activity. Data also exist for the growth of 13 individual microbial species, with EC_{10} values ranging from 13 mg Ni kg^{-1} for *Aspergillus clavatus* to 530 mg Ni kg^{-1} for *Trichoderma viride*.

$NOEC/EC_{10}$ values were available for 11 ***plant species***, ranging from 10 mg kg^{-1} for *Spinacea oleracea* to 1,127 mg Ni kg^{-1} for *Hordeum vulgare*.

Chronic data were available for 6 different species of ***soil invertebrates***, including both soft- and hard-bodied invertebrates. $NOEC/EC_{10}$ values ranged from 36 mg Ni kg^{-1} for reproduction by the springtail *Folsomia candida* to 1,140 mg Ni kg^{-1} for reproduction by the earthworm *Eisenia fetida*.

Bioavailability correction: As clear toxicity differences between various soils were observed, bioavailability correction models (7 in total) were established for 2 plant and 2 invertebrate species, and for 3 microbial processes. The toxicity data from the tested soils showed that among the parameters tested, *i.e.* CEC, pH, organic material (OM), Clay and $Ni_{background}$, the CEC alone consistently explained a large fraction of variability for the 7 species and endpoints tested in the 16 soils (r^2 = 0.60 to 0.92). The CEC range is from 1.8 to 52.8 cmol kg^{-1}, which covers most soils. Accordingly, the intra-species variability in chronic toxicity to nickel may to a large extent be due to differences in soil chemistry. Hence, to reduce soil-type related impact on the determination of an HC5 (and subsequently the PNEC) for a given soil, all data in the nickel soil

[1] Cation exchange capacity (CEC) is a quantitative measure of a soil to sorb cations, and is a function of soil organic matter, clay content, and pH. CEC can be measured at the ambient pH of a soil (which is called ***effective CEC, or eCEC***) or at a buffered pH. eCEC was used in the development of the bioavailability models, and is used interchangeably with CEC in the SIAP and SIAR documents.

ecotoxicity database were normalized to a set of standard soil properties, using the established CEC based models. Although models were established for 7 species, more species were present in the toxicity database. Therefore extrapolation of the normalization model from species with CEC based chronic toxicity models was also performed to species without such a model (cross-species extrapolation, as for the aquatic compartment): for all plants, except *L. esculentum* which has its own model, a *H. vulgare* model was used; an *E. fetida* model was used for all soft-bodied and a *F. candida* for all hard-bodied invertebrates. For all nitrifying organisms a nitrification model was used, maize induced respiration was used for all respiration measures and Substance Induced Respiration was used for all microbial biomass measures.

Research has demonstrated that chronic toxicity decreases over time, and that the relationship is directly related to pH (i.e., ageing is more pronounced at higher soil pH). The relationship between time (equilibration time, tested for up to 15 months) and chronic toxicity has been demonstrated in 3 soils for the same 7 species/processes for which the soil-type bioavailability models were established. A pH-dependent "ageing factor" has therefore been developed and applied to the toxicity data (cf. also the Zinc SIAR). The purpose of the ageing factor is to place data from laboratory experiments, in which soluble nickel was spiked into test soils, into a field-based context, where the majority of soil-associated nickel has been shown to be in the solid phase. Therefore, the pH-dependent ageing factor is applied prior to CEC normalization.

Ecoregion approach: As for the aquatic system it was concluded that statistical approaches based on "reasonable worst case" abiotic factor combinations were not relevant. An Ecoregion approach has instead been developed based on 6 reference soil scenarios that represent typical soil conditions. These include agricultural and natural soils that exhibit wide ranges of textures, pH, and CEC. The Ecoregion approach was developed for conditions typically found in EU soils and its applicability for use in other jurisdictions should be evaluated on a case by case basis (Table 3).

HC5 and PNEC derivation: For PNEC derivation, data for the most sensitive endpoint for a given species were aggregated to derive a species mean ecotoxicity value. Species mean values were used to establish a species sensitivity distribution (SSD), from which an HC_5 was derived. The Predicted No Effects Concentration (PNEC) was derived as a function of the HC_5 and an assessment factor (PNEC = HC5/Assessment Factor).

For each soil Ecoregion scenario, the HC_5 was determined by full cross-species normalization approach resulting in HC_5 values ranging from 8.6 mg Ni/kg in acidic sandy soils to 194.3 mg Ni/kg for alkaline clay soils (Table 3)

Based on the amount, the type and nature of chronic data on soil organisms, remaining uncertainty an Assessment Factor was chosen for the soil nickel effects data set in its present status.

Table 3. Physico-chemical characteristics for six typical soils. Soil pH and CEC were used to normalize soil ecotoxicity data for ageing and bioavailability. HC5 values represent the 5th percentile of the Species Sensitivity Distribution based on BLM-normalized data assuming log-normal distributions.

Type	**Description**	**pH**	**OM %**	**Clay%**	**CEC cmol/kg**	**HC5 mg Ni/kg**
Acid sandy soil	Agricultural soil from arable land	4.8	2.8	7	2.4	8.6
Loamy soil	Agricultural soil from arable land	7.5	2.2	26	20	100.0
Peaty soil	Agricultural soil from grassland	4.7	40	24	35	188.7
Acid sandy soil	Natural soil from forested land	3.0	9	7	6	25.2
Clay soil	Natural soil from wooded land	7.4	4.5	46	36	194.3

Different types	Composite of soils representing agricultural and forested land	6.3	0.6	8.9	10.4	47.5

Summary: A broad range of representative soil types and relevant abiotic parameters were assessed based on extensive soil databases that supported the bioavailability normalization approach described above. Some scenarios were shown to be sensitive independent of the ecoregion they belonged to. In most cases the sensitivity shown was explained by high ambient concentrations, which include contributions of natural background.

Secondary Poisoning

Marine, freshwater, and terrestrial habitats were evaluated, and both mammalian and bird food chains were addressed for each of these habitats.

A tiered approach was developed and applied for both the aquatic and the terrestrial food chain. The default approach suggested by the European Union's Technical Guidance Document was always used as the first tier. If potential risk was concluded from this tier, then in subsequent assessment tiers, refinements on absorption of dietary nickel and the dietary composition of the predators were considered.

Tier 1: *default assessment*

- PNECoral values were derived from reference NOAELs (from long-term studies) without species-specific modification;
- bioavailability of dietborne nickel was assumed to be 100%;
- diets were composed of one food source with a single nickel concentration.

Tier 2: *correction for species specific info on PNECoral*

- Species-specific PNECoral values were developed for relevant consumer organisms.

Tier 3: *correction for bioavailability of the dietborne fraction*

- Bioavailability of dietborne nickel was incorporated into the assessment. Relative absorption factors (RAFs) were calculated from the literature for different relevant dietary components in the mammalian food chain, including a soil RAF and a comprehensive RAF used for other dietary components.

Tier 4: *correction for diet composition*

Use a more realistic dietary composition instead of assuming that the predator consumes only one food source containing nickel.

PECoral

In general, the Tier 1 PECoral values were obtained by applying a relevant Bioaccumulation Factor (BAF) to the PEC in the media of interest (water or soil) for obtaining a tissue concentration in relevant prey organisms chosen according to "the reasonable worst case" principle.

For the ***marine mammalian and bird foodchains***, it was assumed that the cockle *Cerastoderme edule*, which accumulates Ni more than other marine organisms, would be a potential food item for the harbor seal and oystercatcher. At other locations, it was assumed that *C. edule* would not be a relevant food item and that harbor seals and oyster catchers would feed on prey items (e.g., fish) that do not bioaccumulate Ni to the same level. Nickel concentrations in prey items (i.e., the PEC) were estimated from dissolved Ni concentrations in surface water using a BAF of 1631 L/kg for locations where *C. edule* is relevant or 270 L/kg for other food items (realistic worst case BAF for fish and other bivalves is 270).

For the ***freshwater mammalian and bird foodchains,*** the BAF of 270 L/kg was used.

For the ***terrestrial food chains,*** earthworm nickel concentrations (PECoral) were estimated from the Ni concentration in the earthworm's tissue and the Ni content of the soil in the earthworm's digestive tract. A BAF of 0.30 was used to estimate the Ni in the tissue of the earthworm, and it

was also assumed that the soil in the earthworm gut amounted to 10% of their body weight.

For the first two tiers of the ***terrestrial mammalian foodchain,*** it was assumed that shrews will feed exclusively on earthworms. For the third tier it is assumed that shrews will feed on 30% earthworms and 70% other invertebrates, as represented by isopods. A BAF of 0.066 was used to estimate the Ni concentration in isopods.
For Tiers 3 and 4 of the mammalian food chains, bioavailability was taken into account by applying a Relative Absorption Factor (RAF) of 0.025. This RAF value was derived from studies on humans that showed nickel sulfate absorption of 27% when administered with water compared with 0.7% when administered with food (0.7/27 = 0.025, or 2.5%). The terrestrial food chains assume that soil in the earthworm amounted to 10% of their body weight. A separate RAF was calculated for soil-associated nickel. This RAF was based on a rat study in which the relative absorption of soil-associated nickel compared with absorption of nickel sulfate in water ranged from 2.1 to 3.9%, depending on soil type. To be cautious, the highest value of 3.9% was used. Based on a study comparing Ni concentrations between earthworms with and without soil in their guts, it was estimated for earthworms with soil in their guts that 24% of the Ni concentration is bioaccumulated by the earthworm, and that 76% is adsorbed to soil in the earthworm's gut. Thus, the overall weighted relative absorption factor for bioaccumulated and soil adsorbed Ni in earthworms can be calculated as
Weighted RAF for mammals consuming Earthworms =
((fraction associated with worm tissue) x $RAF_{water/food}$) + (fraction adsorbed to soil) x $RAF_{water/soil}$) =
0.24 x (2.5%) + 0.76 x (3.9%) = 3.6%
This weighted RAF was used for exposure scenarios involving earthworm-consuming mammals.

Assimilation efficiencies of Ni will likely vary according to food type, soil composition, consumer organism, and other factors. This variability is accounted for to some extent by the 10-fold assessment factor used in the derivation of the PNECoral, which is intended to account for interspecies variability and lab-to-field extrapolation. The interspecies variation could include differences between humans (upon which the tissue-specific RAF of 0.025 was based) or rats (upon which the soil-specific RAF of 0.039 was based) and other mammals with respect to the efficiency with which Ni from food and soil is absorbed. This approach taken as a whole can be considered to be cautious because the back-calculated critical soil concentration is 60 mg Ni/kg, a value that is within the range of natural background concentrations for some regions of Europe (e.g., Greece and Spain).

Summary:

Aquatic: The freshwater foodchains in the Secondary Poisoning Assessment were generally shown to be less sensitive compared to direct nickel toxicity to aquatic organisms.

Terrestrial: The most sensitive endpoint among terrestrial food chains for the Secondary Poisoning Assessment was based on a PNECoral for shrews, which led to a critical soil concentration of 60 mg Ni/kg.

EXPOSURE

Production and Use (Western Europe)

Ni chloride: is mainly used in the plating sector (71%) and catalyst production (29%). A small but unidentified portion is also used in chemicals manufacturing.

Ni dinitrate: is mainly used for the production of catalysts (50-75%) and the manufacturing of Ni-Cd batteries (10-50%) – together 92.5% of total EU production. An estimated additional 5-10% is used for other applications; including chemical pretreatment of products.

Ni hydroxycarbonate: Approximately 70% of is used for plating, 20% for catalyst production, 5% for pigment production, and lesser amounts in electronic components.

Ni sulphate is mainly used in the plating sector (89%) and catalyst production (11%). A small, but unidentified portion is also used in chemicals manufacturing.

Ni metal: The major uses of primary and secondary nickel metal in the EU for 2000 was the manufacture of stainless steel (71%), non-ferrous alloys (14%), alloy steels (5%), foundry steels (4%), and plating (4%). Other end uses, including Ni-based batteries, catalysts, and chemicals, accounted for less than 3% of total nickel use.

Occupational exposure

Occupational exposure to the five nickel compounds occurs primarily by inhalation of aerosols containing nickel sulfate and by dermal contact. Direct oral exposure (ingestion) is considered to be negligible; however, indirect oral exposure in connection with the inhalational exposures may give a contribution to the internal systemic dose.

Typical exposure levels of inhalable metallic nickel range from 0.004 mg Ni/m^3 for refinery to 0.3 mg Ni/m^3 when metallic nickel is used as a feedstock in nickel battery production. Worst-case levels are substantially higher, ranging from 1.1 mg Ni/m^3 to 5 mg Ni/m^3.

Typical exposure levels of inhalable nickel sulfate range from 0.004 mg Ni/m^3 for production of catalysts and of nickel compounds/salts to 0.07 mg Ni/m^3 for nickel sulfate production, other leaching processes and purification of impure nickel sulfate. Worst-case levels are substantially higher, ranging from 0.15 mg Ni/m^3 to 7 mg Ni/m^3.

Typical exposure levels of inhalable nickel chloride range from 0.002 mg Ni/m^3 for production of catalysts to 0.35 mg Ni/m^3 for nickel chloride production from metallic nickel. Worst-case exposure levels range from 0.3 mg Ni/m^3 to 8.3 mg Ni/m^3.

Typical exposure levels of inhalable nickel dinitrate range from 0.002 mg Ni/m^3 for production of catalysts to 0.27 mg Ni/m^3 for other uses of nickel: chemicals production. Worst-case exposure levels range from 0.05 mg Ni/m^3 to 7 mg Ni/ m^3.

Typical exposure levels of inhalable nickel carbonate range from 0.002 mg Ni/m^3 for use in synthesis of other nickel containing chemicals to 0.1 mg Ni/m^3 for production from nickel salts. Worst-case exposure levels range from 0.9 mg Ni/$m^3$to 7 mg Ni/m^3.

Typical dermal exposure levels of metallic nickel are estimated to be 0.04 mg Ni/day (0.048 µg Ni/cm^2) for contact with coins and tools. Worst-case dermal exposure levels estimated to be 0.12 mg Ni/day (0.143 µg Ni/cm^2) for contact with coins.

Typical dermal exposure levels of nickel sulfate range from 0.027 mg Ni/day (0.046 µg Ni/cm^2) for nickel plating to 0.8 mg Ni/day (0.4 µg Ni/cm^2) for nickel refining and production of nickel compounds/salts. Worst-case dermal exposure levels range from 0.37 mg Ni/day (0.44 µg Ni/cm^2) to 1.8 mg Ni/day (0.9 µg Ni/cm^2).

Typical dermal exposure levels of nickel chloride range from 0.028 mg Ni/day (0.033 µg Ni/cm^2) for nickel plating to 0.8 mg Ni/day (0.4 µg Ni/cm^2) for other scenarios. Worst-case dermal exposure levels range from 0.37 mg Ni/day (0.44 µg Ni/cm^2) to 1.8 mg Ni/day (0.9 µg Ni/cm^2).

Typical dermal exposure levels of nickel dinitrate range from 0.04 mg Ni/day (0.048 µg Ni/cm^2) for use in chemical pre-treatment of metals to 0.8 mg Ni/day (0.4 µg Ni/cm^2) for other scenarios. Worst-case dermal exposure levels of range from 0.4 mg Ni/day (0.48 µg Ni/cm^2) to 1.4 mg Ni/day (0.7 µg Ni/cm^2).

Typical dermal exposure levels of nickel carbonate have been estimated to 0.4 mg Ni/day (0.2 µg Ni/cm^2) and worst-case dermal exposure levels to 0.8 mg Ni/day (0.4 µg Ni/cm^2).

The report recognises that exposure to nickel occurs in welding. The welding process is characterised by the presence of a number of substances potentially hazardous to health, present both as part of the welding materials (rod, core etc.) and as components of the surfaces to be welded. The hazards associated with the process are primarily associated with the fumes generated, and the composition of these fumes depends on the components of the welding process, as well as on the welding method used and need to be considered as a process.

Consumer exposure

Consumer exposure to nickel metal occurs by dermal exposure to nickel-ion releasing products and by oral exposure to the soluble nickel ion.

Consumers are exposed to nickel metal via dermal contact with a range of nickel-containing objects.

One type of exposure to certain nickel-containing objects occurs when contact is directly with undamaged skin, and where the contact is prolonged. Examples of this are jewellery, watches and a

number of other objects. In this case the assessment is made in terms of the measured nickel release rate in µg/cm^2/week.

A second type of dermal exposure is equally direct, but where the exposure time is less prolonged. Examples are coins, tools and other nickel-releasing surfaces. This second type of consumer exposure is similar in all respects to the occupational exposure to the same range of objects, although the frequency of consumer exposure would normally be expected to be less than for occupational exposure.

Insertion of piercing posts in connection with ear piercing or piercing in other parts of the body involves two different types of exposure. Initial insertion of the post involves direct contact with a wound during the period of epithelisation. Following epithelisation, the contact is a contact similar to the "direct and prolonged" contact described above. This form of consumer exposure is already regulated in the EU.

Consumer exposure also includes exposure to nickel in food from nickel-plated and nickel-alloy food-contact materials and kitchen utensils. Whilst the release is related to metallic nickel, the effects are due to nickel dissolved in the food or water.

The nickel release to food from stainless steel surfaces is considered to be negligible in comparison with the amounts of nickel naturally present in food. No information was available on the release of nickel from other nickel-releasing surfaces, such as nickel-iron or nickel-silver alloys, or nickel-plated surfaces, to food. Nickel can be released to drinking water from pipes and taps, and from nickel surfaces in kettles and other water-heating appliances.

The maximum release after descaling of a kettle is calculated to lead to a short-term daily intake of 1.0 mg nickel per day. An average consumer could have a daily intake of 0.24 mg Ni, with a lower range of 0.026 mg Nickel from this source.

The estimated release of nickel into drinking water from taps or piping with nickel surfaces exposed to stagnant water has been calculated as 0.003 mg/kg bw/day.

Consumer exposure to medical uses of nickel (iatrogenic implants, orthodontic materials, release from syringes etc.) is regulated in the EU

The only known consumer exposure to nickel sulfate or nickel chloride is as a component of multivitamin/mineral food supplements. The dose per tablet is often 5 □g Ni for adults (ca. 0.08 µg/kg for a 60 kg adult), but tablets with up to 100 µg Ni for adults (ca. 1.7 µg/kg for a 60 kg adult) have been reported. Tablets for children may contain 1 µg Ni (ca. 0.08 µg/kg for a 12 kg toddler). The recommended dose for many of these mineral supplements is 1 tablet per day.

There is no known consumer exposure to nickel dinitrate or nickel carbonate.

Indirect human exposure

The Indirect Human Exposure assessment describes the indirect exposure of the general population to nickel for the geographical local scales of the nickel producing/using sectors and for the EU regional scale. Indirect exposures include exposure to nickel via drinking water, inhalation of air, ingestion of soil and dust, and through the diet. Indirect exposures are first described as external exposures to humans. Subsequently, these values are converted to aggregate internal doses. The external doses were used for assessing local effects in relation to inhalation (respiratory effects), and internal doses were used for assessing systemic effects. A Combined Exposure scenario was also included where the indirect exposures and the workplace and consumer exposures were aggregated.

External Exposures

For the regional scale, dietary intake was found to be the most important exposure pathway. Over 95 % of the external Ni exposure under normal conditions originates from dietary intake. A diet consisting of foods with very high natural nickel content (e.g., breads, cereals, certain fruits) corresponding to the 99th percentile of the dietary exposure was also evaluated. The indirect exposure at the local scales can be significantly influenced by the air contribution (up to 23 % of the typical external exposure, e.g., refining sector).

Absorbed doses

In order to aggregate exposures by the different pathways, the external exposure values can be first converted to absorbed doses, accounting for the different absorption rates from the different intake media. At the

regional level, food is still the dominant contributor to the absorbed dose. For some industrial sectors, air becomes the most significant source of absorbed nickel.

Environmental exposure

Nickel is a naturally occurring element with a ubiquitous distribution in the environment. It is found in high concentrations in nickel ores. Economically workable deposits of nickel for nickel metal production are ores which can be classified as either sulphidic or laterite (oxides or silicates). Approximately two thirds of the world's known nickel resources for production of nickel metal are in the form of nickel bearing laterites, and the remaining third as sulphides. The principle sulphidic ores contain the mineral pentlandite [Fe,Ni_9S_8] which is almost always found associated with chalcopyrite [$CuFeS_2$] and large amounts of pyrrhotite [$Fe_{1-x}S$]. Occasionally, sulphidic nickel ores can be found in combination with arsenic minerals, such as niccolite [NiAs] and gersdorffite [NiAsS]. Natural sources of airborne nickel include soil dust, sea salt, volcanoes, forest fires, and vegetation exudates.

The main sources of Ni emissions at a continental and regional scale are (% specific to western Europe presented in parentheses below):

- to agricultural soil: application to agricultural soil of phosphate fertiliser (52%), manure (39%), sewage sludge accounts (9%);
- to air: oil combustion (70%) -i.e. industrial combustion processes; power production, refineries, other activities-. Industry (17%) -i.e. metal production and processing, basic organic chemicals production, production of cement, lime, glass, mineral substances or ceramic products- and traffic (10%) are less important sources
- to surface water (direct emissions): waste management (70%) -i.e. in particular waste water treatment plants- and industry (24%) -i.e. metal production and processing; basic inorganic and organic chemicals production.

Important industrial sectors discharging nickel to an off-site waste water treatment plant are the following: metal production and processing (53% of facilities), basic organic chemicals production (16%), installations for surface treatment -i.e. plating- (10%) and waste treatment installations (15%).

Industrial surface water emitters are Ni metal producers (9% of total industrial emissions), multiple steel product manufacturers (5%), Ni chemicals producers (3%) and Ni plating sites (3%).

Industry sectors emitting to air are Ni metal production (12%), stainless steel production (15%), multiple steel product manufacturers (3%) and other steel production (2%).

These data were mainly based on extrapolated emission data from local sites.

Modeled Ni concentrations for the plating sector showed the highest site-specific concentrations for the aquatic and sediment compartments, and also exhibited the greatest variability.

Median PECtotal concentrations ranged from 3.9 µg Ni/L (chemical manufacturing sector) to 5.2 µg Ni/L (powder metallurgy sector) for the aquatic compartment, and from 33.5 mg Ni/kg (battery manufacturing sector) to 85.0 mg Ni/kg (powder metallurgy sector) for the sediment compartment. Median PECtotal values for soil ranged from 5.5 mg Ni/kg (steel sector) to 17.6 mg Ni/kg (chemical manufacturing sector).

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The five substances are candidates for further work. The chemicals possess properties indicating hazards for human health depending on the individual substances, acute oral and inhalation toxicity, skin and severe eye irritation, skin and respiratory sensitisation, chronic inhalation toxicity, genotoxicity, carcinogenicity by inhalation and reproductive toxicity. Other member countries are invited to perform an exposure assessment and if necessary a risk assessment.

Environment: Nickel and the 4 nickel substances considered are candidates for further work. The ionic (bioavailable) form has properties indicating a hazard for the environment (chronic toxicity). Member countries are invited to conduct an exposure assessment for the environment (including

bioavailability assessment) and if necessary an environmental risk assessment**.**