Example F: INORGANIC NICKEL COMPOUNDS.

[Note: Inorganic nickel compounds have not been assessed by SIAM yet. The description below is based on the work of the Danish Environmental Protection Agency under the OECD SIDS and the EU existing chemicals programmes, as well as the discussions held at the OECD workshop on the development and use of chemical categories held in January 2004. The descriptions below might have to be revised once the compounds have undergone assessment at SIAM.]

Step 1: Identification of structure-based category and its members:

75. The category is initially defined as "nickel and nickel compounds". This description is a category already widely used in EU legislation. "Nickel and nickel compounds" includes over 300 compounds of very diverse chemical structure. Numerically, organic nickel compounds outnumber inorganic nickel compounds. The category includes a number of complex compounds, many of which are waste products. The wide diversity of chemical types suggests that whilst it is useful as a category in identifying compounds that contain nickel and may therefore potentially be a source of nickel release, it is not a useful category in the sense that it provides a basis for predicting effects that are similar to all members of the group.

76. A second type of grouping of nickel compounds is also used. This divides nickel compounds into five groups: Metallic nickel, oxidic nickel, sulphidic nickel, soluble nickel and nickel carbonyl. These groups reflect the nickel compounds seen during nickel refinery production, rather than the wider range of nickel chemicals on, or potentially on, the market. These different categories have been used in some countries as the basis for different Occupational Limit Values (OELs) based on differences in the types and potency of different mammalian toxicological effects.

77. There are a number of assumptions underlying any grouping of nickel compounds for estimating their biological properties. The main assumption is that it is the nickel ion that is responsible for the effects to be assessed. This is considered to be a reasonable assumption for the majority of the inorganic anions of nickel compounds and for some organic anions. This implies that in the case of inorganic metal salts, the hazard assessment is based on the known toxicity of the cation.

78. The basis of any grouping would therefore be the water solubility of the nickel salt. Two reports prepared for the Danish EPA by Lars Carlsen[8] have collected and assessed the available data for water solubility of inorganic nickel compounds (Carlsen, 2001a) and organic compounds (Carlsen, 2001b).

79. For inorganic nickel compounds, a grouping of inorganically based nickel species has been suggested. Nickel metal and nickel metal compounds can all be considered as insoluble. Nickel oxides and mixed metal oxides are also very similar in terms of their solubility. In the table below, a grouping of the nickel ligands with Group 13, 14, 15, 16 and 17 ligands is suggested. The term 'insoluble' means that the solubility of the species is less than 10^{-4} mol/L, 'slightly soluble' covers the solubility range 10^{-4} - 10^{-2} mol/L, 'soluble' the range 10^{-2} - $5 \cdot 10^{-1}$ mol/L and 'very soluble' refers to solubility above $5 \cdot 10^{-1}$ mol/L.

80. It should be noted that the group of "insoluble" compounds, with solubility < 10^{-4} mol/L, may nevertheless have a solubility in excess of 1 mg/L, depending on the actual solubility and the molecular

[8] Carlsen L (2001a): Aqueous Solubilities and Complex Stabilities of Ni(II) Species. Part I: Inorganic Ligands. Draft report to the Danish EPA.
Carlsen L (2001b): Aqueous Solubilities and Complex Stabilities of Ni(II) Species. Part II: Organic Ligands. Draft report to the Danish EPA.

weight. Hence substances conventionally thought of as "insoluble" by chemists or toxicologists may still be sufficiently soluble to be regarded as such in evaluating effects on the aquatic environment.

Grouping of nickel species based on inorganic ligands in water (from Carlsen, 2001a).

	Group 13	**Group 14**	**Group 15**	**Group 16**	**Group 17**	**Misc.**
Insoluble	Ni_XB	Ni_XSi	Ni_XP_Y Ni_XAs Ni_XSb_Y $Ni_2P_2O_7$ $Ni_3(AsO_3)_2$ $Ni_3(AsO_4)_2$ $Ni(AsO_3)_2$	Ni_XS_Y Ni_XSe Ni_XTe		$Ni_2Fe(CN)_6$
Slightly soluble		$Ni(CO)_4$ $Ni(CN)_2$ $NiCO_3$ $Ni(HCO_3)_2$	$Ni_3(PO_4)_2$ $Ni[NiP_2O_7]$	$NiSO_3$[a] $NiSeO_3$	$Ni(IO_3)_2$	$Ni_2Fe(CN)_5NO$
Soluble				$NiK_2(SO_4)_2$	NiF_2	
Very soluble	NiB_6O_{10} $Ni(BF_4)_2$	$Ni(SCN)_2$ $NiSiF_6$	$Ni(NO_3)_2$ $Ni(H_2PO_2)_2$	$NiSO_4$ $Ni(SO_3NH_2)_2$[a] $NiSeO_4$	$NiCl_2$ $Ni(ClO_3)_2$ $Ni(ClO_4)_2$ $NiBr_2$ $Ni(BrO_3)_2$ NiI_2	

81. No comparable grouping of organic ligands has yet been carried out (Carlsen, 2001b). In contrast to the inorganic nickel compounds it is not obvious how to group the organically based species based on solubilities alone. Aqueous solubilities are not unexpectedly seen to decrease with increasing molecular weight and increasing carbon content of the ligand. On the other hand, the introduction of hydrophilic and/or polar functional groups, such as OH, C=O, COO^-, NH, SH and SO_3^- cause increased solubilities. Further it should be emphasized that the solubility of the complexes cannot immediately be related to the solubility of the single ligands. Hence, it seems more appropriate to group organically based nickel complexes based on the stability of the complexes. As a first attempt, grouping the individual complexes based on the nature of the ligand appears as an obvious choice, even though significant variations in stability may prevail within the single groups. However, a number of nickel salts of simple organic acids can be considered to behave in a similar way to inorganic salts with a similar solubility.

Step 2: Gather published and unpublished data for each category member.

82. There is a vast database on the human health effects of nickel compounds. 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. However, the data available for any individual nickel compounds can vary considerably. The two compounds for which there is data that covers most endpoints are the two soluble compounds, nickel chloride and nickel sulphate. Much of the database relating to nickel metal is linked to sensitisation.

On the other hand, there is virtually no data at all for most nickel compounds. In particular, data on the organic nickel compounds is extremely limited.

Step 3: Evaluate data for accuracy.

83. Much of these human health data have been reviewed in good quality reviews including UK HSE (1987)[9], IARC (1990)[10], IPCS (1991, 1996)[11], US ATSDR (1997)[12] and a Nordic Expert Group (Aitio, 1995)[13]. NiPERA in collaboration with Eurométaux have also produced a criteria document for nickel and nickel compounds for the European Commission (NiPERA 1996)[14]. 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)[15].

84. In depth reviews of metallic nickel, nickel sulphate, nickel chloride, nickel nitrate and nickel (hydroxy)carbonate have been prepared by the Danish EPA.

Step 4: Construct a matrix of data availability.

85. A matrix of available data included in the draft risk assessment reports prepared under the OECD SIDS and the EU existing chemicals programmes is shown below for nickel metal, nickel sulphate, nickel chloride, nickel nitrate and nickel carbonate[16].

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[9] Toxicity Review 19. The toxicity of nickel and its organic compounds. Fairhurst & Illing. London. HMSO. ISBN 0 11 883961 6

10 IARC Monographs on the evaluation of carcinogenic risks to humans, Volume 49, Chromium, nickel and welding. IARC, Lyon, France, 1990. pp. 257-446.

11 Environmental Health Criteria 108: Nickel. World Health Organisation, Geneva. 383 p.; IPCS (1996): Guidelines for drinking water quality. Volume 2. Health criteria and other supporting information. World Health Organisation, Geneva, 1996 p. 308-313.

12 Toxicological Profile for Nickel. September 1997. US Department of Health and Human Services, Public Health Service.

13 Nickel and nickel compounds. The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals. Arbete och Hälsa vetenskaplig skriftserie 1995:26, no 119. Solna: Arbetslivsinstitutet, 1995: pp. 1-61.

14 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.

15 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.

16 The compound reported as a HPV chemical to IUCLID was nickel carbonate (CAS No. 3333-67-3). In the course of subsequent discussions with the Industry, it became clear that the marketed product was in fact a nickel hydroxycarbonate. 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. As it is not always clear from the study reports which precise carbonate has been tested, the results are shown as "nickel carbonate".

86. Data is also available for some other nickel compounds in the reviews quoted above and from the data included in IUCLID. As no substance-specific reviews have been carried out on these substances, the data available for each substance is regarded as indicative only. Further work is needed to refine this matrix.

87. In addition data is available on the EU provisional categorization supplied by the producer/importer from IUCLID is available for a number of other nickel compounds, including a number of organic compounds and complex waste products such as slimes and sludges. It is not clear whether these have been based on experimental evidence or on assumptions about the properties of the compounds (i.e. application of a group approach).

88. The main nickel compounds studied are those directly associated with the (refinery) production of metallic nickel, and nickel alloys. Some of the intermediate products (nickel matte, ferro-nickel) in this production process do not appear to have been studied. The data on nickel compounds not directly associated with these processes appears to be very limited. The information on "downstream" nickel compounds, and in particular, the organic nickel compounds, is limited. The information available from IUCLID is difficult to interpret as there is little or no experimental data reported for these substances.

Matrix of data availability on selected nickel compounds.

Nickel compound	Environ-mental fate	Ecological effects*			Human Health effects **			
		Fish acute	Daphnid acute	Daphnid chronic	Acute	Repeated dose	Mutagenicity	Developmental
nickel metal* **	dissolution protocol	-	-	-	√	√	(√)	-
nickel oxide	transforma-tion test	√	√	-	√	√	√	-
nickel sulfide / subsulfide	screening test	-	√	-	√	√	√	-
nickel dihydroxide	screening test	-	√	-	√	-	(√)	-
"nickel carbonate"	dissolution protocol.	-	-	-	√	(-)	(√)	-
nickel acetate	soluble	-	-	√	√	-	√	-
nickel sulphate	soluble	√	√	√	√	√	√	√
nickel chloride	soluble	√	√	√	√	√	√	√
nickel nitrate	soluble	√	√	√	√	-	√	-
nickel carbonyl	soluble	-	√	-	√****	-	-	-

Key: "√" denotes data available for the substance/endpoint. There may not necessarily at present be agreement on the interpretation of this data. "(√)" indicates that there is some data, but that additional data may be needed. "(-)" indicates only very limited data from which no conclusions can be drawn. "-" denotes no data available.
Shaded areas show six possible subgroups (the five subgroups shown in step 1 and sparingly soluble nickel hydroxide and carbonate).
*: data concerning other endpoints and species are available and are being considered.
**: data is also available for sensitisation and carcinogenicity
***: nickel metal powder (INCO123) and nickel granules have been tested. Only the powder has been tested in the 28 d dissolution test however
****: data available for inhalational exposure. Data for other nickel compounds is oral data only.

89. The matrix shown above includes the main SIDS endpoints. However, major concerns with nickel and nickel compounds are related to sensitisation and carcinogenicity, endpoints not included in SIDS. Evaluation of these endpoints is important in the evaluation of this particular group of substances.

Step 5: Perform an internal assessment of the category.

90. The subgroup for which most data is available are the soluble nickel salts. The available data suggests that "read-across" within this group is justified. The available data also suggest that the effects of the different nickel compounds are related to water solubility, although different endpoints may behave differently.

91. In applying the aquatic hazard classification rules for nickel compounds, soluble and slightly soluble compounds can be distinguished. For the soluble compounds, no T/D protocol is required. For slightly soluble compounds, the use of T/D protocol, i.e. solubility dependency of pH at environmentally realistic pHs is used.

92. Acute oral toxicity decreases with decreasing water solubility and is of concern for soluble and slightly soluble compounds. Inhalational repeated dose toxicity on the other hand is shown by both soluble and insoluble nickel compounds. There is also evidence of *in vivo* mutagenicity for both soluble and insoluble compounds, although the evidence for insoluble compounds is much less than for soluble compounds. Whilst there is an effect on developmental reproductive toxicity for the soluble nickel compounds, there is little data on which to evaluate this effect in slightly soluble or insoluble compounds.

93. Whilst the environmental effects of nickel carbonyl appear to be consistent with the results expected from its water solubility, its effects on human health are not like any of the other nickel compounds studied. The valence state of nickel in this compound in Ni(0) rather than Ni(II) in most of the other compounds studied.

94. The available data for metallic nickel for key endpoints such as carcinogenicity is not adequate to assess the effects of the metal.

Step 6: Prepare category test plan.
Step 7: Conduct necessary testing.
Step 8: Perform an external assessment of the category.

95. Additional testing is currently underway to evaluate certain aspects of the carcinogenicity of nickel compounds. Metallic nickel is being tested following inhalational administration and nickel sulphate following oral administration.

96. Industry has initiated a research programme concerning the influence of abiotic factors on the (chronic) ecotoxicological effects of nickel using the BLM theory[17]

97. There are no plans at the present time for specific testing aimed at providing data on this category as a whole.

Step 9: Fill data gaps by read-across, extrapolation, interpolation etc.

[17] Biotic Ligand Model

98. The use of read-across for specific endpoints within the limited group of substances for which data is available is clearly acceptable. This being the case, it seems reasonable to consider to what extent the same approach can be applied to the much larger group of "nickel and nickel compounds".

99. In cases where there are clear similarities to the compounds considered above, the use of read-across to evaluate the hazards of these compounds would seem justified. For example, soluble nickel(II) salts would be expected to show the same effects as the other soluble salts evaluated on the basis of their measured data.

ANNEX 2

DEFINITIONS

1. Structure-Activity Relationships (SARs) and Quantitative Structure-Activity Relationships (QSARs), collectively referred to as (Q)SARs, are theoretical models that relate chemical structure to a physicochemical property, environmental fate parameter, toxicological (human health) or ecotoxicological (environmental species) effect.

2. A SAR is a qualitative association between a chemical substructure (called a structural alert or pharmacophore) and an effect or biological activity. The association can be positive (if the chemical substructure is associated with the *presence* of the effect/activity) or negative (if the chemical substructure is associated with the *absence* of the effect/activity). A structural alert is a two-dimensional fragment, whereas a pharmacophore is a three-dimensional arrangement of key molecular features.

3. Structural alerts are hypotheses that are generally based on the observation that, within a set of chemical structures, the proportion of chemicals containing the fragment and exhibiting the presence (or absence) of the effect/activity is greater than the proportion of chemicals lacking the fragment and exhibiting absence (or presence) of the effect/activity. An example would be the assumption that a new chemical entity containing an aromatic amine grouping is likely to exhibit skin sensitising effects (Cronin et al, 2003).

4. Pharmacophores are hypotheses that are generally based on molecular modeling studies in which similar chemicals are compared in terms of their three-dimensional shape and distribution of charge, and commonalities are observed in the three-dimensional arrangement of key features between chemicals exhibiting the presence (or absence) of a certain/activity. An example would be a pharmacophore for predicting the estrogenicity of steroidal molecules (Fang et al, 2001).

5. A QSAR is a quantitative (mathematical) relationship between a numerical measure of chemical structure, or a physicochemical property, and an effect/activity. QSARs often take the form of regression equations, and can make predictions of effects/activities that are either on a continuous scale or on a categorical scale. Thus, in the term "QSAR", the qualifier "quantitative" refers to the nature of the relationship, not the nature of the endpoint being predicted. An example of a QSAR would be the prediction of acute toxicity to an invertebrate species (*Tetrahymena pyriformis*) by means of a regression equation with the partitioning behavious (log P value) of the chemical as a descriptor (Schultz et al, 2002).

6. A Quantitative Activity-Activity Relationship (QAAR) is a mathematical relationship between two types of biological activity. In general, a QAAR expresses the correlation between a biological endpoint in one species and a "similar" endpoint in another species. A QAAR can be used to extrapolate from an invertebrate species to a vertebrate species, thereby reducing the need for animal experimentation. An example would be the prediction of acute toxicity to the guppy fish by using data on acute toxicity to the ciliated protozoan *Tetrahymena pyriformis* (Seward et al., 2002).

References

Cronin, M.T.D., Walker, J.D., Jaworska, J.S., Comber, M.H.I., Watts, C.D. & Worth, A.P. (2003a). Use of quantitative structure-activity relationships in international decision-making frameworks to predict ecologic effects and environmental fate of chemical substances. *Environmental Health Perspectives* **111**, 1376-1390.

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Fang, H., Tong, W., Shi, L.M., Blair, R., Perkins, R., Branham, W., Hass, B.S., Xie, Q. Dial, S.L., Moland, C.L. & Sheehan, D.M. (2001). Structure-Activity Relationships for a Large Diverse Set of Natural, Synthetic, and Environmental Estrogens. *Chemical Research in Toxicology* **14**, 280-294.

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プログラム

■開会の挨拶　13:30～13:40

林　真（国立医薬品食品衛生研究所　安全性試験研究センター変異遺伝部）

■セッション1　13:40～15:15

座長:江馬　眞（国立医薬品食品衛生研究所　安全性試験研究センター総合評価研究室）

・OECDにおけるカテゴリーアプローチの現状

Bob Diderich (OECD/EHS)

・化学物質安全性評価の為のカテゴリーアプローチ

林　真（国立医薬品食品衛生研究所　変異遺伝部）

鎌田 栄一（国立医薬品食品衛生研究所　総合評価研究室）

■セッション2　15:15～16:05

座長:江馬　眞（国立医薬品食品衛生研究所　総合評価研究室）

・物理化学性状・環境運命におけるカテゴリーアプローチ

川原 和三（化学物質評価研究機構　安全性評価技術研究所）

・生態毒性分野におけるカテゴリーアプローチの検討について

白石 寛明（国立環境研究所　化学物質環境リスク研究センター）

■休　憩　16:05～16:25

■セッション3　16:25～17:25

座長:林　真（国立医薬品食品衛生研究所　変異遺伝部）

・化学工業界におけるカテゴリーアプローチの課題

菅原 尚司（日本化学工業協会　化学品管理部）

・カテゴリーアプローチと化学物質安全対策

江原 輝喜（厚生労働省　化学物質安全対策室）

・総合討論

■閉会の挨拶　17:25～17:30