EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL

Directorate C - Public Health and Risk Assessment
C7 - Risk assessment

SCIENTIFIC COMMITTEE ON HEALTH AND ENVIRONMENTAL RISKS (SCHER)

Opinion on

Risk Assessment Report on

NICKEL (CAS-NO.: 7440-02-0, EINECS-NO.: 231-111-4)
NICKEL CARBONATE (CAS-NO.: 3333-67-3, EINECS-NO.: 222-068-2)
NICKEL CHLORIDE (CAS-NO.: 7718-54-9, EINECS-NO.: 231-743-0)
NICKEL DINITRATE (CAS-NO.: 13138-45-9, EINECS-NO.: 236-068-5)
NICKEL SULPHATE (CAS-NO.: 7786-81-4, EINECS-NO.: 232-104-9)

Human health part

Adopted by the SCHER
during the 11th plenary of 4 May 2006

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1. BACKGROUND

Council Regulation 793/93 provides the framework for the evaluation and control of the risk of existing substances. Member States prepare Risk Assessment Reports on priority substances. The Reports are then examined by the Technical Committee under the Regulation and, when appropriate, the Commission invites the Scientific Committee on Health and Environmental Risks (SCHER) to give its opinion.

2. TERMS OF REFERENCE

On the basis of the examination of the Risk Assessment Report the SCHER is invited to examine the following issues:

(1) Does the SCHER agree with the conclusions of the Risk Assessment Report?

(2) If the SCHER disagrees with such conclusions, it is invited to elaborate on the reasons.

(3) If the SCHER disagrees with the approaches or methods used to assess the risks, it is invited to suggest possible alternatives.

3. OPINION

3.1 General Comments

The health part of the document is of good quality, it is comprehensive and the exposure and effects assessment follows the Technical Guidance Document (TGD). The Risk Assessment Report (RAR) mainly relies on a number of recent reviews on the toxicology of nickel and its salts and covers most of the studies relevant for exposure and hazard assessment of nickel. In addition to information available on the five nickel compounds under review, information on some other nickel compounds was taken into account as appropriate. Further to the individual reports on individual nickel salts and metallic nickel, a “summary report” is presented by the Member State Rapporteur. This certainly helps to increase transparency of the assessment, and it may be worthwhile to include the overall conclusions in this “summary report”.

However, parts of the RARs and the summary paper have redundancies or describe general aspects of toxicology; the RAR may be condensed to improve readability of the document. The SCHER also recommends moving the chapter on cell transformation tests from the mutagenicity to the carcinogenicity section.

The human health part of the RAR is separated into a general discussion on health effects of nickel 2+ ions, which usually are the nickel species responsible for toxic effects and a detailed discussion of the toxicity of nickel metal and four specific nickel salts.

As usual, the exposure assessment develops a number of scenarios for the different nickel derivatives considered in the RAR and gives Margin of Safety (MOS) values for both reasonable and worst case assessments of human exposures.

Genotoxicity

In earlier epidemiological studies assessing effects of inhalation exposures to soluble nickel compounds, an increase in chromosomal aberrations was reported in peripheral lymphocytes of workers in electrolytic, nickel refining or in nickel plating plants. A more recent study in workers of an electrolytic nickel refinery, where state-of-the-art protective measures are applied, showed no increased formation of micronuclei in epithelial cells of the buccal mucosa. There was a higher incidence of metaphases with gaps, but no significant increases in sister chromatid exchanges in lymphocytes of persons exposed to nickel oxides and sulphides at a nickel smelter. Increases in the frequency of chromosomal aberrations were not observed in peripheral lymphocytes of workers exposed to metallic nickel.

There is clear evidence for the *in vitro* genotoxicity of nickel salts. Although most of the classical bacterial and mammalian cell culture mutagenicity tests yielded negative results, positive effects were generally seen in studies on chromosomal effects (chromosomal aberrations, sister chromatid exchanges, micronuclei), and tests for DNA damage and repair. Mutations in the TP53 tumour suppressor gene have been demonstrated after chronic exposure of human cells to nickel salts.

In vivo, soluble nickel salts resulted in induction of chromosomal aberrations and gave positive results in the Comet assay. Both soluble and insoluble nickel compounds can cause DNA breaks and DNA-protein crosslink *in vivo*. Nickel chloride and nickel sulphate gave both positive and negative results in micronucleus tests after intraperitoneal and oral (nickel sulphate) administration.

No adequate data are available to demonstrate the genotoxicity of metallic nickel.

Nickel chloride gave negative results in the dominant lethal test in mice. However, based on evidence of *in vivo* genotoxicity in somatic cells, the possibility that germ cells are affected by nickel salts can not be excluded.

The Member State Rapporteur proposes conclusion (i)[1] for nickel chloride, nickel sulphate, nickel carbonate and nickel nitrate, since there is a need for further studies to evaluate the possible effects on germ cells, but "further testing is not considered practicable". SCHER concurs with conclusion (i) and would appreciate justification why further testing was considered "not practicable".

SCHER also agrees with conclusion (i) for nickel metal because there is a need for further studies to evaluate the possible genotoxic effects of metallic nickel (depending on the results of the inhalation carcinogenicity study currently performed with nickel metal).

Carcinogenicity

Nickel compounds are considered as human carcinogens based on epidemiological studies, mechanistic information, and evidence from animal studies. The overall findings indicate that

[1] *According to the Technical Guidance Document on Risk Assessment – European Communities 2003:*

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

nickel ions generated in target cells are critical determinants for the carcinogenic process. This has resulted in the consideration and evaluation of nickel and nickel salts as a single group regarding classification for carcinogenicity.

Epidemiological studies

Epidemiological studies in Welsh, Finnish and Norwegian cohorts of refinery workers have shown strong evidence of a dose related increase in lung cancer risk in association with the exposure to water-soluble nickel compounds. The lack of evidence of risk associated with water-soluble nickel among a cohort of Canadian electrolysis workers is explained by lower exposures to water-soluble forms as well as exposure to less soluble forms. The Finnish study also indicated an increased risk of nasal cancer. Less evidence for a causal relationship between exposure and lung cancer risk exists for nickel sulphides and oxides, and no clear evidence of an increased lung cancer risk due to exposure to metallic nickel is available.

Animal studies

A series of long-term inhalation experiments was performed by the U.S. National Toxicology Programme (NTP, 1996) in rats and mice with aerosols of nickel subsulphide, nickel oxide, or nickel sulphate hexahydrate for 2 years. In rats, tumours were found in a dose-dependent manner after exposure to nickel subsulphide, some evidence of carcinogenicity was found for nickel oxide. No evidence of carcinogenicity was seen in male mice, and an equivocal result for nickel oxide in female mice. For the water-soluble nickel sulphate hexahydrate, no carcinogenic activity was seen, either in mice or rats, possibly due to the relatively low lung burden of nickel, which was approximately 6 times lower as compared to that obtained with the lowest exposure concentrations of nickel subsulphide.

A number of animal studies on the carcinogenicity of nickel metal following inhalation or intratracheal instillation have been performed. Local neoplasm were observed in most of the studies; however, all the studies suffered from inadequacies and are not considered appropriate for the assessment of the carcinogenic potential of nickel metal following inhalation. No inhalation or intratracheal studies were available for nickel chloride, nickel nitrate, and nickel carbonate.

The carcinogenicity of nickel sulphate following oral exposure has been studied earlier in rats and dogs, and in a recent OECD 451 compliant carcinogenicity study in rats. This study did not show any treatment related increase in tumours related to the exposure and confirmed the earlier negative results. No data regarding carcinogenicity of nickel chloride, nickel nitrate, nickel carbonate, and nickel metal following oral administration in experimental animals were available. There is some evidence, though limited, that soluble nickel compounds may act as tumour promoters by this route.

There are no data on carcinogenicity following dermal exposure of nickel compounds.

Some evidence exists for local carcinogenicity of nickel compounds following direct injection at various sites to experimental animals.

Conclusions

Regarding occupational exposures by inhalation of nickel and its salts, the RAR derives conclusion (iii) for many of the developed exposure scenarios regarding repeated dose toxicity, even when using reasonable exposure assessment approaches. Conclusion (iii) in these cases is supported by SCHER.

The RAR also concludes that nickel salts, after inhalation exposures, are carcinogenic in humans based on the evaluation of tumour incidences in several cohorts of workers exposed to nickel or Ni-salts by inhalation. Conclusion (iii) for the developed occupational scenarios with inhalation exposure to nickel is justified since high cancer risks are predicted using unit risks derived from the occupational studies. Moreover, no threshold for the carcinogenicity of nickel can be identified based on epidemiology and the available experimental studies on nickel carcinogenicity after inhalation in rodents.

However, the RAR should elaborate the reasons why Ni-salts with low solubility are more potent then readily soluble Ni-salts. Based on the description in the RAR, a particle effect resulting in lung overload may be assumed as a possible mode-of-action for lung tumours.

A number of biochemical studies suggest that nickel ions are the active species and that the release of nickel ions is responsible for the genotoxic and carcinogenic effects of all forms of nickel. Nickel ions from readily soluble nickel salts are slowly taken up into mammalian cells through plasma membrane ion channels. In contrast, nickel metal and the less soluble nickel sulphides and oxides are taken up by phagocytosis. Metallic nickel was phagocytized by alveolar macrophages of exposed rats (Johansson et al. 1980) and also in vitro by CHO cells (Costa and Mollenhauer 1980). Nickel subsulphide was also phagocytized by CHO cells (Lee et al. 1995). Inside mammalian cells, less soluble nickel compounds and nickel metal result in the release of nickel ions.

A much higher intracellular bioavailability of poorly soluble nickel compounds as compared to that of readily soluble nickel salts explains the higher potency of poorly soluble nickel salts and metallic nickel. The concentration of intracellular nickel ions was more than two orders of magnitude higher after phagocytosis of less soluble nickel salts as compared to uptake of soluble nickel salts. For example, in CHO cells treated with a suspension of nickel sulphide (10 mg/l), binding of nickel ions to nucleic acids was 300 to 2 000 fold higher as compared to incubation with the same concentration of soluble nickel salts (Harnett et al. 1982). After the phagocytosis of nickel subsulphide, very stable ternary protein-nickel-DNA complexes were formed in the nuclei of CHO cells (Lee et al. 1982) and intracellular nickel ion concentrations in the mmol/l range were calculated for poorly soluble nickel compounds.

This aspect needs to be put into context in the RAR to explain the conclusions of the former CSTEE regarding time-integrated intracellular concentrations of Ni^{2+} as the determinant of Ni-carcinogenicity.

Regarding oral exposures, most of the exposure assessments in the developed scenarios give high MOS. In addition, an adequate carcinogenicity study did not result in increased tumour incidences and the RAR concludes that oral exposure to nickel is not associated with a carcinogenic risk. The formal approach regarding risk assessment therefore results in conclusion (ii). The SCHER accepts this conclusion; however, it recommends that the conclusions needs to be viewed with caution since nickel ions are the active species responsible for tumour induction and nickel ions may also be absorbed after oral exposure to nickel salts.

Only the use of nickel salts in food supplements, due to the sensitizing properties of nickel, result in conclusion (iii), which is also supported by SCHER.

The SCHER also agrees with conclusion (ii) for the dermal route taking into account the risk reduction measures that are already being applied.

The SCHER also agrees with the conclusion (i) for nickel metal because there is a need for further studies to evaluate the inhalation carcinogenicity of nickel metal.

The SCHER notes that the risk for indirect exposure via the environment has not been addressed.

3.2 Specific Comments

Two carcinogenicity studies are mentioned in the RAR, whose results are indicated to be available in 2004 resp. 2006. If the results of these studies are available, they should be included into the final assessment.

4. REFERENCES

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6. ACKNOWLEDGEMENTS

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