UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

July 11, 1986

OFFICE OF
THE ADMINISTRATOR

Hon. Lee M. Thomas
Administrator
U.S. Environmental Protection
Agency
Washington, D.C. 20460

Dear Mr. Thomas:

The Science Advisory Board's Environmental Health Committee has completed its review of the Office of Research and Development's Health Assessment Document for Nickel. The Committee carried out its review through its Metals' Subcommittee which met on March 24-25, 1986. The Subcommittee's report is attached.

The document appropriately characterizes the current scientific literature on the carcinogenicity of nickel compounds. This current revised document is much improved in a number of ways over the previous draft. The Subcommittee identifies some remaining revisons that the Agency staff should incorporate into the final document before its final publication.

The Board thanks you for the opportunity to present its scientific comments on this issue and requests that a formal Agency reply be prepared in response to the attached report.

Sincerely,

Norton Nelson
Chairman
Science Advisory Board

Richard A. Griesemer
Chairman
Environmental Health Committee

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

June 9, 1986 SAB-EHC-86-026

Dr. Richard A. Griesemer
Chair, Environmental Health Committee
Science Advisory Board
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

OFFICE OF
THE ADMINISTRATOR

Dear Dr. Griesemer:

The Metals' Subcommittee of the Environmental Health Committee met on March 24-25, 1986 in Farmington, Connecticut, to review the draft final Health Assessment Document for Nickel (EPA/600/8-83/012F; September, 1985). Subsequently, members of the Subcommittee prepared individual comments. This letter summarizes the Subcommittee's major conclusions.

The Environmental Health Committee reviewed a previous version of the document in September, 1983. The Subcommittee agrees that the current draft is responsive to our earlier comments. It now is clearer and more comprehensive, and with the corrections suggested by the Subcommittee, should be a scientifically accurate document. Since staff indicated that further editing is underway, our detailed comments have been transmitted directly to the Office of Research and Development (ORD). In addition, the Subcommittee recommends that ORD resolve some technical problems that remain in the three areas described below before the document is released in final form.

(1) As the document notes repeatedly, different forms of nickel exhibit different profiles of toxicity. Nickel subsulfide is appropriately acknowledged as presenting the most serious carcinogenic hazard, but the document lacks clarity beyond that conclusion. The scientific terminology from section to section is not always consistent, the chemistry of nickel is, at times, presented inaccurately, and the understanding of nickel manufacturing processes is incomplete. Moreover, the nickel-ion hypothesis, which asserts that the proximal carcinogenic form is divalent nickel ion in solution, seems overstated, especially on page 8-210.

(2) The discussion of nickel absorption, distribution, metabolism and elimination lacks a firm grasp of terminology and principles because of numerous instances of confusing and imprecise phrasing. For example, "clearance" and "elimination" are used interchangeably, but these are different processes. The term, "retention time," is used in a confusing way. The definitions and roles of metal binding proteins are presented inaccurately. The understanding of the principles of inhalation toxicology and of relevant empirical data seem limited, which leads in turn to incorrect assumptions and conclusions about the role of respiratory mechanics and function. As with other assessment documents, body surface area is used to correlate delivered doses between animals and humans. This is an incorrect assumption for substances delivered by inhalation.

(3) Neither the animal nor the European epidemiology data seem to be used properly for quantitative risk assessment. The animal data are seriously flawed and have limited utility for either extracting definitive conclusions or assessing human risk. For example, little confidence can be placed in a data set in which control animals exhibit 31% survival. The epidemiology data lack reliable exposure estimates and do not reveal much familiarity with the complexities of the manufacturing process. The quantitative risk assessment based on European epidemiology relies on U.S. cancer mortality rates for unexposed persons, despite the differences in these rates for U.K. and Norwegian population studies. This inappropriate adjustment could seriously bias the unit risk estimates derived from these studies.

We appreciate the opportunity to comment on this public health issue and hope that our comments are useful to the Science Advisory Board and the Agency.

Sincerely yours,

Bernard Weiss

Bernard Weiss, Ph.D.
Chair, Metals' Subcommittee

Ronald Wyzga

Ronald Wyzga, Sc.D.
Vice-chair, Metals' Subcommittee

U.S Environmental Protection Agency
Science Advisory Board
Environmental Health Committee
Metals' Subcommittee
March 25, 1986

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Executive Secretary

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DIVISION OF TOXICOLOGY
Toxicology Training Program
Environmental Health Sciences Center

April 28, 1986

Dr. Daniel M. Byrd III
Executive Secretary
Science Advisory Board
USEPA
401 M Street, S.W.
Washington, D.C. 20460

Dear Dr. Byrd:

Please find enclosed my post-meeting comments on HAD - Nickel - Speciation. I am also forwarding a copy to Bernie Weiss.

Sincerely,

Tom Clarkson

Tom Clarkson
Professor

tw/cmkb
enc.

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HAD - NICKEL - SPECIATION

TOM CLARKSON

POST-MEETING COMMENTS

INTRODUCTION

The HAD is well written and addresses the key issues raised in previous SAP reviews. These post-meeting comments are directed towards the speciation of nickel and its compounds - the physical and chemical species that contain nickel.

Speciation is a theme that permeates this document. Indeed the previous SAB review stressed its importance in all aspects of the HAD. One of the major issues - the "nickel ion" hypothesis for carcinogenesis devolves around the speciation of nickel. This brief post-meeting review will be presented under a number of sub-headings.

TERMINOLOGY

The public comments from INCO indicated ambiguities in the HAD. Sometimes the word "nickel" is used to indicate the element, sometimes to refer generically to all forms of nickel. Clearly this problem is common to all HAD's dealing with metals. In the case of mercury, the problem was solved by using the terms metallic mercury or elemental mercury when referring to the element. I do not regard this as an important issue but "down the line" it would be useful to develop consistent terms for all the metal HADs.

Public comments at the meeting drew attention to the many physical forms of nickel oxide. One of the public written comments (INCO) used the term "oxidic Nickel". Unfortunately some of the original publications do not always identify the specific physical form used in the study. Questions were also raised at the meeting on the use of the designation "chemical compound" for nickel oxides or complex oxides of nickel and other metals such as copper as the atomic proportions are variable. It was suggested that the word substance be used. I do not think this issue is sufficiently important to justify a complete check of all the publications on "nickel oxide" used in the HAD. The on-going "Nickel Speciation Research Project" in which the EPA is participating would help clear up this ambiguity for any future documents on nickel.

THE MANUFACTURING PROCESS

A thorough knowledge of the manufacturing process is essential to identifying each species of nickel of importance to human exposure. The public comments from one of the manufacturers emphasizes this point - "The retrospective estimation of environmental conditions can be done only by people familiar with the plants and processes and with access to industries records and personnel". Clearly the authors of the HAD are at a disadvantage in having to use

"second-hand" and frequently incomplete information in the published literature. It is obvious from the written comments and from those given at the meeting that the HAD has not identified all the species of nickel and other substances involved in human exposure at various stages of the manufacturing process. In this respect, the comments from the two principal manufacturers - INCO and Falconbridge - are specially important. Their detailed written comments on nickel species that exist at stages of the manufacturing process should be used to improve both the accuracy and scope of the HAD's treatment of speciation during manufacture, e.g., Table 8-1 is clearly incomplete. INCO's comments on speciation are too numerous to be detailed here.

ATMOSPHERIC NICKEL

The public comments agree with the HAD that currently available methods do not allow speciation of nickel at concentrations of total nickel found in the ambient atmosphere. Calculations made at the meeting indicate that direct speciation will remain unattainable in the foreseeable future. This lack of information is a critical gap in our knowledge in view of the controversy over which species of nickel may be regarded as carcinogenic.

HAD has attempted through one of its contractors to calculate the most probable species from thermodynamic and other considerations - in all, 19 species were identified. The public comments urge that a more practical approach could be made by measuring the forms of nickel in the undiluted emission sources to the atmosphere. Techniques are available to speciate nickel into water soluble forms, Ni_3S_2, metallic nickel and "nickel oxide". In addition, it will be necessary to know the relative contributions from the different emission sources and the residence time of each species in the atmosphere. These estimates clearly cannot be included in the current HAD but should remain an important objective for the future.

TOXICITY AND CARCINOGENICITY

The HAD adequately covers the importance of speciation in determining toxicity and carcinogenicity. Some of the earlier papers may not have satisfactorily identified the precise species of nickel, e.g. the specific form of nickel oxide.

Theories on mechanisms of carcinogenesis are appropriately mentioned in the HAD but it remains for future research to further elucidate these mechanisms. The so-called "nickel-ion" hypothesis is at best vague and interpreted differently by different people as at the meeting. One interpretation is that the nickel ion reacts directly with DNA to initiate the carcinogenic process. However, as noted by Nieboer, many other divalent metal ions react with DNA but do not produce cancer. So what is special about nickel ions? Theories on bioaccumulation must be added to account for carcinogenesis. To further complicate the picture, Nieboer has presented evidence that a soluble small molecular complex of nickel can cause the cellular machinery to produce "di-oxygen free radicals" that have mutagenic properties. The HAD correctly describes this putative mechanism as a hypothesis in the main text but unfortunately mentions it in the important summary paragraph on page 8 - 210 in an attempt to justify classifying "all compounds of nickel" as "potential human carcinogens". Instead, it is suggested that the first paragraph of section 8-5 should be rephrased. The text starting "However, there is a reasonable

probability...to the end of the paragraph..."is not well understood" should be deleted and replaced by "The question of the carcinogenicity of other nickel compounds remains open and is therefore an important subject for further investigations."

Chapter 3. Nickel Background Information

General Comments

The background information should be directed more strongly towards those nickel compounds and their special properties which may have some relevance to health effects. Thus, the physical and chemical properties of nickel subsulfide, nickel carbonyl and nickel oxides should be featured.

The electronic structures of nickel and nickel ions and the effects which they have on the properties of the metal and the compounds and complexes of nickel should be explained.

The use of nickel metal in finely divided form as a catalyst in the hydrogenation of oils should be mentioned. The possibility of nickel entering the food chain via this route should be evaluated. Nickel's ability to serve as a catalyst in these reactions may be important evidence in understanding some of its biological interactions.

Nickel metal atoms have two 4s electrons and eight 3d electrons, two of which are unpaired. Formation of the nickel II ion involves the loss of two 4s electrons. The two unpaired electrons in the 3d shell of the metal and nickelous ion give rise to paramagnetism. There are indications that catalytic hydrogenation by hydrogen in the presence of nickel metal in finely divided form entails the dissociation of hydrogen molecules into atoms within the nickel metal luttice. The decrease in paramagnetism as hydrogen gas is absorbed by the metal is evidence that the unpaired elections in the nickel atoms are being paired with those in the dissociated hydrogen atoms. The formation by NiII of stable complexes with cyanide ion also occurs with loss of paramagnetism.

Ground rules should be established for use of the word nickel so that it is always clear whether the reference is to the elemental state or a compound or ion of the element.

The information should be presented in a more direct manner - the writing style needs to be changed to accomplish this. For example, the first two paragraphs on p.3-13 could be rewritten in a more concise manner.

"Brief has described several methods which range in sensitivity from 0.008 to 0.10 g for the determination of nickel carbonyl (Brief et al, 1965). A chemiluminesience method based upon the reaction between nickel carbonyl and ozone is faster and

sensitive down to parts per billion (Stedman et al., 1979)."

There is a considerable amount of material included which out of context of the source documents provides little useful information and is sometimes intelligible only to readers who are already thoroughly familiar with the subject.

P.3-1

Comments on Specific Material in Chapter 3

"... nickel content of some nickel-containing minerals" is redundant.

Has or has not native metallic nickel in a pure form been observed? (What does rarely, if ever, imply?)

Elemental nickel dissolves in diulte acids, not only dilute oxidizing acids. The statement that "even oxidizing salts do not corrode nickel because the metal is made passive, or incapable of displacing hydrogen, by formation of a surficial oxide filin" is taken out of context and requires further explanation.

The existence of a true -1 state of nickel, that is, nickel acting as a nonmetal by adding electrons does not make chemical sense.

P.3-2 Table 3-1

Nickel Arsenite should be Nickel Arsenate

According to the text in p.3-3, the basic salt $2NiCO_3 3Ni(OH)_2 4H_2O$ "is the most important form" yet it does not appear in the table (Is it the most important commercial form?)

The melting point and boiling points given for nickel nitrate hexahydrate are highly questionable; decomposition rather than melting and boiling are involved.

P.3-3

Greater attention should be given to the formation of nickel oxide which is an important process because of its relevance to the nickel emitted into the environment as a result of combustion.

The nickel-ammonia complex is $Ni(NH_3)6^{++}$ in solution - the hydroxide ion is not part of the complex in solution.

"When dissolved ... and is rendered soluble" is redundant.

Cations form complexes with ligands

P. 3.8 Section 3.2

This section would be easier to write and easier to read if it were organized in a different manner.

1. Sampling methods
2. Preparation of samples for instrumental or colorimetric analysis
3. Instrumental analysis

Analysis of most air, water or soil samples are currently performed by atomic absorption with the use of inductively coupled plasma spectroscopy expanding. After the sample preparation step, the measurement of the nickel concentration in the prepared solutions is essentially the same regardless of the type of environmental sample.

Particulate matter may be solid or liquid. Nickel compounds occur in the atmosphere as particulate matter - they do not necessarily have to be associated with other atmospheric pollutants. Referring to nickel as having to be associated with particulate emissions is confusing.

P. 3.9

The melting and boiling points of nickel are 1455°C and 2920°C; referring to nickel as a volatile trace element in streams at temperatures up to 500°C is inappropriate.

High volume samplers are used for ambient air monitoring. Because of instability it is not likely to find nickel carbonyl in the ambient atmosphere.

3.2.2

The phrase "in its elemental state" implies presence of nickel as the metal which is not the intent of the statement.

The meaning of the third sentence is not clear as stated.

Identification of the nickel compounds present in an ambient air sample is very difficult because of the very small amounts usually present mixed in with a complex matrix of other particulate matter and the changes that attempts to separate trace amounts often have on the nature of the compounds present.

P. 3.13

The discussion on sampling should either be expanded by providing a better description of the sampling methods or shortened by providing more detailed references. I suggest the latter.

The statement: "Any of the following three methods are recommended: "is misleading. The state: "The sample is removed by a valve regulating flow from a clean Teflon line inserted into the sampling bottle. " is awkward - valves do not remove samples and samples are not removed from the sampling bottle.

P.3.14

The discussion of preconcentration does not belong under sampling.

Under 3.2.2 (Air) the detection limit of the AAF method is given as 0.005 ug/ml; under 3.2.4 the detection limit is given as 0.05 mg/l (U.S. EPA 1979)

"Standard Methods for the Examination of Water and Wastewater (1985)" gives a detection limit of 0.02 ug/ml by flame and 0.001 ug/ml by graphite furnace.

Because the detection part of the analysis of either air samples or water samples by atomic absorption involves the same procedure, the discussion of atomic absorption should be given in one place with these obvious discrepancies resolved.

P. 3-15

The first two sentences in 3.2.7 say very little and should be eliminated.

P. 3-16

The heading of Section 3.3 should be "Sources of Atmospheric Nickel" rather than "Nickel in Ambient Air". The text is concerned predominantly with sources and not ambient air.

The information in Section 3.3 should be summarized in tabular form with references. The five main groups of sources together with the nickel species emitted and emission factors. (Amounts of nickel emitted per unit activity), where available, would be the components of the table. The discussion would focus on the table and could be considerably shortened.

The availability of emission factors for different types of operations is of great importance to environmental control work because they provide major guidance in the allocation of the resources dedicated to the elimination of a problem. See the discussion in Section 3.6.1. Note the estimate of up to 80% of nickel from human activities as coming from fossil fuel combustion.

P. 3-24

Table 3-2 would be more appropriately placed in section 3.3.2 than under analytical procedures.

The statement is made that neutron activiation analysis is not performed on atmospheric nickel samples "because no suitable states exist in the nuclei of nickel isotopes". How is this statement reconciled with the discussion of NAA on P. 3-11?

P. 3-25

The return to another discussion of the same five source groups and the separation of "Nickel Species in Water" from "Concentration of Nickel in Ambient Waters" repeats the organization under air. This argues for a restructuring of chapter 3 which unifies discussion of sources that release nickel into the environment, their impact on air, water and soil and the pathways into the human body then represent.

3-26/3-34

The author continues to have problems identifying nickel species in the ionic state. Soluble nickel salts, especially in highly dilute solutions exist as ions which are relatively independent of each other. Statements such as "This nickel is likely to be discharged as the Ni^{+2} ion or as dissolved nickel salt (sulfate chloride, etc.)" imply incorrectly that Ni^{+2} can exist either as the independent ion or in solution as $NISO_4$.

The map legend (p.3-33) does not indicate the significance of the counties which are shown without coloring.

In the text the Southeast basin is said to have means ranging from 85.1 to 754 ug/l while in Table 3-3, the range of means is 45.4 to 77.6. The Northeast had a maximum of 9,140 ug/l in 1980 but its 85th percentile was 105 compared to one of 173 for the Southeast which had a maximum of only 900. This shows the desireability of frequency distribution statistics for such data sets.

The text is again at variance with the table. "... for the Southeast Basin in 1980 where the maximum reported value was 1500 ug/l but 85 percent of the remaining samples contained less than 130 ug/l". Table 3-3 shows 900 and 173 for the same statistics.

3-34/3-38

Oil and coal used for space and hot water heating should be included with power utilities as sources of nickel in soil. Space and hot water heating emissions usually occur at lower altitudes with less opportunity for dispersion that those from tall stacks. Incineration of urban wastes also should be cited as a source of soil contamination.

In Section 3-6.1 it is reported that combustion of oil alone accounts for 83% of atmorpheric nickel from human activities. Space and hot water heating are major contributors.

P. 3-40

Nickel in Food - Should restrict the discussion to the nickel content of different foods. Section 4.1.2, "Gastrointestual Absorption of Nickel", is the proper place to discuss the relationship between intake and fecal excretions of nickel.

P. 3-42 Section 3.6

The last sentence in the first paragraph should be rewritten.

Edward Brand
4/28/86

F. WILLIAM SUNDERMAN, JR., M.D.,
Departments of Laboratory Medicine and Pharmacology, University of Connecticut School of Medicine
263 Farmington Avenue, Farmington, Connecticut, 06032, Telephone 203/674-2328

10 March 1986

Mr. Daniel Byrd
Executive Secretary
Science Advisory Board (A-101F)
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, DC 20460

Dear Dan:

In preparation for the meeting on 25 March 1986 of the EPA Metals Subcommittee to consider the Health Assessment Document for Nickel, I have prepared the following line-by-line citations of some points in the document that may need clarification or correction:

p iv, ¶2, line 11. The word "brain" should be omitted, unless the statement is modified to specify nickel carbonyl.

p xiv, line 29. My initial "F." should be placed before "William".

p 2-4, ¶1. Soya beans and soya products contain an average of 5.5 mg Ni/kg (range 1.1 to 7.8) and cocoa contains 9.8 mg Ni/kg (range 8.2 to 12), according to Nielsen and Flyvholm (1984).

p 2-4, ¶2. Volcanic emissions may be cited as an additional natural source of atmospheric nickel.

p 2-4, ¶3. Human parenteral exposures to nickel are of importance in relationship to iatrogenic sources, such as implanted orthopedic prostheses, hemodialysis treatment, and injections of nickel-contaminated drugs and X-ray contrast media.

p 2-9, ¶3, line 5 and p 2-12, ¶6, line 5. The statements on post-partum hypernickelemia should be deleted from the summary. The original observations of Rubanyi et al. (1982) are dubious, owing to analytical problems; post-partum hypernickelemia has not been observed in a follow-up study by Nomoto et al. (1983).

p 2-13, ¶1, line 1. Is there evidence that family history is predictive of susceptibility to nickel sensitization, on the basis of hereditary predisposition?

p 2-13, ¶2, last 2 lines. The measurements by Gutenmann et al. (1982) of nickel in cigarette smoke do not agree with earlier measurements (Menden et al. 1972, Wescott and Spincer, 1974, Perinelli and Carcigno, 1978). This matter is unsettled and further research is needed. Studies by Alexander et al. (1983) do indicate that the nickel in mainstream smoke is not present as nickel carbonyl. The statement that "nickel in mainstream smoke is "minimal" is imprecise and controversial and should be deleted.

p 3-11, ¶2, line 6. The unit should be "µl" rather than "ml".

p 3-15, ¶4, lines 2-3. The statement that "neutron activation analysis and colorimetric procedures are also used" is incorrect and should be deleted. Instead, a statement can be inserted that "anodic-stripping voltametry and isotope-dilution mass spectrometry are also used".

p 3-16, ¶1, line 14. The reference to Nomoto and Sunderman (1970) is out-of-date. More up to date references are Stoeppler (1981,1984) and Sunderman (1984).

p 3-23, ¶2, line 3. The importance of nickel exposures from mold-making in glass bottle factories should be mentioned (Raithel et al. 1981,1985).

p 3-40, ¶4-6, and Table 3-8. Except for the study by Myron et al. (1978), the cited studies on nickel concentrations in foods are out-of-date. More recent references are Ellen et al. (1978), Nielsen and Flyvholm (1984), and Flyvholm et al. (1984).

p 3-42. A paragraph on nickel in bacteria and other microorganisms might be appropriate at the end of section 3.5.

p 3-42, ¶4. The citation of Weast (1980) (CRC Handbook on Chemistry and Physics) can be deleted; the paper by Hassler (1983) refers to an unpublished report; the paper by Gutenmann et al. (1982) refers to nickel in smoke from tobacco grown on municipal sludge-amended soil. Additional references that may be cited are given above.

p 4-1, ¶1, line 6. Parenteral exposures of humans to nickel from prostheses, medications, hemodialysis, etc., should be mentioned, as discussed by Sunderman et al. (1986).

p 4-9, ¶1. The discussion of nickel in cigarette smoke should be modified, as indicated for p 3-42, ¶4.

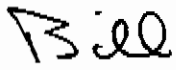
p 4-18, Table 4-2. The dosages given for the mouse experiment of Oskarsson and Tjalve (1979) are erroneous (4.6 µg Ni/kg). Moreover, the footnotes of the NAS table have been omitted. The footnotes, which specify the intervals between last injection of $^{63}NiCl_2$ and death, are necessary for interpretation of these experimental data.

p 4-20 to 4-22.	Nickel concentrations in human milk might be discussed (Mingorance and Lachica, 1985; Feeley et al., 1983).
p 4-24, ¶4.	Evident analytical problems in the study by Rubanyi et al. (1982) should be mentioned, and the contrary findings of Nomoto et al. (1983) should be discussed.
p 5-8, ¶2, line 7.	DL-alanine (not alaline).
p 5-13, ¶4.	Additional cases of cancers at the sites of implanted nickel-containing prostheses have been reported (see references cited by Linden et al., 1985).
p 5-23, ¶4.	The findings of Hopfer et al. (1985), showing that the erythrocytosis is mediated by enhanced erythropoietin production should be mentioned.
p 8-116, ¶2, line 22.	The word "tested" should be changed to "found".
p 8-157, footnote.	Change "cm^3" to "m^3".

In general, the present document is substantially improved, in comparison to earlier drafts. Unless you disagree, I do not believe that the specific points that are mentioned in this letter need detailed consideration by the Metals Subcommittee. I suspect that our discussions in Farmington will be centered upon the controversial proposition that "there is a reasonable probability that the ultimate carcinogenic form of nickel is nickel ion" and that "on this basis, all compounds of nickel might be regarded as potential human carcinogens . . ." (p 8-210).

Looking forward to seeing you on 24 March, and with cordial regards, I am,

Sincerely yours,



F. William Sunderman Jr., M.D.
Professor of Laboratory Medicine
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/ms

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Electric Power
Research Institute

April 14, 1986

Dr. Daniel Byrd
Science Advisory Board
US/EPA A-101F, Rm 508
Washington, DC 20460

Dear Dan:

I have reviewed the Nickel Health Assessment Document and offer the following comments about the quantitative risk assessment.

Animal Studies.
The data from the Ottolenghi et al. study were used to undertake a quantitative risk assessment for nickel. I have great concern about using these data for two reasons. First of all, one-half of the control and treated animals were injected intravenously with hexachlorotetra-flourobutane, an agent used to induce pulmonary infarction. There is no available information to indicate whether there may be any synergism or antagonism resulting from the simultaneous exposure of this drug and nickel subsulfide, which also largely affected the lungs. At a minimum the Ottolenghi et al. data set should be subdivided into two groups for risk assessment purposes. Those animals injected with hexachlorotetrafluorobutane and those which received no injection. If the risk assessment results are similar, the data could be concerned.

I am also very uncomfortable with the very high mortality rate in the nickel-exposed and control groups in this study. Apparently only 5% of the exposed group and 31% of the control group survived. It would be useful to have some guidelines about minimally acceptable survival rates before a data set is subjected to a quantitative risk assessment.

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In addition, clearly-articulated caveats should be attached to any quantitative results using this study -- even if the results are only used to compare the "best" animal study with epidemiology results. The comparison may not be meaningful.

Epidemiology Studies

Four data sets were used for these analyses. The Huntington, W.Va. data are taken from a study by Enterline and Marsh, an apparently carefully undertaken study. The analyses derived from this data set are reasonable and clearly articulated.

Data from Copper Cliff, Ontario were the second data set analyzed. I have two concerns with the analyses of these data. First of all, exposure is poorly characterized and rough exposure estimates are used in the analyses. Since the selection of exposure values can influence the results, I suggest that there be some type of sensitivity analysis undertaken for this study showing how risk (potency) estimates vary as exposure estimates vary. Secondly, the analysis used a background lung cancer rate of .036, derived from U.S. white male data. There is some difference between the U.S. and Canada as seen from the attached figure; but of greater concern is the increase over time in lung cancer rates. A recent EPA publication (U.S. Cancer Mortality, Rates and Trends, EPA600-1-83-015A) shows that the lung cancer mortality rate for white males in the U.S. has increased from 29.6 (1950-59) to 46.8 (1960-69) to 64.0 (1970-79) per 100,000. Given this volatility, it is important that the correct background rate Po be used in the risk assessment calculation for the Copper Cliff data. The use of .036 may be incorrect.

The third study used in the analysis was from Clydach, Wales. The analysis of these data suffer from similar problems as the Ontario data except the extrapolation of a U.S. background rate to Wales may be more questionable than extrapolation to Canada. Figure 1 demonstrates how much higher male lung cancer mortality rates are in England and Wales over the U.S. This study may also suffer from some confounding of exposure as practically all of the lung cancer deaths apparently were exposed to arsenic. The analysis should show how any arsenic exposure would impact the risk estimates.

The final study analyzed is of a Kristiansand, Norway population. Concerns about this analysis are similar to those for the Copper Cliffs analysis. The attached figure demonstrates the extrapolation of U.S. background lung cancer mortality rates to Norway may be dangerous, as Norwegian rates appear to be considerably lower than U.S. rates. The analysis for this study is also not clearly articulated. A table analagous to Table 8-47 would be helpful here so that the assumptions made in the analysis would be clearer.

Overall Comment

I am somewhat troubled by the use of "median of the range" risk estimate. Since this apparently turns out to be the average of the highest and lowest risk estimates, it is dominated by the larger number. A better approach might be to derive a median estimate for each study and take the median of the medians.

I hope the above are useful. Obviously, if any clarifications are desired, please let me know.

Sincerely,

Dr. Ronald Wyzga
Technical Manager
Environmental Risk Assessment

Enclosure

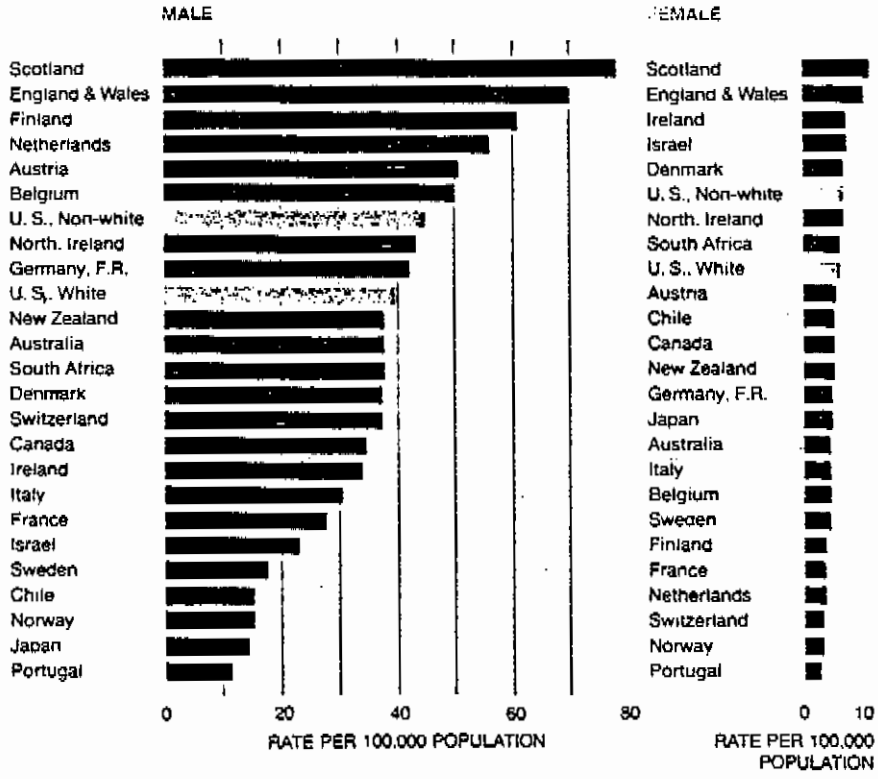
cc: Bernie Weiss

REW/acc

Dr. Daniel Byrd, 4/14/86
Enclosure

FIGURE 1

FIGURE 16. AGE-ADJUSTED MORTALITY RATES FOR MALIGNANT NEOPLASMS OF THE LUNG, BRONCHUS, AND TRACHEA IN VARIOUS COUNTRIES, 1966-1967.



Source: Levin, D. (1975) Cancer Rates and Risks, 2nd edition, U.S.H.E.W. NIH 75-691.

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DEPARTMENT OF PHARMACOLOGY

March 27, 1986

Dr. Daniel Byrd
Executive Secretary
Science Advisory Board (A-101F)
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, D.C.

Dear Dr. Byrd:

I have prepared a list of comments on the Health Assessment Document for Nickel. These comments relate specifically to sections 4.2.1 - 4.4 of the document. Evaluation of the remaining portion of section 4 is being conducted by Dr. Oberdoerster.

General Comments on Sections 4.2.1 - 4.4

1. In view of the controversy over the "Ni^{+2} hypothesis", it seems appropriate to include a discussion of the metabolism of nickel compounds to Ni^{+2} in tissues. Is there evidence for Ni^{+2} being a common metabolite of nickel compounds? Reference is made to this possibility in section 4.2.2. (P3) where the conversion of nickel carbonyl to Ni^{+2} is mentioned.

2. When possible, the elimination half times should be stated precisely, as these values are very useful.

3. The expressions "clearance", "retention" and "intake" are used incorrectly in places.

4. A uniform set of units should be selected to express concentrations of nickel.

Specific Comments on Sections 4.2.1 - 4.4 :

4.2.1 Nickel in Blood :

1. P1, 1.1 : The meaning of the statement "Blood is the main vehicle for transport of absorbed nickel." is not at all clear. How is the term "absorbed nickel" defined? Is nickel that enters the epithelial cells of the intestine by crossing the mucosal membrane considered to have been absorbed? Is it meant that blood is the predominant route by which nickel is distributed to other tissues (e.g. rather than lymph)? Can the relationship

between the concentration of nickel in blood or serum and the body burden of nickel be stated in precise terms?

2. P2, 1.8 : Change "no" to "not".

3. P3, 1.2 : Change "clearance" to "elimination". The term "clearance" has a very specific meaning. It refers to the volume of a compartment from which a substance is removed over a given length of time. Thus, the units of clearance are volume per unit of time (e.g. ml/min). It should not be confused with rates of elimination, rate constants for elimination processes or with half-times for elimination. There are several places in the text where this discrepancy occurs. It is a minor point, however, for consistency, a uniform terminology should be used.

3. P4, 1.1 : Change "clearance of nickel" to "kinetics of elimination of nickel".

4. P4, 1.4 : Can the elimination half-times be stated precisely here?

5. P6, 1.3 : Change "may be the factor..." to "may be an important factor in the transfer of nickel from blood to other tissues.". Blood is a tissue.

6. P7, 1.7 : Change "histidine may serve to..." to "histidine may facilitate the movement of nickel from the serum into other tissues.".

7. P8, 1.2 : Change "labeled nickel" to "radiolabeled nickel".

8. P8, 1.3 : What is alpha-2-nickolplasmin? Is this the same as nickelplasmin (p. 4-13, 1.30)?

9. P9, 1.2 : Change "which reflect" to " that may reflect". Is this range of binding of nickel to serum albumin the result of differences in binding characteristics of serum albumin or does it reflect differences in the binding characteristics or amounts of other binding ligands in the serum (e.g. nickelplasmin, histidine)?

4.2.2.1 Tissue Distribution of Nickel: Human Studies

1. P3, 1.11 : Change "that the element..." to "that the accumulation of nickel does not increase with increasing age.".

2. P3, 1.18 : Change "ppm" to "ug/g". It would help if similar units for concentration were used throughout the document.

3. P6, 1.5 : Does this mean that accumulation of nickel in lung, but not other tissues, increases with increasing age? If so why not state this precisely?

4.2.2.2 Animal Studies :

1. P2, 1.3 : What is meant by the expression "elevated, rapidly cleared levels of nickel"? Is it meant that the levels of nickel in these tissues were elevated in animals that inhaled nickel carbonyl vapor and that the accumulated nickel was eliminated quickly?

2. P3, 1.5 : The basis for this presumption is not clear.

3. P3, 1.9 : Is this pathway of metabolism of nickel carbonyl a hypothesis or has it been established? It is highly relevant to the "Ni^{+2} hypothesis" that nickel compounds can undergo conversion to the divalent ion in tissues. Also change "erythrocytes and tissues" to "erythrocytes and other tissues".

4. P6, 1.2 : Change "metal transport protein" to "metal binding protein". A role for metallothionein in the "transport" of metals has not been established. This is to distinguish metallothionein from other proteins (e.g. transferrin) that have been shown to function in the transport of metals in the extracellular or intracellular compartments.

5. P6, 1.4 : Convert the units "mmol/Kg" to "ug/Kg" for consistency with other notations.

6. P7, 1.10,12,13 : Convert these values to a consistent set of units.

7. P8 : What mechanism could regulate nickel intake? Is it meant that absorption of dietary nickel from the gastrointestinal tract is regulated or that the levels of nickel in tissue are maintained constant as the amount of nickel in the diet is increased?

4.2.3 Subcellular distribution of Nickel :

P5, 1.9 : It is not at all clear why endocytosis would deliver insoluble nickel adjacent to the nucleus. What is meant by this statement?

4.3 Retention and Excretion of Nickel in Man and Animals :

P2 : Is the term "retention half-time" synonymous with "elimination half-time"? What is meant by the term "retention rate"? Does this mean that 30% of the ingested nickel (400 ug Ni/day) is absorbed from the gastrointestinal tract? If so, the elimination half-time of 1200 days seems to be very high. What is menat by the term "retention time"?

P3, 1.8 : What is meant by the term "daily intake retention figure"? The information that is discussed in P2 and P3 are very important and need to be presented very clearly by using precise terminology to describe the elimination Kinetics.

P5 : Change "major clearance route" (1.1) to "major excretory route". Also, it is not clear why variations in the concentration of nickel in urine

are the result of analytical limitations. The urine flow rate vries 50 to 100 fold as function of body water content and diet. If the rate of urinary excretion of nickel was relatively constant in humans of agiven size or age, the concentration of nickel in urine would also vary by this amount.

P6, 1.1 : Change "clearance route" to "excretory route".

P6, 1.8 : Change "clearance" to "excretion".

P8, 1.2 : Is the measurement of nickel in hair a useful indicator of the body burden of nickel or is it not?

P9, 1.1 : Change "clearance" to "excretion" or "elimination".

P10, 1.2 : Change "clearance" to "elimination".

P11, 1.7 : Can the elimination half times be stated precisely?

P12, 1.1 : What is meant by the expression "the pattern of labeled-nickel urinary excretion"? Also, what is meant by a "ligating moiety"?

Respectfully,

Gary L. Diamond, Ph.D.

GLD/lm

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DEPARTMENT OF RADIATION BIOLOGY
AND BIOPHYSICS

May 28, 1986

Dr. Daniel M. Byrd, III
Executive Secretary
Science Advisory Board
US EPA
401 M Street, S.W.
Washington, DC 20460

Dear Dan:

Thank you for your letter of May 21 with the draft committee and subcommittee letter reports on the review of the nickel HAD. Unfortunately, I had overlooked an error on page two of my comments: The formula should read:

$$A_t = \frac{a}{b}(1 - e^{-bt})$$

I apologize for this oversight and I would like to ask you to correct it before submitting it to the SAB. I have no further comments on the draft letter. Your memo and letters did reach me on Tuesday, May 27.

With kind regards.

Sincerely yours,

Günter Oberdörster, D.V.M., Ph.D.
Associate Professor of Toxicology

jh

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DEPARTMENT OF RADIATION BIOLOGY
AND BIOPHYSICS

April 23, 1986

Dr. Daniel Byrd III
Executive Secretary
Science Advisory Board
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410 M Street, S.W.
Washington, D.C. 20460

Dear Dan:

Please accept my apologies for sending these comments on the Ni document - as requested by you and Bernie Weiss - so late. I hope the people working on the document can use my comments, if they or you need additional clarification, please contact me.

Sincerely yours,

Günter Oberdörster, D.V.M., Ph.D.
Associate Professor of Toxicology

GO/jh

Attachment

COMMENTS ON NICKEL HAD (Günter Oberdörster)

Chapter 4: Metabolism.

It may be useful to include a general diagram of the metabolic model of Ni-kinetics. I have attempted a draft of such a model, and if possible, EPA could put some number of transfer rates into this model. It gives the reader a quick and general idea of major metabolic pathways and points out the target sites.

Specific comments:

p. 4-1: relative solubilities of Ni-compounds in biologically relevant media are discussed. While these are useful to have, they may not as easily be useable for predicting in vivo elimination rates as it is stated on page 4-1. It is known, for example, that insoluble CdO is rapidly solubilized in the lung, and probably the most important mechanism for this is the solubilization in the lysosomes of the alveolar macrophages. This was recently shown by Lundborg et al. (1984, 1985) for MnO_2, and the low pH of the lysosome (pH4) may account for this. Thus, more emphasis should be placed on the in vivo solubility; in addition, particle size plays an important role in this process, for 2 reasons: (1) the phagocytosis is dependent on the particle size, (2) the solubilization rate is slower for larger particles.

p. 4-4: The conclusion drawn from the Wehner and Craig study (1972) - that absorption of NiO in the period of 45 days was negligible - should be judged under the experimental conditions: the concentrations being used were 2-160 mg/m^3, and this may lead to a decrease in lung clearance of particles and possibly also of NiO particles. For example, we showed that exposure for several weeks to 50 $\mu g/m^3$ of NiO - a very low concentration - led to a highly significant decrease of the lung clearance of particles in the rat (Oberdörster et al., 1980, in: Nickel Toxicology, p. 125, Academic Press). We also showed that lung retention of inhaled NiO has a half time of 36 days. This could possibly be included in the document.

p. 4-5: The term "dose-lung deposition relationship" (line 1) is unclear. Is it exposure - lung deposition relationship?

On the following pages, the terms clearance rate - which is the amount being eliminated per unit time - and retention half-time - which is the time during which 50 percent of the initial amount is eliminated using a monoexpoential model -are used indiscriminately such as "clearance half-time" or even "clearance rate half-time." This should be changed.

p. 4-7: Clearance rate is given as 72 hours (last paragraph); it should be retention half time. This number was derived from urinary excretion, based on the Corvallo and Ziemer study (1982). However, the Ni compounds used in the 2 studies were different, and it can be expected that intratracheally instilled "moderately" soluble Ni-carbonate will be cleared to a large extent into the Gl-tract and is then excreted through the feces. Therefore, the T 1/2 of 72 hours is in all likelihood lower.

p. 4-8: First paragraph: It can be expected that accumulation of NiO in the lymph-nodes of the lung will be seen when the lung is overloaded. This is not specific for NiO, but for any particle, as has been shown for TiO_2 by Ferin et al. (1980) when the lung was burdened with too much TiO_2. What is "retro-ciliary" removal? (second paragraph)-probably meant is muco-ciliary. I don't see that a half time of 34 and 21 days for dissolution of Ni subsulfide in vitro is "roughly equivalent" to an in vivo retention T 1/2 of 12 days. It is not, and it shows - as mentioned earlier - that in vitro dissolution rates cannot simply be extrapolated to in vivo dissolution rates. In this context, it might be mentioned again that the rate of solubilization is of importance in addition to the solubility per se.

Chapter 8.3. Risk estimates based on animal studies.

p. 8-156: I am not certain - and it needs some better justification - how the duration of the experiment (L_e) should be included in the formula at the bottom of the page. The dose retained in the lung over an exposure period depends very much on the biological half time of the compound; for example, if T 1/2 is longer than the total dose (expressed here by total exposure) it is very much different than it would be if the T 1/2 is shorter. So, I believe, the retention of Ni in the lung should be included in the formula. This could be done according to

$$A_t = \frac{a}{b}(1 + e^{-bt})$$

where A_t is the amount retained at time t, a is the amount being deposited each day and b is the elimination rate ($b = \frac{\ln 2}{T\ 1/2}$).

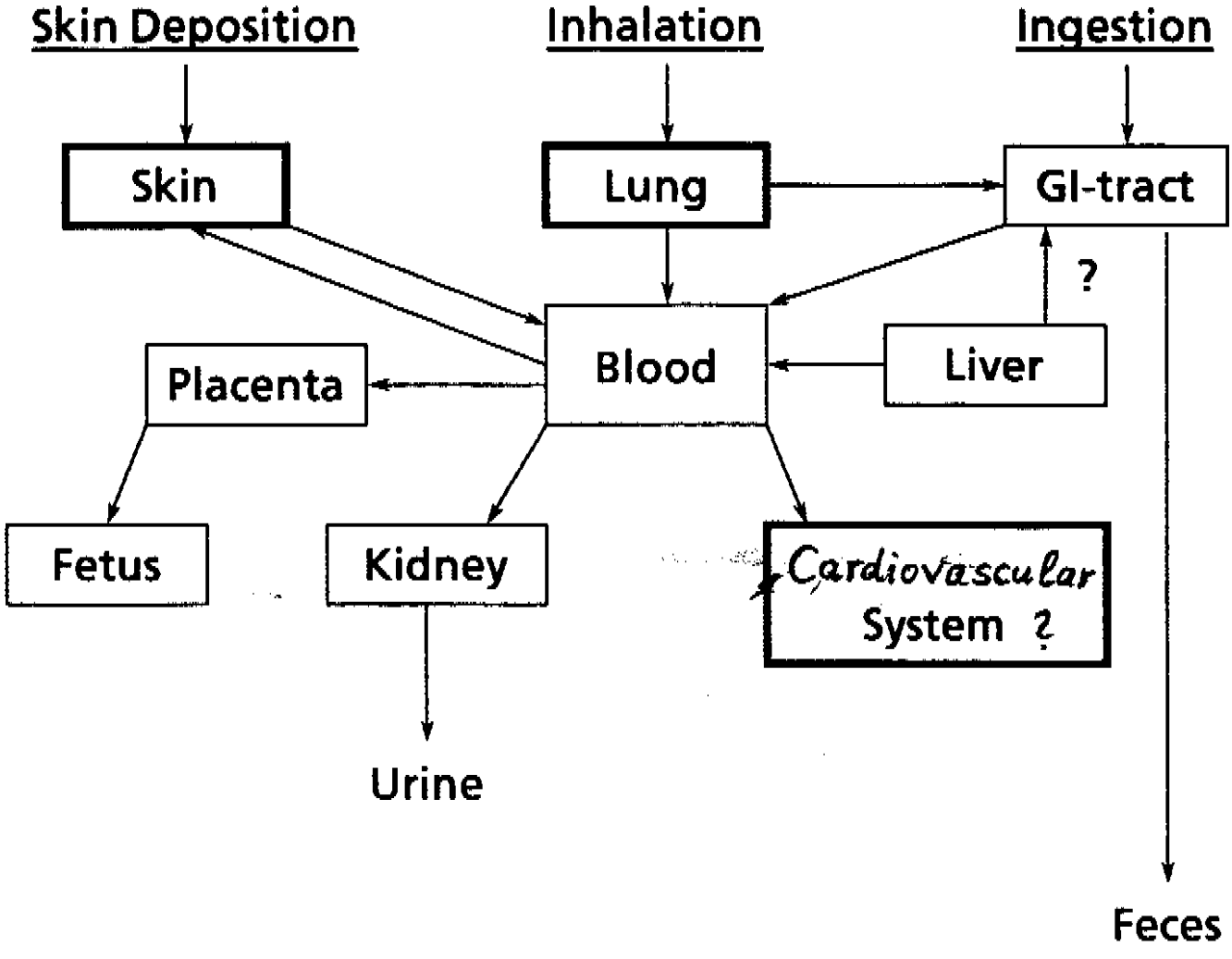
p. 8-157: first paragraph deals with a completely water-soluble gas or an aerosol and a poorly water-soluble gas. Ni carbonyl is insoluble in water, its T 1/2 in air is only about 100 seconds. To which category does it belong here? Aerosols are not absorbed proportionally to the amount of air breathed in, factors like particle size will affect deposition and subsequent absorption. Therefore, Ni_3S_2 cannot reasonably be expected to be absorbed (?) (probably meant - deposited) proportionally to breathing rate. The distinction between "absorption" (-leading to an effective dose) and "deposition" (resulting in a deposited dose) of an aerosol should clearly be made. (I attach a copy of pages 8-157 and 8-158, from which some handwritten suggestions for changes can be taken).

p. 8-161: Line 2 - it should be 970 $\mu g/m^3$ nickel subsulfide. Likewise, in the table on this page the compound is nickel subsulfide.

p. 8-162: Calculation of equivalent lifetime continuous exposure (top of page) for calculation of equivalent human dosage cannot be done without taking into account and knowing retention of inhaled Ni in rats and humans (see comments for p. 8-156).

A few general remarks on the extrapolation of experimental animal data to humans seem in place. In this and other Health Assessment Documents, body surface area is used to correlate delivered doses in humans and animals. It would be more appropriate to use lung surface area, more specifically bronchial and alveolar surface area in rats and humans for calculating a "surface area dose." Enough information on lung morphometry is available to attempt those calculations. There is probably a difference in tumor sites between the animals and humans, namely bronchial cancer in Ni-exposed workers and possibly more peripheral tumors in the rats. The significance of this difference for extrapolating from animal studies to human could be pointed out, i.e., stating that such extrapolations are not well supported and will limit an estimation of tumor risk for humans derived from animal studies. The clearance of inhaled dust in the bronchial region is normally very fast, unless bronchial clearance mechanisms are impaired. This could happen during a high exposure situation or - at lower exposure concentrations - when there is a toxic effect on bronchial clearance mechanisms. It is also possible to calculate the deposited alveolar dose in humans and compare it to a calculated bronchial dose. This then could be compared to the respective doses in animals for the same particle size. The result will show that bronchial and alveolar doses are different in man and animals after inhalation of the same particle size. From such calculations a particle size for animal studies can be estimated that would approximate the human lung dose and that should be used in planned animal studies.

NICKEL METABOLISM



Critical or target organs

perhaps some numbers could be put on the different transfer and elimination or absorption routes.