Nickel Ion Bioavailability Workshop
Discussion Questions
January 6, 2010

In vitro and Experimental Animal Data

1. Do the available *in vitro* and *in vivo* data support the conclusions of Goodman et al. (2010) regarding:
    a. carcinogenicity of the various forms in animals
    b. respiratory toxicity
    c. clearance
    d. cellular uptake (ion transport, phagocytosis) and intracellular dissolution
    e. transport to the nucleus

    Are there other available data (either supportive or contrary) relevant to the above and is there potential for alternative interpretations of the data regarding nickel carcinogenicity in animals?

Epidemiology Evidence

2. Goodman et al. (2010) conclude that the epidemiological data support both the nickel ion hypothesis and the bioavailability hypothesis. They conclude that the epidemiological data are not sufficiently robust for determining which hypothesis is most appropriate, but are consistent with the nickel ion bioavailability hypothesis. Do the available epidemiology data support this conclusion? Could the data support a different conclusion? Do the data support one hypothesis over another? Should other available data be discussed?

Overall Review of Hypothesis

3. How strong is the overall integration of the *in vitro* data, and human and experimental animal data (by relevant routes of exposure) to support the bioavailability hypothesis. What evidence is counter to this proposed hypothesis?

4. Are there other hypotheses that might explain the data better than the bioavailability model (e.g., a tumor-promoting mechanism that does not depend on direct nuclear interactions; or evocation of tumors based on lung inflammation, the nickel ion hypothesis, the amount of nickel inhaled or retained in the lung, or something else)?

5. In focusing on nickel reaching the nucleus, the authors suggest that, even if the effects of the nickel ion in the nucleus are assumed to be via genotoxicity, a "practical threshold" for initiation of carcinogenicity exists. Please comment on this assertion.

6. The bioavailability hypothesis focused on lung cancer. ICNCM (1990) also found that several forms of nickel were associated with increased nasal cancer risk in the epidemiology studies, but nasal cancer was not reported in any of the experimental animal studies with inhaled nickel. Should the bioavailablity hypothesis (or other

hypotheses addressing nickel carcinogenicity) consider other tumor types in addition to the lung?

7. Can an overall weight of evidence conclusion be made at this time? If not, what further analyses might help?

8. Are there other issues or questions that should be discussed relative to the nickel ion bioavailability hypothesis and its relevance to understanding the potential for carcinogenicity from nickel exposure?

Data Needs

9. Data needs are identified and discussed in the manuscript. Should additional data needs be added or deleted? Please rank the data needs according to which are essential to identify the determinants of nickel carcinogenicity and explain the differences observed among the various forms.