February 22, 2012

DEEOIC Note: The responses below are provided by Dr. Jay Brown, author of Haz-Map. Haz-Map is entirely the creation of Dr. Brown and while the DEEOIC provides funding (through Paragon) to prioritize chemicals for inclusion into Haz-Map, Dr. Brown's determinations are independent of DEEOIC. As such DEEOIC did not edit or alter his responses in any way.

Committee on Review of the Department of Labor's Site Exposure Matrix (SEM) Database

Questions for Jay Brown:

1. What are your criteria for determining causality? For cancer outcomes? For non-cancer outcomes? (examples, strong versus convincing, IARC categories?)

In general: Is there consensus in occupational medicine textbooks that this occupational disease is caused by these hazardous agents? Can the disease be prevented by good occupational hygiene practices? Occupational cancer: Is it a Group 1 carcinogen in the "Occupation" chapter in Schottenfeld & Fraumeni's *Cancer Epidemiology and Prevention, 3rd Edition*? See table 18-3 entitled, "Substances and Mixtures That Have Been Evaluated by IARC as Definite (Group 1) Human Carcinogens and Are Occupational Exposures."

> Simply observing a difference in the probability of an outcome between two groups that differ on X is not sufficient condition for causation because it does not distinguish between causation and spurious or indirect association, produced by "confounders" or ancillary causes. The notion of "causation" requires that the cause somehow actively "produce" its effect, which is captured operationally by the requirement that *active manipulation of the cause should produce a change in the probability of the outcome*. For example, if one saw that students with poor visual acuity typically sat closer to the front of a classroom, one would not call the seating arrangement a "cause" of their poor eyesight unless it could be shown that seating them farther back improved it." [Steven Goodman and Jonathan Samet. "Cause and Cancer Epidemiology" in *Cancer Epidemiology and Prevention*]

2. What are the criteria for determining that there is no causal link to an occupational exposure or more research is needed? What is difference between blue, yellow, and red highlighted diseases from your handout?

Is there a causal relationship as defined in the response to question #1? The handout of occupational diseases in Haz-Map shows that there is little basis for debate for most of these diseases. There is a consensus in occupational medicine textbooks that these are established occupational diseases. I highlighted the ones that I thought were debatable: yellow (some occupational cancers and the diseases recently added to the More Research Needed category), blue (birth defects and female reproductive effects), and lavender (Parkinsonism). There is a rule in Haz-Map for handling occupational cancers. See my response to question #1 above. Birth defects and female reproductive effects are not covered by the

EEOICPA. Although environmental causes of Parkinson's disease (e.g. pesticides, manganese, and trichloroethylene) have been proposed, the well-designed epidemiology study (Firestone et al.) included in the handouts shows that no causal relationships have been established.

3. How do you select new chemicals or diseases to review?

    - All chemicals in the NIOSH Pocket Guide
    - All chemicals that cause occupational asthma.
    - All chemicals that cause allergic contact dermatitis.
    - All chemicals that cause the other Adverse Effects.
    - All chemicals in HSDB (excluding drugs, alloys, and natural biochemicals).
    - Chemicals profiled in monographs of US or European regulatory agencies.
    - All chemicals sent to me by Bernie Kokenge from the SEM database.
    - All diseases in the SHE(O) list of Mullan and Murthy.
    - All diseases in occupational medicine textbooks.
    - The "More Research Needed" diseases were added this year after looking in eight textbooks of occupational medicine and 200 journal articles retrieved from PubMed to find any other possible occupational diseases not yet in Haz-Map.

4. How often do you update diseases and chemicals? How do you select those to update? If a decision is made not to link a chemical with a disease, when is the decision re-examined?

The first chemicals added to Haz-Map have the lowest ID numbers. So, lower ID number is one criteria used to find chemicals that need reviewing based on newer resources available. Chemicals and diseases are continuously reviewed as questions are asked and new chemicals added are compared to chemicals already in the database. Periodically, all journal articles in selected journals are reviewed. The last reviews were done in 2008 and 2011. The selected journals are: Am J Ind Med, Chest, Int Arch Occup Environ Health, J Occup Environ Hyg, J Occup Environ Med, Occup Environ Med, and Scand J Work Environ Health.

Although accidents happen and there will probably always be isolated cases of silicosis or asbestosis, the general trend over the past 50 years is that occupational toxicology cases are becoming increasingly rare because of the work to prevent them by industrial hygienists, epidemiologists, public health professionals, and occupational medicine physicians. Many chemicals have been banned are severely restricted. The recommended workplace standard for benzene was 100 ppm before 1947 and then reduced to 35 ppm. [Wong, 1999, PMID 10450237] The current PEL is 1 ppm, and the TLV is 0.5 ppm. Estimated annual TWA benzene exposures were 137 ppm in 1940 and 4 ppm in 1970. [ACGIH Documentation of TLVs and BEIs] The average blood lead level of the US population dropped from 12.8 ug/dl in 1976 to 2.83 ug/dl in 1991. [PMID 8028141] The same is true for occupational cancers, "Over the past 50 years, it is likely that the number of occupationally induced cancers has decreased in western countries." [Siemiatycki, p. 344]

The practical implication of this trend is that studies of current work cohorts are not likely to discover new agent-disease relationships with which to "update" the database.

> The characterization of an occupation or industry group as a "high-risk group" is strongly rooted in time and place. For instance, the fact that some groups of nickel refinery workers experienced excess risks of nasal cancer does not imply that all workers in all nickel refineries will be subject to such risks. The particular circumstances of the industrial process, raw materials, impurities, and control measures may produce risk in one nickel refinery but not in another or in one historic era but not in another. [Siemiatycki et al. "Occupation" in *Cancer Epidemiology and Prevention*]

In other words, these industrial "experiments" have served to show us the necessity of safe chemical handling. Now that we have learned the proper industrial hygiene practices, it is not likely that these experiments will recur. In this sense, much of occupational toxicology is historical. Like cigarette smoking and lung cancer, the story has already been told, and any future studies will only fill in some of the details of the story.

5. When using individual studies for information, how do you assess the study's quality (study type, bias, sample size, etc)?

See the study of Parkinson's disease by Firestone et al. in which a number of potential weaknesses of case control studies are addressed: confirmation of diagnosis, interview bias, and recall bias.

"It is emphasized that not all epidemiological studies are equally informative or of equal quality. Some have low statistical power and provide little information on risks; others are so susceptible to potential or actual biases that findings have little or no validity. It is important to consider methodological issues when interpreting the evidence from different studies, and it is the consistency of findings in different studies conducted by different investigators in different parts of the world that is most informative." [John Boice. "Ionizing Radiation" in *Cancer Epidemiology and Prevention*.]

6. How do you use animal and epidemiological data and how is it included or weighted into causal decisions?

For occupational cancers, I follow IARC in the way it synthesizes animal and epidemiological data. For acute occupational diseases, animal data is sufficient if the routes of entry correspond. Examples of such acute occupational diseases include poisoning by pesticides, solvents, simple asphyxiation, hydrofluoric acid, and toxic pneumonitis. A special rule is applied to toxic pneumonitis. Any corrosive substance has the potential to produce toxic pneumonitis as an adverse effect. Any of these substances designated as "TIH" (Toxic Inhalation Hazards) in the 2008 Emergency Response Guidelines are also listed in Haz-Map as the occupational disease "Pneumonitis, toxic." Other acute diseases with special rules are "Asphyxiation, chemical" and "Hemolytic anemia." In Haz-Map, there is a distinction between adverse effects (includes animal toxicology and human poisonings by ingestion cases) and occupational diseases (cases of workers made ill after inhalation or skin absorption). Therefore, chemicals are linked to the diseases "Asphyxiation, chemical" and "Hemolytic anemia" only if occupational cases (and not just ingestion cases) have been reported. Likewise, all chronic occupational diseases in Haz-Map are based on reports of occupational cases.

7. What are your criteria for picking resources? The reference list is long and varied, with many different purposes and methodology.

The best and most up-to-date resources are selected. Accuracy is improved by cross referencing. Cross referencing also enables one to compare resources and to get different perspectives. The value of different perspectives can be seen in the parable of the seven blind men and the elephant. Is there concurrence? Is there a body of knowledge that supports the agent-disease link?

8. Who reviews your data entry and data extraction and who verifies the information as accurate?

Much of the data entry for the first draft is cutting and pasting from ChemIDplus, HSDB, and other Internet resources. Difficult lists are based on the work of experts, e.g., Malo & Chan-Yeung for occupational asthma and IARC for cancer. Ann Gravatt reviews new chemicals. Principles I used for data extraction were published in my journal article, which was one of the handouts. Preliminary work is first published on my website and presented at monthly conferences.

9. How is new information in new textbook additions identified?

I read new chapters and material written by new authors. I check all references already in Haz-Map to see if any changes have been made.

10. What do you submit to NLM, do they review/verify the content? If so, what is the process?

Ann Gravatt reviews all chemicals (synonyms, CAS #s, formulas, and OELs). She sends corrections to me, and I make changes to my copy of Haz-Map. Haz-Map is published with new chemicals and her corrections.

11. What is NLM's Role in Haz-Map?

Haz-Map is like an electronic textbook. NLM is the publisher.