

As requested, I have provided a list of my major concerns. These concerns focus on DMC activities as well as the Site Exposure Matrix (SEM) and the proposed SEM 'protocol'. I welcome this opportunity to provide constructive comments and I am sure you share my interest in better serving EEOICP claimants by improving the quality of the DMC opinions and assuring the scientific integrity and validity of SEM.

I - Improving the Quality of District Medical Consultant (DMC) Opinions

In my opinion the following steps should be considered:

- Formally review DMC credentials. This process should include a review of each DMC's educational attainment, training, professional experience, board certification, malpractice experience and a check of their status with the National Physician Data Bank.
- Require training and/or certification for DMCs before a DMC can be considered as an expert to assess impairment. Currently DMCs can perform impairment assessments based on self reported experience.
- Convene scientific advisory groups to assess difficult medical and causation issues.(eg issues include interaction between ionizing radiation and chemical exposures, assessing risk among claimants with multiple chemical exposures, and various causal relationships between chemicals and adverse health effects). This could be accomplished using local experts from NIOSH, OSHA, NCI and local universities.
- Assure that a process is in place to carry over of ionizing radiation exposures from Part B to Part E for case development and assure that the combination of ionizing radiation and chemical exposures is considered in claim development and adjudication. For example, a claimant with leukemia who had both benzene and ionizing radiation will likely be at risk of leukemia from both exposures.
- Reduce DMC costs and potential bias, particularly for high earning "internal" DMCs. This could be accomplished by using full or part-time medical officers to replace internal DMCs or by further limiting the number of cases reviewed by internal DMCs.

II - SEM "Protocol" and Database

My understanding is that there have been concerns about the decision-making process utilized to develop the exposure/disease linkages within the Site Exposure Matrix (SEM). Particularly, there is concern that an established protocol for decision-making for these linkages within SEM has not been previously established. It is my understanding that the developers of SEM relied on Dr Jay Brown for decision-making regarding the establishment of exposure/health linkages and that there is now some concerns about the basis and validity for some of those decisions. In my opinion the goal at this point should be to assure the scientific integrity & validity of the exposure/disease linkages by reviewing the rational basis for the exposure/disease linkage decisions.

A - General Finding: An initial review of SEM reveals a number of limitations. For example, 1) the list of diseases is incomplete (eg major disease categories such as dementia, cardiovascular disease, psychiatric disorders are not listed) and 2) some linkages in SEM are inconsistent or incomplete. This situation can lead to false positive and/or false negative conclusions when SEM is used as a decision tool for developing claims.

In addition, there are some missing links – eg MBK (a solvent) and neuropathy is an established association but not found in SEM; Carbon disulfide is not linked to cardiovascular disease or psychosis in SEM, although both are well appreciated associations. Further, a claims examiner

(CE), reviewing a claim for thyroid disease, under Part E, for example, would not find a link to ionizing radiation.

Alternatively, there are some exposure/disease links present in SEM that are not “established” (eg engine exhaust and chronic renal failure).

B - SEM Limitations

1 – SEM has not been peer reviewed; Evidence for the exposure/disease linkages was reviewed and linkages were established by one physician, thus presenting the potential for error (both false positive and false negatives) and introducing the possibility of bias. Assuring the scientific validity of scientific findings routinely relies on the peer review process. I recommend that the SEM decision-making protocol and SEM decisions (both positive and negative) be subject to a peer review process.

2 – SEM is not exhaustive or complete (as noted upon SEM login); In addition, some inconsistencies are noted, (as indicated as above).

3 – SEM does not, in general, provide explicit decision rules to determine what constitutes sufficient evidence for an “established” linkage. Thus, it is not known what “tips” a decision either to link or not to link an exposure to an outcome, contributing to possible inconsistencies.

4 – SEM does not consider combinations of exposures, (a term known epidemiologically as interaction); This is a particularly critical limitation of this database as the database is used as a tool to evaluate claims for workers at possible increased risk of adverse health events arising from a) combined chemical and ionizing radiation exposure, and b) multiple chemical exposures.

5 – SEM does not provide detailed methods of the decision-making process utilized for linking exposure and disease. These unaddressed issues include an explanation of procedure used for weighing the evidence based on: a) data quantity, b) data quality, c) study design, and d) use of and weight given to animal compared to human data.

6 – SEM relies on HAZMAP. HAZMAP’s stated purpose is for prevention, (Haz-map, according to Dr Brown, was developed to look at “high level mapping” for “prevention” and the “big picture”); Use of HAZMAP for “decision-support” requires, at a minimum, more explicit methodology and detailed user guidance concerning the interpretation of findings and limitations.

7 – SEM only contains “established links”. This will omit “suspected” or “probable” links. It is generally appreciated that many exposure/disease linkages are not “yes/no” associations. Rather, they depend on the characteristics of the populations studied and robustness of the data and study findings.

8 – SEM only provides limited references or comments. The SEM user must refer back to Hazmap to find more complete (though not exhaustive) list of relevant references and comments; There are limited comments on key issues considered in causal evaluations including latency, and exposure considerations (such as duration, intensity or route of exposure) or interaction. Some comments in Hazmap are inconsistent w/SEM conclusions (eg benzene and CLL).

9 – SEM relies on “Hazmap”, but Hazmap linkages are not all carried over to SEM (eg search on the outcome “nephrotoxic” yields 190 exposures in Hazmap, none include engine exhaust); A search in SEM on nephrotoxic yields mostly metals, no solvents but does include engine exhaust.

10 – SEM provides only limited guidance for interpreting the results by a user. Claims examiners and other users require full disclosure of SEM’s limitations and guidance regarding the proper interpretation of a positive or negative exposure/disease linkage (eg Appendix A of SEM User’s Guide – notes “Review Guidance Documents”).

11 – SEM is based on the assumption of “sufficient exposure”, but an explanation of what “sufficient exposure” means is not provided.

C – Review of Hazmap Linkages

There are basically two critical issues related to assuring the scientific integrity & validity of the exposure/disease linkages and for a review of the rational basis for the exposure/disease linkage decision-making. These include:

1 - Logistic Considerations

A comprehensive review of the linkages in SEM is a considerable task and presents daunting logistic considerations. SEM includes approximately 130 possible health outcome categories and 8000 chemicals. Thus, there are many thousands of possible linkages for review, even if only one health outcome link per chemical is assumed. If multiple health outcomes can be linked to each chemical, the number of linkages would be multiplied further. Decision-making by the developers of SEM has led to both positive links and negative links. Each type of link can be pivotal to the development of a claim under EEOICP. Thus, although there are more than 1200 reported positive exposure/disease links, each negative decision requires review as well.

A review of the exposure/cancer linkages by the program's toxicologist, which reportedly reflect IARC's findings, still leaves more than 1200 reported positive exposure/disease link and thousands of negative links to be validated.

Further, assuring the validity of the decision made to develop SEM requires a review of the evidence (eg books, articles, etc) that was relied upon to draw those conclusions. I do not have access to the set of books and articles that were used in this process, nor, do I believe, does anyone in EEOICP.

Cross-checking positive exposure/disease linkages with a textbook, as has been proposed, will not serve to validate the database. First, it depends on which text is used in the cross-checking process. The program will have to determine which book, if any, is deemed the sole authoritative source for causal information. Second, if a single text would serve the program's needs, then development of the SEM exposure/disease linkages by reviewing a large amount of the occupational medical and toxicological literature would seem to have been unnecessary. Further, reliance on a single text is not congruent with the program's many procedures that require a review of the totality of evidence. In this case, the totality of the evidence includes all the books and publications on the topic of toxicology and occupational medicine. Finally, checking the positive links does not validate the negative links, which can also impact claim development. In addition, there may be evidence that was not identified in the original search that may now be both available and relevant. Textbooks, too, become quickly out-dated as new scientific evidence emerges. In sum, due diligence ideally requires a literature search, review and assessment of the toxicological and occupational studies available in PubMed (the National Library of Medicine's database of medical literature) for each of the 8000 chemicals.

2 - Ethical Considerations

Assuring the scientific integrity of both the "protocol" and findings requires peer review. Peer review generally means scrutiny and validation by a group of independent and objective experts. This process requires a community of experts who are qualified and impartial. A peer review process can be accomplished by an ad hoc group of expert reviewers and does not necessarily require bringing experts from outside of the DC Metro area.

Thus, one person cannot logistically or ethically assure the scientific integrity of the exposure/disease findings in the SEM database.

D - Suggestions

- 1 – Modify and expand the SEM User Guide to provide clear guidance on the interpretation of findings generated by a SEM search. Presently the User Guide notes only "review guidance docs" in Appendix A;
- 2 – Provide a clear and detailed list of the limitations of SEM (as noted above) for CEs and other users. Currently, for example, there is no mention of the concept of interaction in Appendix B (note, Appendix B of SEM refers to situations with possible multiple exposures).

3 – Annotate linkages with comments regarding latency, interaction, duration of exposure; add caveats (for example, about possible “fuzzy” linkages versus established linkages, “population” vs “individual” causal considerations, potential controversies and evaluate the quality and quantity of the data).

4 – Update linkages periodically and provide the date of the last update.

5 – Initiate comprehensive peer review of the proposed protocol and data-base to determine the scientific validity and utility of the SEM data-base.

6 – Consider the need for ad hoc expert consultants to review proposed “fuzzy” linkages.

E – Options

I realize that this effort will take considerable time and effort. Thus, I suggest that the program begin by requesting copies of the documents that have served as the rational basis for SEM decisions made by Dr Brown for review at the National Office of EEOICP by qualified experts. Ideally, Dr Brown should provide a synopsis of each of his findings that may serve as a rational basis for his decisions.

I provide these recommendations based on my 30 years of experience in the field of occupational medicine and epidemiology. However, I realize too, that it may be in the program’s interest to gather a group of qualified experts in the field of occupational medicine to provide their recommendations on how a SEM protocol should both be developed and reviewed and how the SEM database linkages should be validated. Similarly, it may be useful for a group of qualified experts in the field of occupational medicine to review my recommendations regarding improving DMC opinions. As always, I look forward to working with you and EEOICP staff on these important issues.

I would be happy to discuss these concerns with you at your convenience.

Sincerely yours,