FINAL

ONE HUNDRED-AND-EIGHTY THIRD MEETING OF THE
NORTH CAROLINA SCIENCE ADVISORY BOARD ON TOXIC AIR POLLUTANTS (NCSAB)

Proceedings of the January 27, 2016 Teleconference

Dr. Starr called the meeting to order at 3:05 PM. NCSAB members Drs. Thomas Starr, Ivan Rusyn, Woodhall Stopford, Dave Dorman, and Jane Hoppin were in attendance. Ms. Therese Vick of Blue Ridge Environmental Defense League (BREDL) and Dr. Candace Prusiewicz from DAQ was also in attendance.

Approval of December 2, 2015 Minutes
Meeting minutes from the 182nd NCSAB meeting held on December 2, 2015 were approved as written.

Meeting minutes that have been approved by the NCSAB are posted on the Division of Air Quality website at http://daq.state.nc.us/toxics/risk/sab/sab_minutes.shtml.

Acrolein Discussion

Dr. Starr asked Dr. Dorman to lead the discussion about acrolein as he was the most knowledgeable board member with regard to this substance. Dr. Dorman began by saying that he thought the board had done a good job at the last meeting summarizing the acrolein literature. He indicated that he had conducted a literature search through PubMed to determine what (if any) research had been done on acrolein since the publication of his research in 2008. He indicated that a few studies had been published but it was unclear how informative they would be to the discussion.

Dr. Dorman addressed Dr. Rusyn's question from the last meeting regarding whether any Benchmark Dose Modeling (BMD) was performed using animal lesion data. He replied that all his research data had been shared with the EPA but no BMD modeling analysis had been conducted. He also said that although there were sufficient data to support BMD modeling, the raw data was archived at the Hamner Institute for Health Sciences. He did not have access to the individual animal data.

Dr. Rusyn offered to run the BMD analysis if dose group and incidence data were available. He indicated that individual animal data were not necessary. Dr. Dorman replied that such data were compiled and available in the published 2008 research papers. He indicated that Tables 1 through 3 in Dorman et al.,2008 contain the incidence data for the three types of lesions scored at the different time points. Dr. Rusyn said that his research group could model every data point and present the results on the same graph (BMD, BMDL) for easier viewing. Dr. Dorman offered to provide the data in an EXCEL format to help facilitate Dr. Rusyn's analysis. Dr. Rusyn indicated that he would forward the link for a paper by his group about BMD modeling published in Environmental Health Perspectives.

Dr. Starr inquired if the lesion incidence data was reported as (number of animals with a specific lesion type) divided by (total number of animals examined) and if both the numerator and denominator values were included in the publication. Dr. Dorman replied that the lesions were reported as incidence rates (as opposed to severity and incidence rates). He explained that they had analyzed multiple nasal sections at different points in time for epithelial hyperplasia or metaplasia and reported the lesion incidence rate of each.

Dr. Starr asked Dr. Rusyn if CatReg (Categorical Regression, an EPA software) was included as part of their BMD software package. Dr. Rusyn replied that he was not certain. Dr. Dorman point out that the published tables also contained mean values for the severity scores for lesions in which a statistically significant difference from controls was observed. Dr. Starr thanked Dr. Dorman and indicated that such a variable could be used as a covariate in the BMD analyses.

Dr. Starr cautioned that the acrolein data to be used for the BMD modeling exercise had a very sharp dose-response. In such instances, the model tries to fit a step-like function to the data which may result in the model selecting a value greater than the No Observed Adverse Effect level (NOAEL). Dr. Rusyn indicated that visual inspection of the graphs produced by the model would prevent this. This is not actually a problem, although others may view it as one.

Dr. Dorman pointed out that one advantage of the inhalation studies conducted at CIIT was that they were more extensive than previous acrolein inhalation studies. Dorman et al., 1998 analyzed 6 nasal sections compared with Feron et al., 1977 which analyzed only 3 nasal sections. In addition, Dorman et al., 2008 established a NOAEL of 0.2 ppm (equivalent to 0.46 mg/m^3) for different nasal lesions. With regard to chronic studies, Dr. Dorman noted when he had worked with the National Research Council (NRC) to derive a maritime chronic exposure level for acrolein, the NRC did not have a high degree of confidence in long-term hamster inhalation studies due to differences in nasal sensitivities between hamsters and more traditional models like rats.

Dr. Dorman asked the board if they had any additional questions from the previous meeting that had not been addressed. Dr. Starr still had questions regarding the overall uncertainty factor used by Cal EPA in their derivation of a chronic air value for acrolein. He thought that California may have "double counted" when calculating their uncertainty factor.

He noted that the uncertainty factor was derived using a factor of 10 for interspecies and a factor of 10 for intraspecies effects. Dr. Dorman pointed out that the additional factor of 2 was used for the exacerbation of asthma in children resulting in a multiplicative uncertainty factor of 200. Dr Starr noted that the fluid dynamic model used to make the extrapolation from rats to humans essentially accounted for dosimetric interspecies effects so using a factor of 10 for pharmacokinetic effects was essentially "double counting".

Dr. Dorman said that in his work with other agencies reviewing acrolein data, chronicity had not been observed. A "C x t" profile (concentration and time) was not apparent, therefore a time adjustment for long-term or lifetime effects was questionable. Acrolein, like other reactive aldehydes, exerts local effects rather than chronic systemic effects following exposures. He indicated that the NRC focused on short-term effects for nasal irritants and did not put much stock in long-term effects. Dr. Dorman noted based on pathology results, he was not certain that the effects of acrolein adhered to Haber's Rule. He thought that the time correction used by Cal EPA in their risk assessment for acrolein presumed a Haber's Rule-type response and was therefore very conservative.

Dr. Starr summarized by saying that acrolein's effect would be solely a concentration effect rather than a "C*t" effect. Dr. Dorman indicated that acrolein exhibits a "C*t" response for acute irritancy but is not as linear as Cal EPA presumed. Dr. Starr inquired if Dr. Dorman agreed that the pharmacokinetic model used by Cal EPA inherently compensated for interspecies dosimetric effects. Dr. Dorman agreed it did.

Dr. Dorman noted that there have been a few additional papers published since 2008 looking at alternative CFD/PBPK models (Computational fluid dynamics/ physiologically-based pharmacokinetic modeling). They do not necessarily inform a different number but rather support the findings of Schroeter et al 2008. Dr. Starr inquired if the relationship between the local flux and the local airborne concentrations is linear in the modeling or is the scaling non-linear with respect to the flux at a specific site compared with the flux at a different site. Dr. Dorman replied that the toxicokinetic side of the modeling will appear linear when doing it as a combined CFD/PBPK model due to the non-linear depletion of glutathione.

Dr. Starr inquired if Dr. Dorman had any idea if acrolein was an endogenous chemical like acetaldehyde. Dr. Dorman did not recall if acrolein was an endogenous chemical similar to acetaldehyde and formaldehyde. He said that the relative potency of ambient aldehydes was acrolein > formaldehyde > acetaldehyde. Dr. Rusyn shared that he had located an on-line reference describing acrolein as an endogenous metabolite.

Dr. Dorman noted a dearth of published human studies with acrolein since 2008. He identified a paper by de Castro of the Center for Disease Control (CDC) who investigated acrolein and the prevalence of asthma attacks in the United States. De Castro reported an approximate 8% increase in risk of one asthma attack for the previous year associated with ambient acrolein concentrations ranging from 0.05 - 0.46 µg/m^3 (concentrations close to the Cal EPA REL). Dr. Dorman pointed out that the authors reported a marginally significant increase with a reported odds ratio of 1.08. He asked that other board members with more experience in statistics review the de Castro paper and evaluate the significance of the odds ratio. Dr. Hoppin volunteered to review the epidemiological aspects of the paper. Dr. Starr thanked Dr. Hoppin for volunteering to review the paper.

Dr. Stopford thought the Texas (TCEQ) risk assessment was well done. He described an 18-month inhalation study in rats by LeBouffant et al., 1980. Rats were exposed to 8 ppm acrolein for 1 hour/day, 7 days/week for up to 18 months. No cancer effects were observed. Dr. Stopford reviewed how Texas had derived their uncertainty factor (10 for intraspecies differences and 3 for interspecies differences for a multiplicative value of 30 (TCEQ Development Support Document for Acrolein, 2015). Dr. Stopford felt more comfortable with the methodology used by Texas than by California. Dr. Starr agreed. Dr. Dorman agreed that the Texas approach was aligned more closely with risk assessments conducted by other agencies (ie. Maine and National Research Council (NRC)). He pointed out that once an acute value is established, the chronic value is very close to it because of the steep dose-response.

Dr. Starr wondered why acrolein has not been studied in longer duration studies (2 year studies) similar to acetaldehyde and formaldehdye. Dr. Starr indicated that if there were no further discussion, he would move on to the public forum part of the meeting.

Public Forum
There were no comments from the public.

Other Business
There was no other business.

Planning for March 30, 2016 Meeting
Dr. Prusiewicz inquired if she should research endogenous levels of acrolein for the next meeting or if board members would identify papers for further discussion. Dr. Rusyn said that he had sent an email with such a publication to Dr. Prusiewicz for distribution to the board.

Dr. Dorman inquired how the board will use the endogenous acrolein data. Dr. Rusyn said it will be included in the final write-up for informational purposes. He asked Dr. Prusiewicz to review the publication to see if some values could be located. Dr. Dorman offered to help Dr. Prusiewicz with that exercise.

Dr. Prusiewicz asked the board about acute human studies. Dr. Dorman said that the human study by Weber-Tschopp is the study used most often by groups setting an acute exposure level for acrolein. Cal EPA chose to use Darley et al., 1960 because it yielded a 10% lower value; however the study is not considered as robust as the Weber-Tschopp study. Dr. Prusiewicz indicated that she lacked access to a translated version of the German Weber-Tschopp publication. Dr. Dorman offered assistance in obtaining a translated version of the paper.

The meeting was adjourned at 3:45 PM.

Respectfully submitted,

Candace Prusiewicz, Ph.D., D.A.B.T.
Liaison, Science Advisory Board

Note: During the meeting, board members electronically forwarded relevant publications to Dr. Prusiewicz who later compiled and distributed to all board members. Publications distributed post-meeting were:

- De Castro BR (2014). Acrolein and asthma attack prevalence in a representative sample of the United States population 2000-2009. PLoS ONE 9(5): e96926 doi:10.1371/journal.pone.0006926.
- IARC (1995). IARC monograph on the evaluation of carcinogenic risks to humans (Dry cleaning, some chlorinated solvents and other industrial chemicals) Vol 63, 337-372.
- Mogh A, Ghare S, Lamoreau B, Mohammad M, Barve S, McClain C, and Joshi-Barveg S. (2015). Molecular mechanisms of acrolein toxicity: Relevance to human disease. Tox Sciences, 242-255 doi:10.10931/toxsci/kfu233.
- Wignall, JA, Shapiro AJ, Wright FA, Woodruff TJ, Chiu WA, Guyton KZ, and Rusyn I (2014). Standardizing benchmark dose calculations to improve science-based decisions in human health assessments. Env. Heath Perspec 122 (5), p 499-505.

References

Darley, E., J. Middleton, and M. Garber. 1960. Plant damage and eye irritation from ozone-hydrocarbon reactions. *Agricul Food Chem* 8(6):483-484.

Dorman, DC; Struve, MF; Wong BA; Marshall MW; Gross EA and Wilson GA. (2008). Respiratory tract responses in male rats following subchronic acrolein inhalation. Inhalation Toxicology 20:205-216.

Feron VJ, Kruysse A, Til HP, et al. 1978. Repeated exposure to acrolein vapour: Subacute studies in hamsters, rats and rabbits. Toxicology 9:47-58.

Le Bouffant l., Martin JC, Daniel H, Henin JP, and Normand C. (1980). Action of intensive cigarette smoke inhalation on the rat lung. Role of particulate and gaseous cofactors. J Natl Cancer Inst 64: 273-284.

Schroeter JD; Kimbell JS; Gross EA; Wilson GA; Dorman DC; Tan YM and Clewell HJ. (2008). Application of physiological computational fluid dynamics models to predict interspecies nasal dosimetry of inhaled acrolein. Inhalational Toxicology 20:227-243.

Struve; MF; Wong VA; Marshall MW; Kimbell JS; Schroeter JD and Dorman DC. (2008). Nasal uptake of inhaled acrolein in rats. Inhalation Toxicology 20:217-225.

Texas Commission on Environmental Quality (TCEQ) Development Support Document for Acrolein (2015). Office of the Executive Director.

Weber-Tschopp, A., T. Fischer, R. Gierer, and E. Grandjean. 1977. Experimentally induced irritating effects of acrolein on men. *Int Arch Occup Environ Health* 40(2):117-30.

These minutes were accepted at the 184th NCSAB meeting on March 30, 2016.