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Comments to the Ethylene Oxide SAB CAAC
September 30, 2014

I make these remarks today as an independent consultant on behalf of the American Chemistry Council (ACC). I am currently a professor emeritus in medicine at the University of Vermont and have been involved in mutagenesis research for over 40 years. My comments are directed to EPA's draft Charge Question #5 which is: "Please comment of the accuracy, objectivity and transparency of the revised draft assessment, with particular emphasis on genotoxicity". I would like to suggest an additional related Charge Question. The additional Charge Question is: "How well is it demonstrated that a direct, DNA reactive mutagenic MOA is the only MOA for all tumors attributed to ethylene oxide?" I thank the committee for this opportunity.

In specific response to Charge Question #5, I congratulate the EPA on their review of the genotoxicity of ethylene oxide (EO), which constitutes as complete a genotoxicity profile as is currently available for this chemical. Rather than questioning the completeness of the profile, my comments are directed to the use of these data in determining an EO mode-of-action (MOA) for cancer (additional Charge Question). The EPA has determined this MOA to be direct, DNA reactive mutagenicity, and appears to consider this the **only** MOA for **all** tumors. My remarks are directed first at the lack of clarity of the process used in EPA's determination of this MOA and second, at the assumption that this is the only plausible MOA for all tumors attributed to EO.

Comments regarding the determination of a direct, DNA-reactive mutagenic MOA

- Positive genotoxicity data by themselves do not constitute sufficient evidence to determine this MOA.

- Application of a MOA analysis framework based on “KEY EVENTS” for assessing a chemical carcinogen’s cancer MOA provides clarity and scientific rigor to the process.
- Key events are early, necessary and quantifiable precursor steps in the pathogenesis of cancer.
- The earliest of the key events in tumor development due to chemicals acting via a direct, DNA reactive mutagenic MOA deal with mutation induction in the target tissue before tumor development.
- To establish a direct, DNA-reactive mutagenic MOA, it necessary to demonstrate pro-mutagenic DNA adducts in the target tissue for cancer. This has not been done for EO.
- EPA should specify which tumors they deem to be induced via a direct, DNA reactive mutagenic MOA and their reasons for these determinations.

Comments regarding alternative biologically plausible modes of action

- Initial amplification of pre-existing (background) *K-Ras* mutations in lung mediated by oxidative stress modifying Ras signaling in mice exposed to EO, with experimental support, has been postulated as an early event in lung tumor production in this animal model.
- Modern studies of the pathogenesis of human lymphoid tumors suggest a MOA independent of initiation by a “single hit” resulting from an external mutagen. Lymphomas are typically associated with immunological factors such as infections, immunosuppression and autoimmunity rather than chemicals. Double strand breaks (DSBs) due to physiological processes (V(D)J recombination, class switching, AID hypermutation) coupled with pathological DSB (e.g. due to ROS, aberrant immune response) conspire to initiate these malignancies.

The EPA is asked to reconsider their insistence on only a linear, non-threshold extrapolation for risk assessment for all tumors in recognition of biologically plausible pathogenic processes being involved in at least some EO associated tumors.

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