Introduction

Walden Dalbey, MA, PhD, DABT (DalbeyTox, LLC)

40 years in toxicology with >20 years running inhalation labs (included studies on metalworking fluids). Currently consulting since retirement.

Reviewed report on CIMSTAR® 3800 for ILMA

Eleven pages of comments were sent to NTP, many asking for clarification in the report. Only a few selected comments are presented today.

Characterization of Exposures

Methanol, ethanolamine, and 1-amino-2-propanol were identified as relatively volatile components (pp. 36, H-6), but it was not clear if a vapor phase was monitored during the exposures.

The specific method for gravimetric measurement of the aerosol phase was not clear (p. 33). Hexane extraction was performed, but it was not clear if the extract or the residue was weighed and what either represented in terms of substances in the MWF.

The composition of the aerosol is not apparent. (See p. H-6.) The substances from the original MWF that are included in the values for aerosol concentration are not apparent.

Criteria for Evidence of Carcinogenicity Sometimes Unclear

Prostate tumors in male rats – "equivocal" because incidence is outside range of historical controls?

Brain tumors in male rats – Report might benefit from a discussion of brain tumors in males and females combined, particularly given a lack of dose-response in exposed males and tumors in female controls.

Lung tumors in mice – Is "overall rate" based on number of TBA regardless of how many tumors an individual has? If so, that's not clear in this section or elsewhere.

Skin Tumors

The report concluded that there was *equivocal evidence of carcinogenic activity* in female Wistar Han rats based on the combined incidences of squamous cell papilloma and keratoacanthoma of the skin.

- Basis for the decision is unclear since results are neither statistically significant nor dose-related.

- The conclusion is further compromised because an increase was not observed in exposed male rats, although male controls did have 1 basal cell carcinoma and 1 keratoacanthoma.

Skin Tumors Continued

The report further states that animals "received significant dermal exposure to CIMSTAR 3800 during the 2-year whole body inhalation study due to condensation of the liquid aerosols on the fur and skin".

- Is statement inferred from the presence of tumors or based on observations of the animals or measurement of deposition?
- How much deposited aerosol did the animals ingest and what might have been the effect of that ingestion?
- Was such deposition unique to this study? For example, did an electrostatic charge on the aerosol lead to unusual deposition?
- Has similar deposition on the fur happened in other inhalation studies with particles in this size range? Are there implications for those studies?

Genetic Toxicology: Mutagenicity in *E. coli*

Report states (page 88) that CIMSTAR 3800 "was mutagenic in *Escherichia coli*". However,

- High dose was 10,000 mg/plate (twice the recommended maximum dose in OPPTS 870.5100).
- A doubling of the number of revertants was not seen.
- Even so, conclusion in Table E1 was "weakly positive".
- As stated on page E-2, there "is no minimum percentage or fold increase required for a chemical to be judged positive or weakly positive, although positive calls are typically reserved for increases in mutant colonies that are at least twofold over background."
- Please reconsider the decision to call the results "weakly positive" and "mutagenic" or provide a rationale for retaining the wording.

Mistake in written comments: 10 mg/plate given as the high dose should have been 10,000 mg/plate.