

**Marvin A. Friedman PhD, DABT,
DATS**

Senior Scientific Advisor

SNF S.A.S.

**Comments on
Mutagenic MOA as the Key
Event in Carcinogenicity**

Proposed Mode of Action

Draft IRIS report

- Reasons for a genotoxic MOA are listed (p. 144)
- Hormonal MOA also discussed; the justification has “relatively little support for a hormonal pathway”

Comments:

- Limited evidence supports a mutagenic MOA for the rodent carcinogenicity data; and,
- Significant evidence to support a hormonal MOA
- Virtually all genotoxicity studies have been

Evidence of Mutagenic MOA

1. *AA is metabolized to DNA-reactive epoxide, GA.*

Comments: True.

Evidence of Mutagenic MOA

2. *AA & GA genotoxic in Big Blue mouse with significant increase in lymphocyte Hprt and liver cII mutations.*

Comments:

- Hprt is due to large deletions — chromosome based and globally recognized as non-linear.
- Micronucleus response has a threshold.
- *cII*, a small viral genome, even when tested at toxic doses, has marginal effects. No observed increase in mutation frequency at lower, non-

Evidence of Mutagenic MOA

3. *GA DNA adducts detected “in all relevant tissues in both males and females where tumors have been reported”*

Comments:

- DNA adducts found throughout exposed rodents in both target and non-target tissues
- There is no evidence that DNA binding is associated with any toxicity or tissue damage
 - Such damage expected with a substance that induces transversions and frameshift mutations

Evidence of Mutagenic MOA

4. *GA mutagenic in short-term bacterial assays.*

Comments:

- While GA is active in Ames test, AA is negative even when tested at more than 200 times the dose, with and without metabolic activation.
- GA adducts are not in the base pairing region and therefore have little impact on coding.

Evidence of Mutagenic MOA

5. *GA is mutagenic in somatic cells and in male mouse germ cells (heritable translocations)*

Comments:

- Recent studies in L5178Y and *tk* suggest these responses are due to oxidative stress.
- Translocations are reproductive events, protein related and not relevant to carcinogenicity.

Evidence of Mutagenic MOA

6. *AA induces heritable translocations and specific locus mutations in male mouse germ cells following*

Comments:

- The induction of dominant lethal mutations and heritable translocations in germ cells are reproductive phenomena and unrelated to tumorigenicity of AA

Evidence of Mutagenic MOA

7. *Positive mouse lymphoma (ML) assay results*

Comments:

- Recent studies demonstrate that ML results are due to large deletions (chromosomal alterations) and not transversions or frameshift mutations.
- No conclusive evidence that chromosomal lesions in ML are relevant to carcinogenicity due to the unusual mouse lymphoma genome.

Evidence of Mutagenic MOA

8. *Dominant lethal mutations occur in subchronic studies at same doses as carcinogenicity*

Comments:

- Occurrence of dominant lethal mutations at 2.8 mg/kg in rats has no bearing on acrylamide tumorigenicity as these occur in mature sperm and are a result of protamine reaction and not DNA reactivity.

Summary of Comments

- Genotoxicity data are limited and largely restricted to mice.
- Hormonal data are robust and explain the carcinogenic response in the rat bioassays.