

MOUSE LUNG TUMOR MODE OF ACTION CONSIDERATIONS

CROSS CUTTING ISSUES



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Bioactivation seems to be the key event in MOA

Multiple chemicals

Some structural similarities

Appreciable enzymic (2F2) similarities

The enzyme is present at very low levels in rats and
at exceedingly low levels in humans (Strupp et al., 2012)

Exclusive MOA in mice?

Relevance to humans?

Can we conclusively rule out metabolite formation in
tissues other than mouse lung??

How well can we summarize molecular, cellular changes
leading to tumors from 2F2-derived metabolites?

Are some early events unique to 2F2-derived metabolites?

- Are they seen following exposure to other (2F2 non-substrate) chemicals?
- Are they seen in other tissues, species?

A Potentially Informative Academic Approach ...

Is a harmonized approach to non-cancer and cancer risk assessment based on precursor events in tumorigenic MOA feasible?

What would the cancer risk be at the RfC based on such an event?

What benefit will we derive from identifying CYP2F2-mediated metabolism as the key event in a unique and humanly non-relevant MOA for this or any group of chemicals?

