COMMENTS TO EPA SCIENTIFIC ADVISORY BOARD

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(1)

ETHYLENE OXIDE

- MOA FOR CANCER = DNA-REACTIVE GENOTOXICITY
- LOW POTENCY MUTAGEN
- LOW POTENCY CARCINOGEN

(2)

DNA-REACTIVE GENOTOXIC MOA

- **DNA-Damage – Mutation Paradigm**
- **Mutation (irreversible change in DNA structure that leads to change in genetic information content) at either the gene or chromosome level is the critical KEY EVENT in carcinogenesis***
- **A chemical that functions only through a DNA reactive genotoxic MOA cannot produce cancer under conditions where it does not produce mutations**
- ***DNA damage = DNA lesion =DNA adduct is NOT A MUTATION: Mutation production is a function of cellular activity***

(3)

ETHYLENE OXIDE

DNA Adducts

N7G*

N3A

N1A

O^6G

N^6A

N3C→N3U

N3T

*** N7G > 80% of total adducts = marker adduct (4)***

ETHYLENE OXIDE:

A Normal Metabolic Product Produced Endogenously

<u>Normal Background 7HEG Adduct Levels</u>

- ***Rodents ~ 2 – 3 adducts per 10^7 Guanines***
- ***Humans Background levels are higher (5)***

ETHYLENE OXIDE
(*In Vivo Mutagenicity and Carcinogenicity)*

Must Exceed Background Levels of DNA Adduct Formation in Order to:

Induce Gene Mutations
Produce Cancer in Rodents
Increase Cancer Risk in Humans

(see Walker et al. 2000 Carcinogenesis 21:1661)

(6)

ETHYLENE OXIDE

7HEG DNA Adducts in Humans

NO SIGNIFICANT INCREASE OVER BACKGROUND IN HUMANS OCCUPATIONALLY EXPOSED TO 2 – 5 PPM EO

(van Delft et al., 1994, Carcinogenesis, 15:1867)
(7)

ETHYLENE OXIDE MUTAGENICITY STUDIES

- ***In Vitro***: **GAP shows average LEECs to be between 1.0 and 10.0 µg/ml* (equivalent to blood concentrations at inhalation exposures > 150 ppm for 4 h in mice**)**

- **Rodents, (*In Vivo*):** ***Minimal to no effects at either the gene or chromosome level for physiologically administered chronic exposures < 10 ppm***

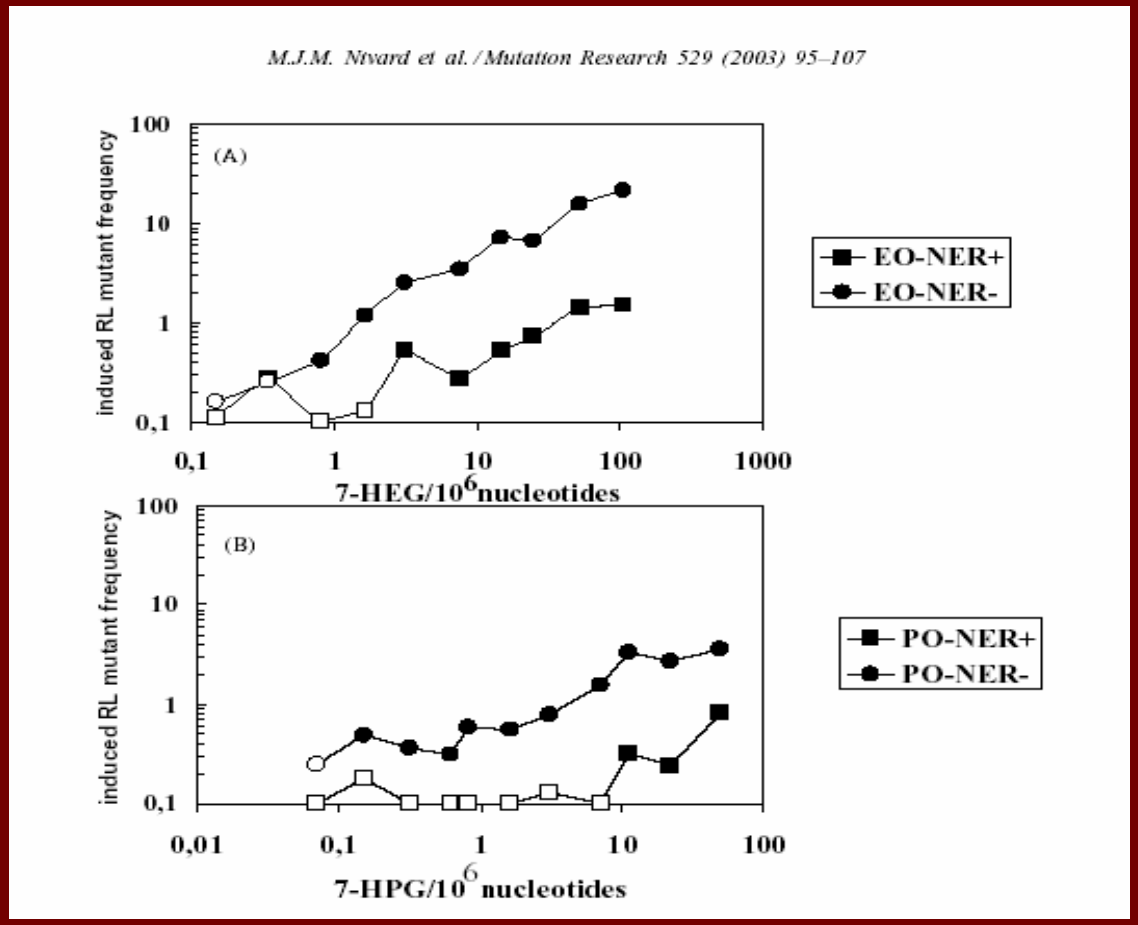
- **Humans:** ***No gene mutations < 5.0 ppm (TWA); Chromosome mutations (in PBL) require high concentration acute exposures or chronic exposure levels ~ 20 – 25 ppm.***

(Multiple references in Panel's Response to EPA [12-8-06})

**** = Waters et al., 1998, ** = Brown et al., 1998***

EO DROSOPHILA STUDIES: EFFICIENT REPAIR = WEAK MUTAGENICITY (no mutations until N7G DNA adduct levels reach 31.0 x 10^{-7} in NER+ flies, or 8.0 x 10^{-7} in NER- flies)

(9)



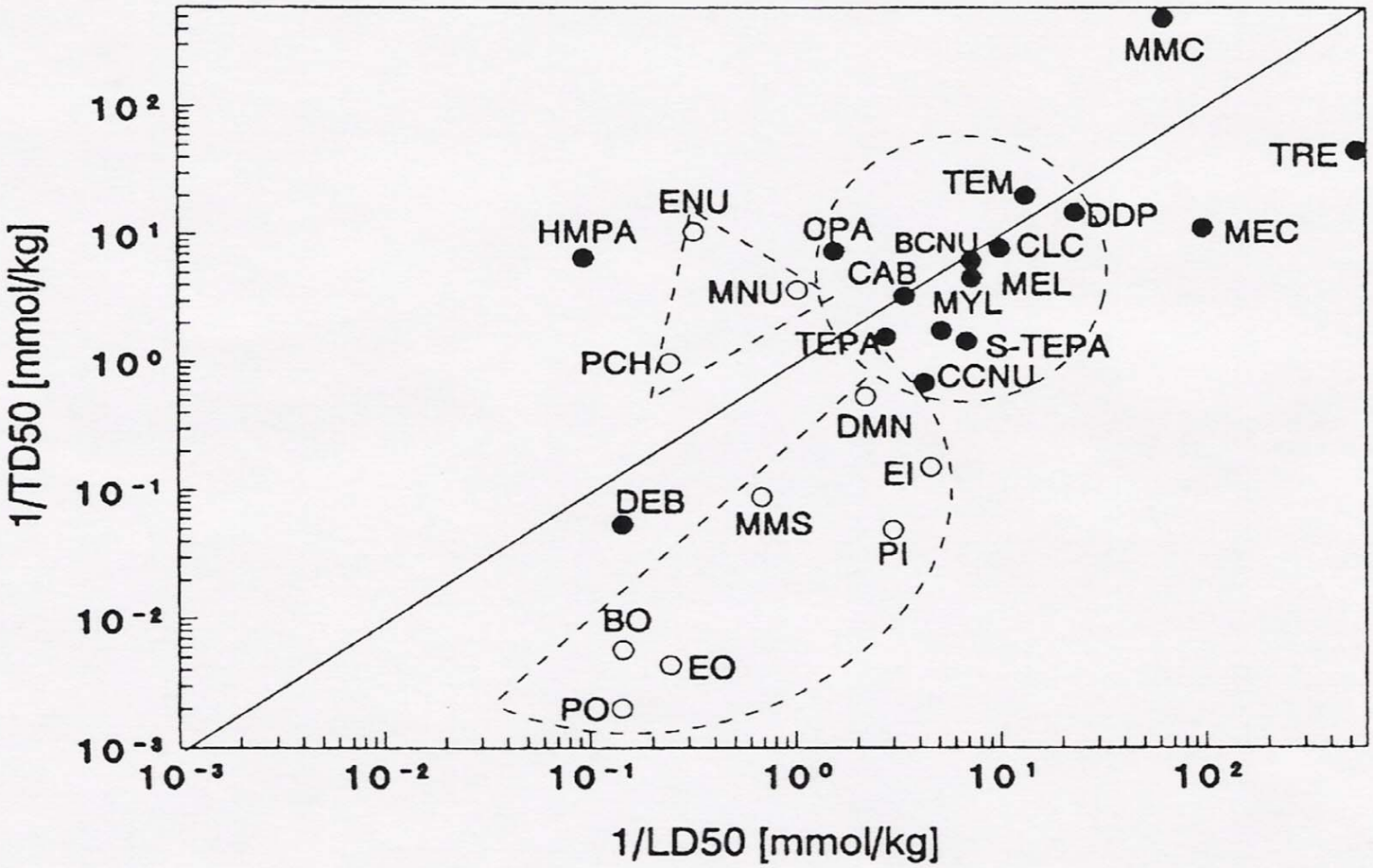


Fig. 12. Carcinogenic potency ($1/TD_{50}$, life-time doses) of alkylating agents in rodents in comparison with acute toxicity ($1/LD_{50}$).

Vogel et al. (1998) Mutation Res. 400:509-540 (10)