Classical 'One Chemical at a Time' Toxicology Cannot Address the Cabin Air Quality Problem

20/09/17 Imperial College

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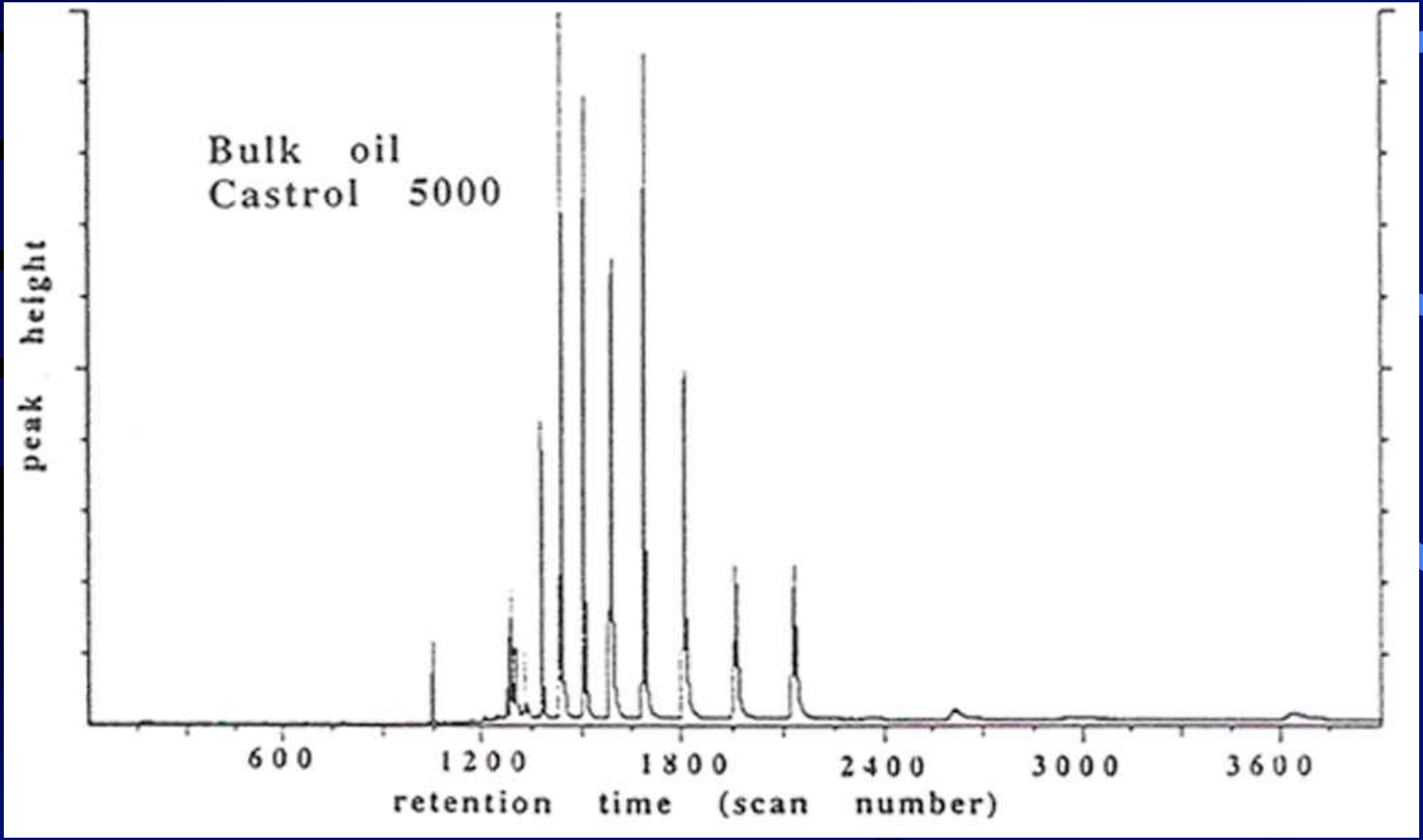
Background

- Medically qualified. Toxico-pathologist
- 6 years experience in regulatory toxicology as Member of UK Government Advisory Committee on Pesticides
- Published in the field of toxicology testing of chemical mixtures of OPs

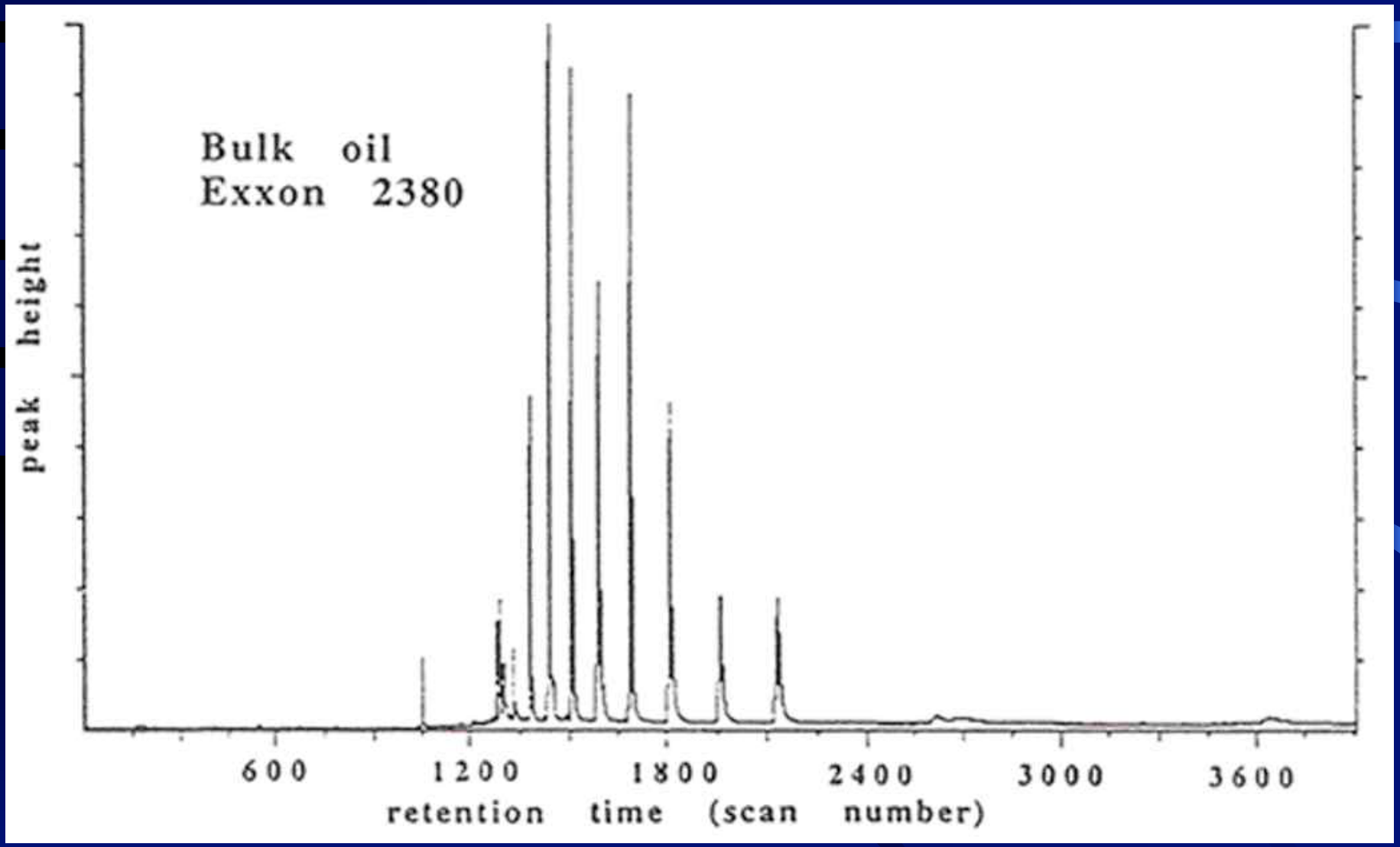
Complex mixtures

- Technical preparations of organic chemicals are not pure – they consist of a racemic mixture of enantiomers and isomers
- When the constituents of modern synthetic turbine oils are heated in low oxygen in an engine, pyrolysis products are added to the mixture making it more complex

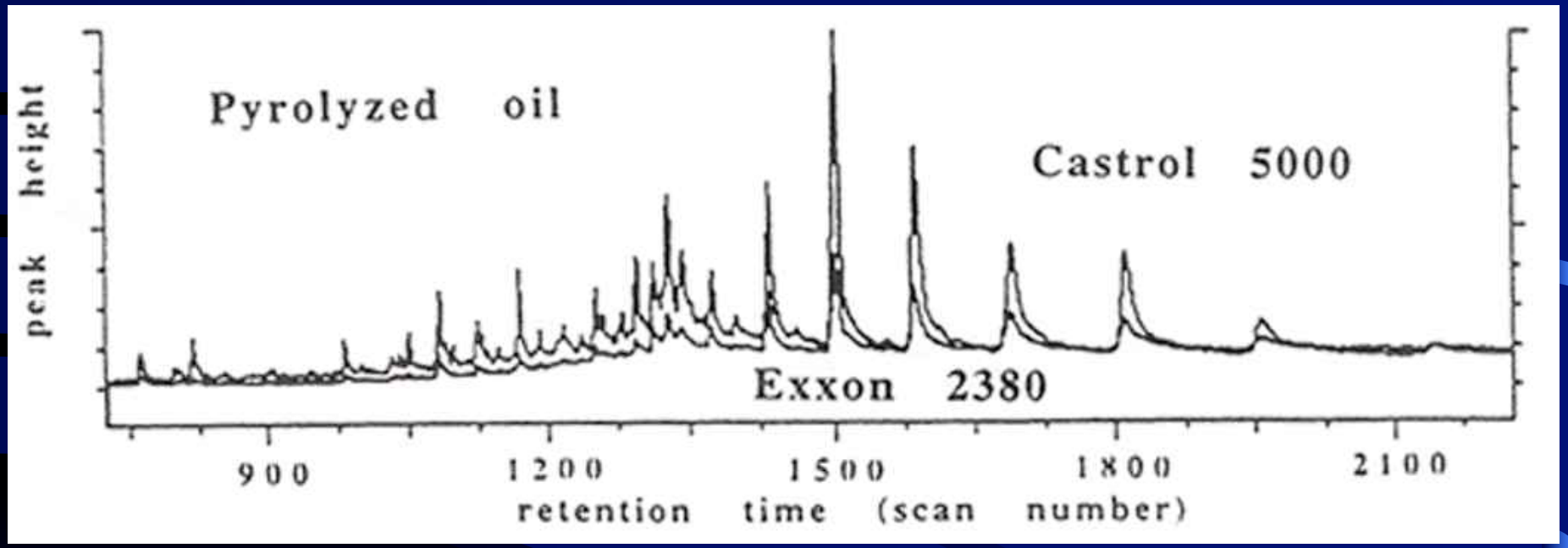
C van Netten, V Leung (2000) Comparison of the Constituents of Two Jet Engine Lubricating Oils and Their Volatile Pyrolytic Degradation Products
Applied Occupational and Environmental Hygiene 15(3): 277–283, 2000



Unused oil


Bulk oil
Exxon 2380
peak height
600
1200
1800
2400
3000
3600
retention time (scan number)

Used oil


Pyrolyzed oil
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Exxon 2380
peak height
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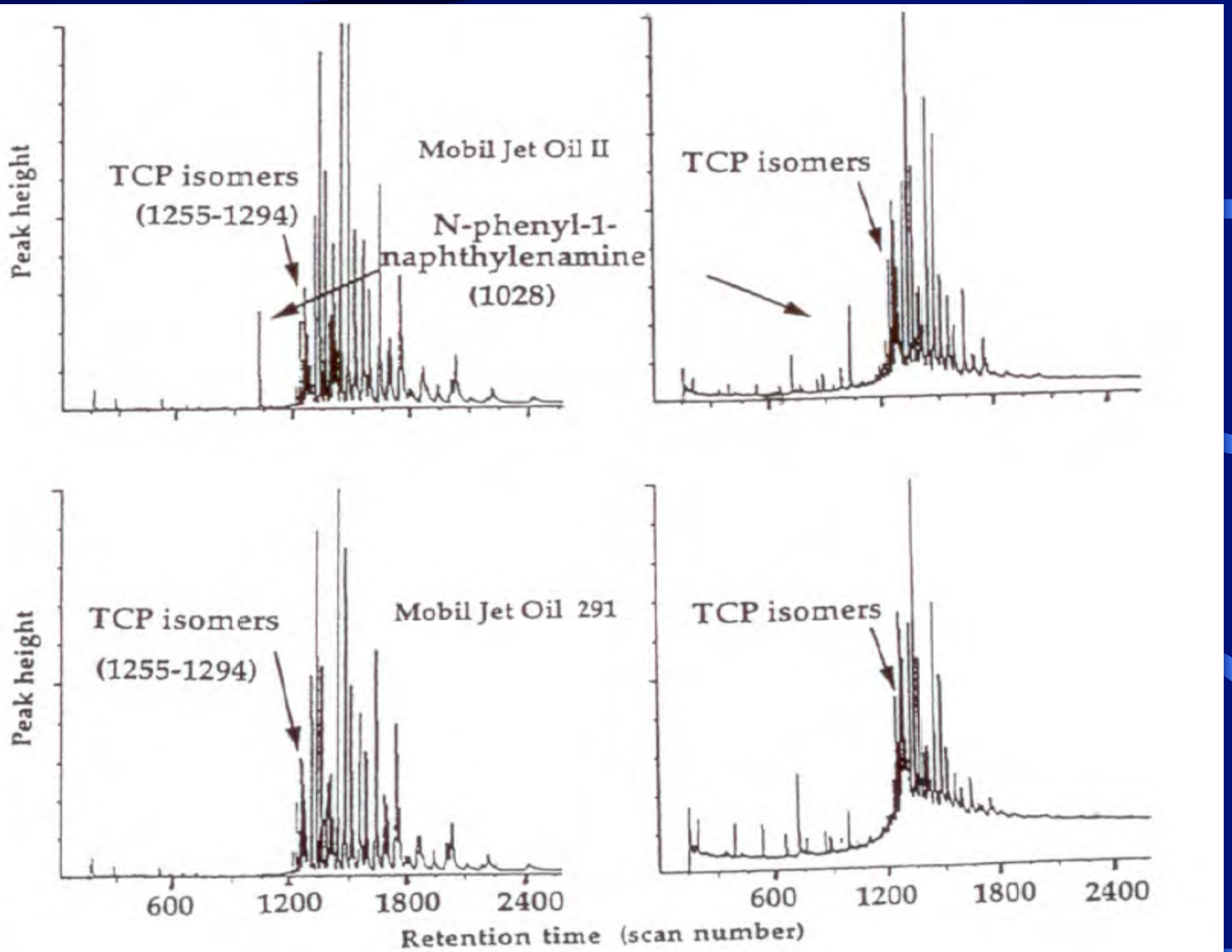
1200
1500
1800
2100
retention time (scan number)


Peak height
TCP isomers
(1255-1294)
Mobil Jet Oil II
N-phenyl-1-
naphthylenamine
(1028)
TCP isomers
Peak height
TCP isomers
(1255-1294)
Mobil Jet Oil 291
TCP isomers
600
1200
1800
2400
600
1200
1800
2400
Retention time (scan number)

Regulatory Risk Assessment – 4 phases

- **Hazard identification** – requires insight and understanding of the system in question
- **Hazard assessment** – costs time and money for hard science – positive findings require action
- **Exposure assessment** – can be very expensive and, for human exposure, complex
- **Risk assessment** – depends totally on the 1st three steps

Hazard Identification

- Acute effects of exposure to OP compounds
  - Impaired coordination, visual disturbance etc
- Chronic effects of repeated low dose exposures to OP compounds –CNS damage
- Developmental threats to vulnerable groups - fetus and young children
- ROUTE OF ENTRY

Hazard Characterisation

- An enormous amount of peer reviewed scientific information on the hazard characterisation of OPs, and in particular of TCP and its metabolites is extant.
- However it comes from many different types of study: acute toxicology, sub-acute toxicology, multi-generation studies, developmental tox, etc

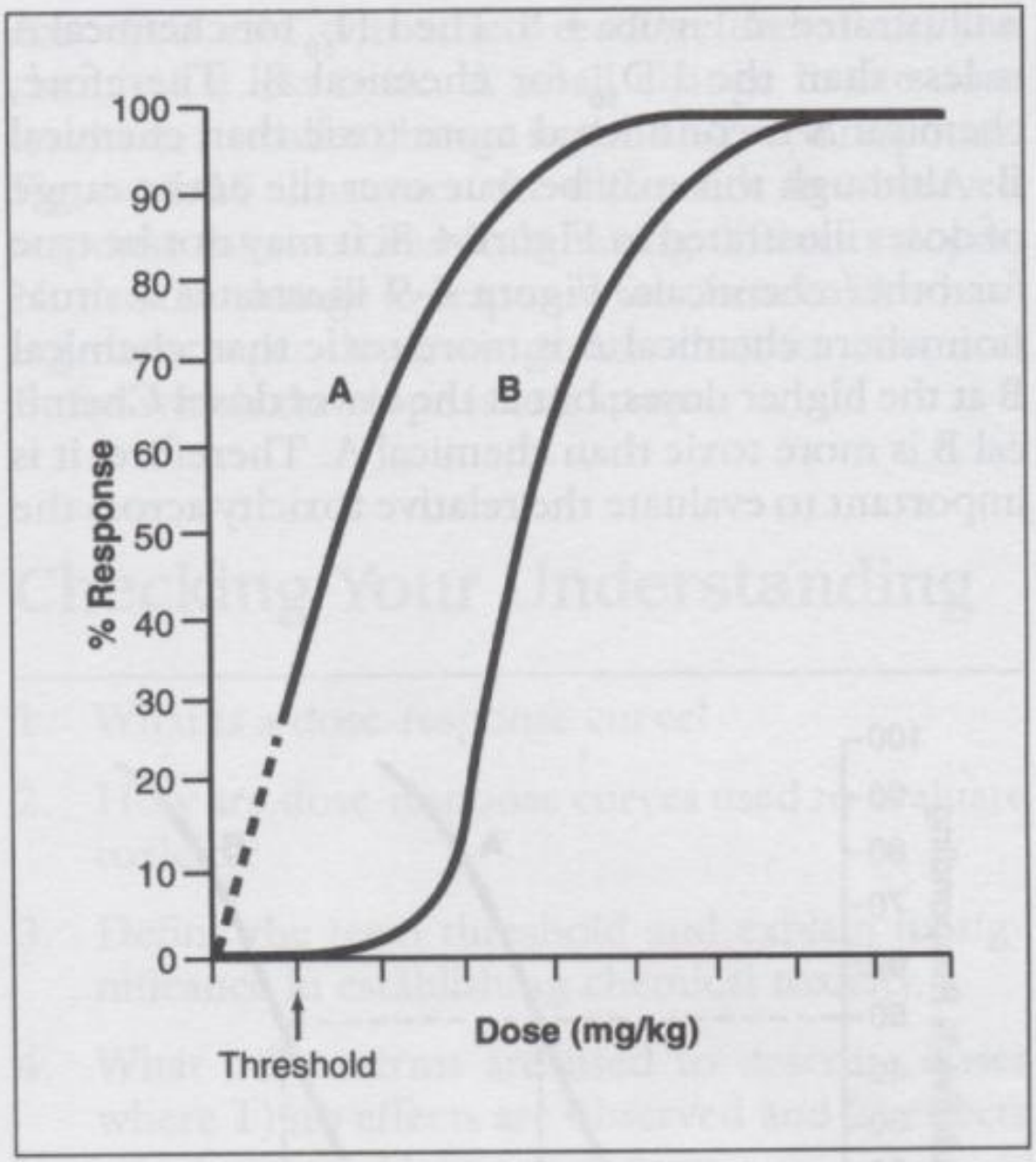


Figure 4-7: Two dose-response curves, one illustrating a

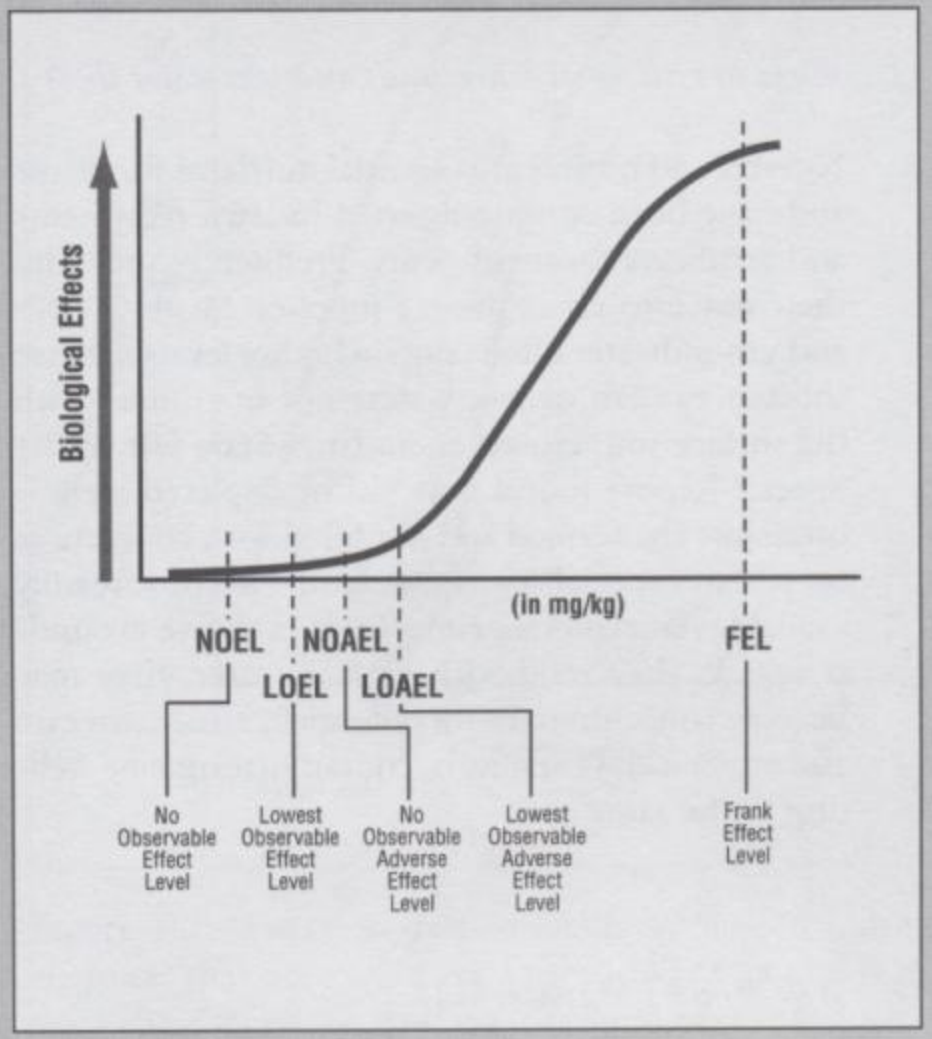
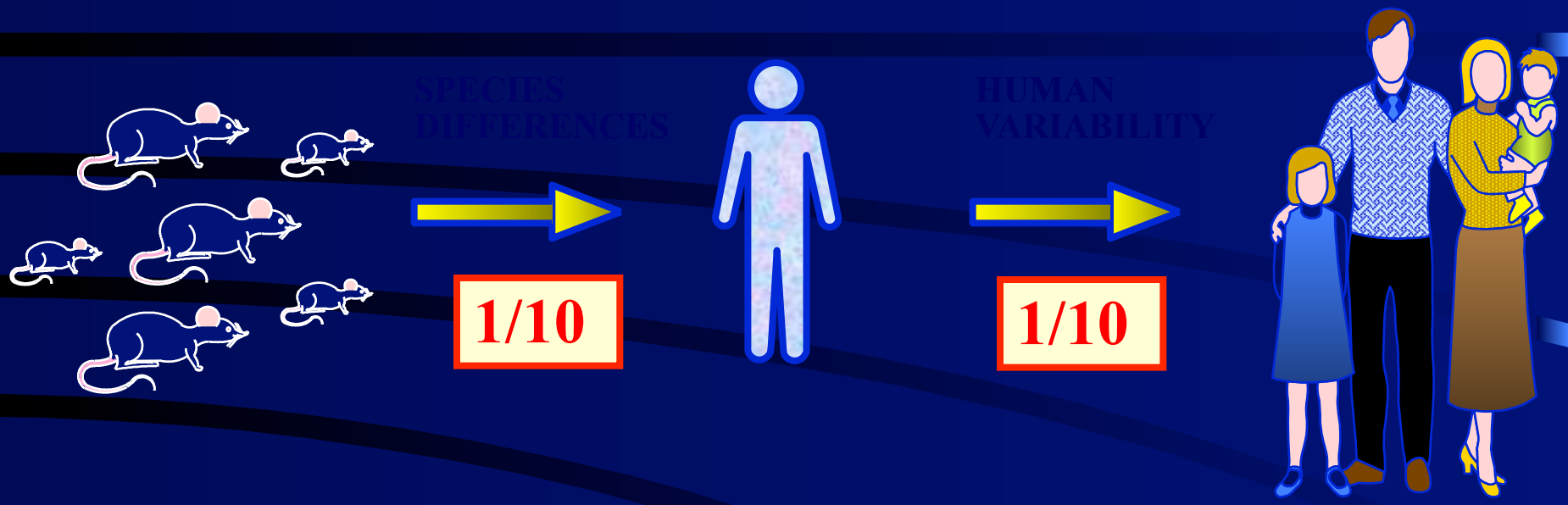


Illustration of the locations of various effect-no effect levels on a dose-response curve. *Reprinted with permission from Ecobiochen D.*, The Basis of Toxicity Testing, *Copyright CRC Press, Boca Raton, FLA 1990/1992.*

Which study to use? The most sensitive!

- Acute toxicity
- Sub-acute toxicity
- Chronic toxicity
- Reproductive toxicity
- Teratogenicity
- Multigenerational studies
- Neurobehavioural (functional) toxicology

From NOEL to ADI



Assessment factors extrapolate from a group of test animals to an average human and from average human to potentially sensitive sub-populations,
so ADI is typically 1/100th, or less, of NOEL

Is a safety/uncertainty factor of 100 enough for children?

- -US FQPA legislation makes provision for another factor of up to 10 to protect those in development, i.e. 10x10x10 = 1,000
- -Recent report of the Dutch Health Council of the Netherlands (GZB/VVB-993063, 7th June 2004) notes that in young animals in some circumstances even single exposures to some pesticides can be enough to produce an effect. The report acknowledges that children take in pesticides from multiple sources and recommends that additional uncertainty or safety factors of between 3 and 10 be considered to protect health during the developmental period, pending a period of further research.

Exposure scenarios

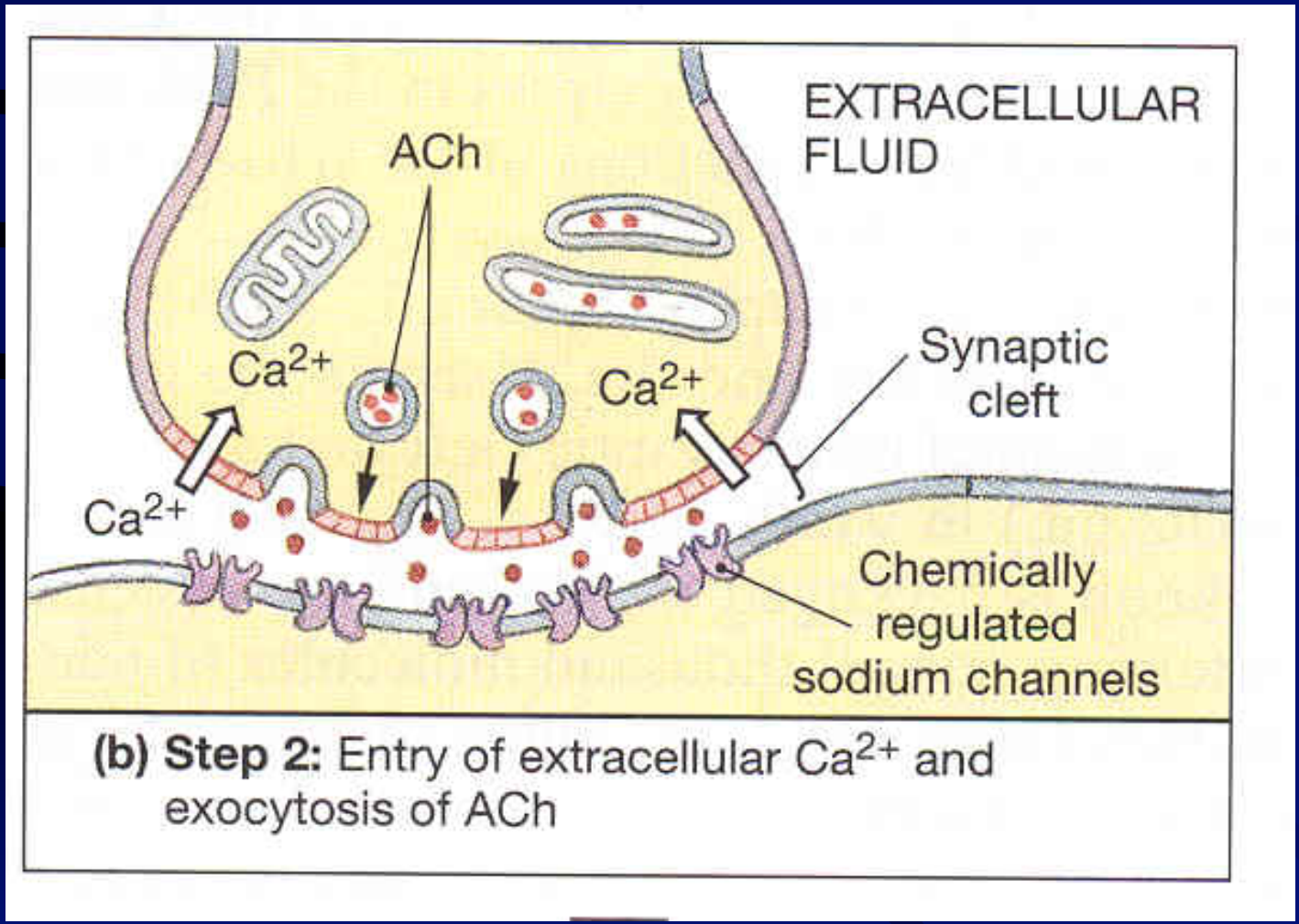
- Many studies which confirm that low level exposure of cabin crew and passengers is the norm
- High level exposure (fume events) on occasion

Classical High Dose OP

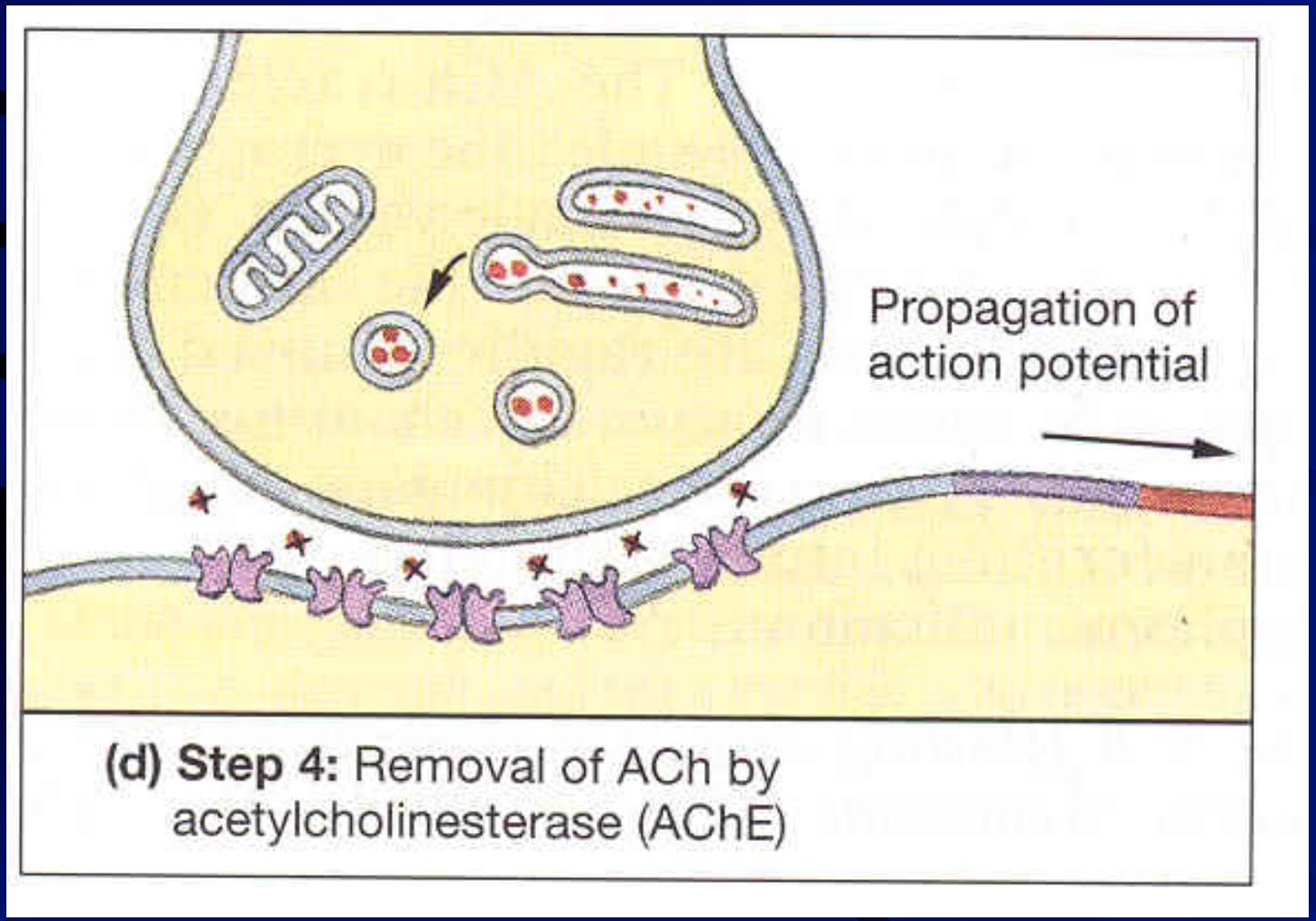
Short duration high dose

“Nerve gas” type symptoms

Release of acetyl choline



-ve feedback. Enzyme destroys acetyl choline



Effects of OPs

- MUSCARINIC
- Increased secretions
- Constriction of pupils & bronchi
- Abdominal cramps
- Bradycardia (slow heart)

- NICOTINIC
- Fasciculations
- Tachycardia

- CNS
- Headache, dizzyness,anxiety, confusion, convulsions, coma

OPIDN

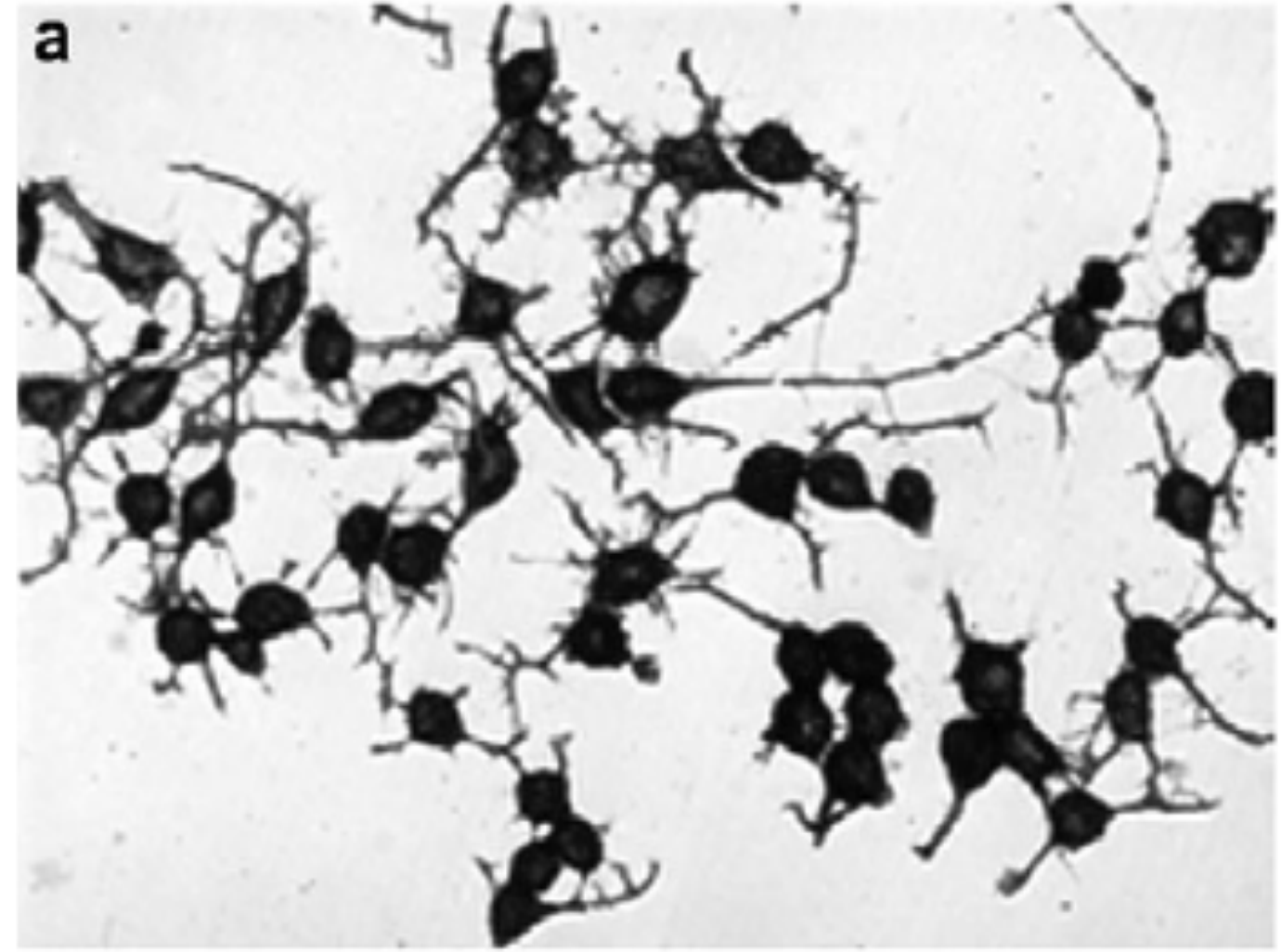
- Organo-phosphate induced delayed neuropathy
- Acknowledged to be the consequence of a high dose exposure event
- In the Committee on Toxicity (COT) review this was the only outcome considered
- OPIDN does not match the symptoms reported by Michaelis et al (2017)

Toxicology of mixtures

Ten Years of Mixing Cocktails: A Review of Combination Effects of Endocrine-Disrupting Chemicals. Andreas Kortenkamp *EHP* (2007) 115:98

- **Implications for Regulatory Strategies**
- It is evident that the traditional chemical-by chemical approach to risk assessment is inadequate when dealing with EDs (and chemicals with other toxic profiles). The biological reality of combination effects from exposure to multiple agents at low doses highlights the potential for underestimating risks when mixture effects are not taken into account.

Neurite outgrowth assay



Two at a time

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Synergistic Interactions between Commonly Used Food Additives in a Developmental Neurotoxicity Test

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A lot of work!

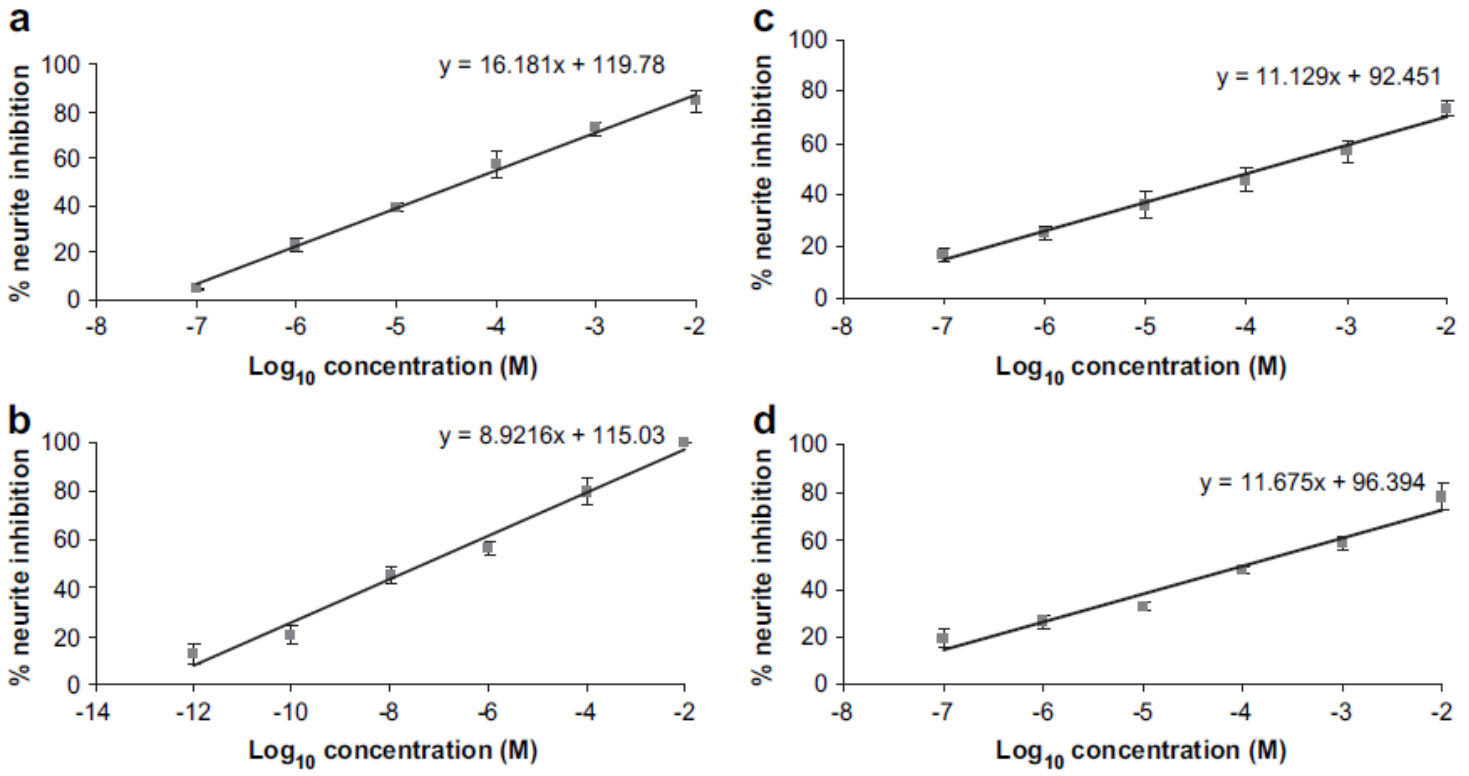
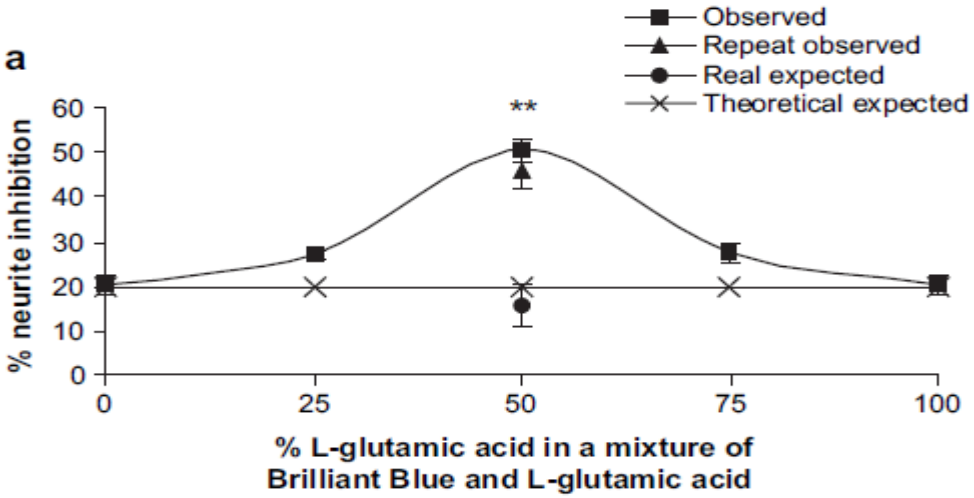


FIG. 1. Graphs of $\log_{10}$ concentration versus effect were plotted for each substance: L-glutamic acid (a), Brilliant Blue (b), aspartame (c), and Quinoline Yellow (d). Error bars represent standard error of the mean ($n = 4$). The concentration at which 50% reduction in neurite outgrowth from NB2a neuroblastoma cells in vitro was achieved was assessed for each additive (IC_{50}), and concentrations producing lower ($IC_{20–25}$), higher (IC_{70}) or no inhibition of neurite outgrowth were also determined from the concentration-response curves, for use in experiments to assess possible combination effects.



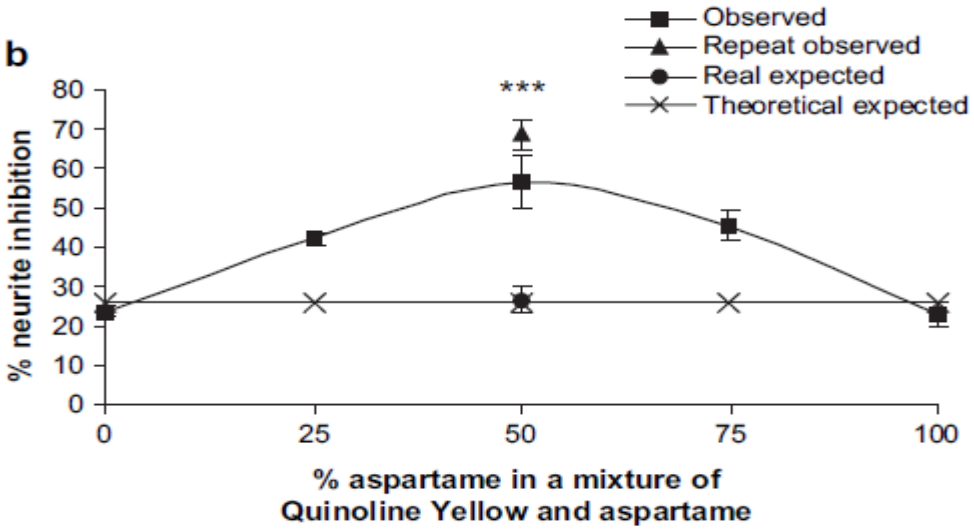


FIG. 2. Results show the relationship between inhibition of neurite outgrowth from NB2a neuroblastoma cells and the percentage of each compound in a mixture. Error bars represent standard error of the mean ($n = 4$). Both combinations of Brilliant Blue with L-glutamic acid (a), and Quinoline Yellow with aspartame (b) produced significantly more inhibition of neurite outgrowth than the individual compounds, $^{**}p < 0.005$ and $^{***}p < 0.0001$, respectively.

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Toxicology 173 (2002) 259–268

TOXICOLOGY

www.elsevier.com/locate/toxicol

Interactions between pesticides and components of pesticide formulations in an in vitro neurotoxicity test

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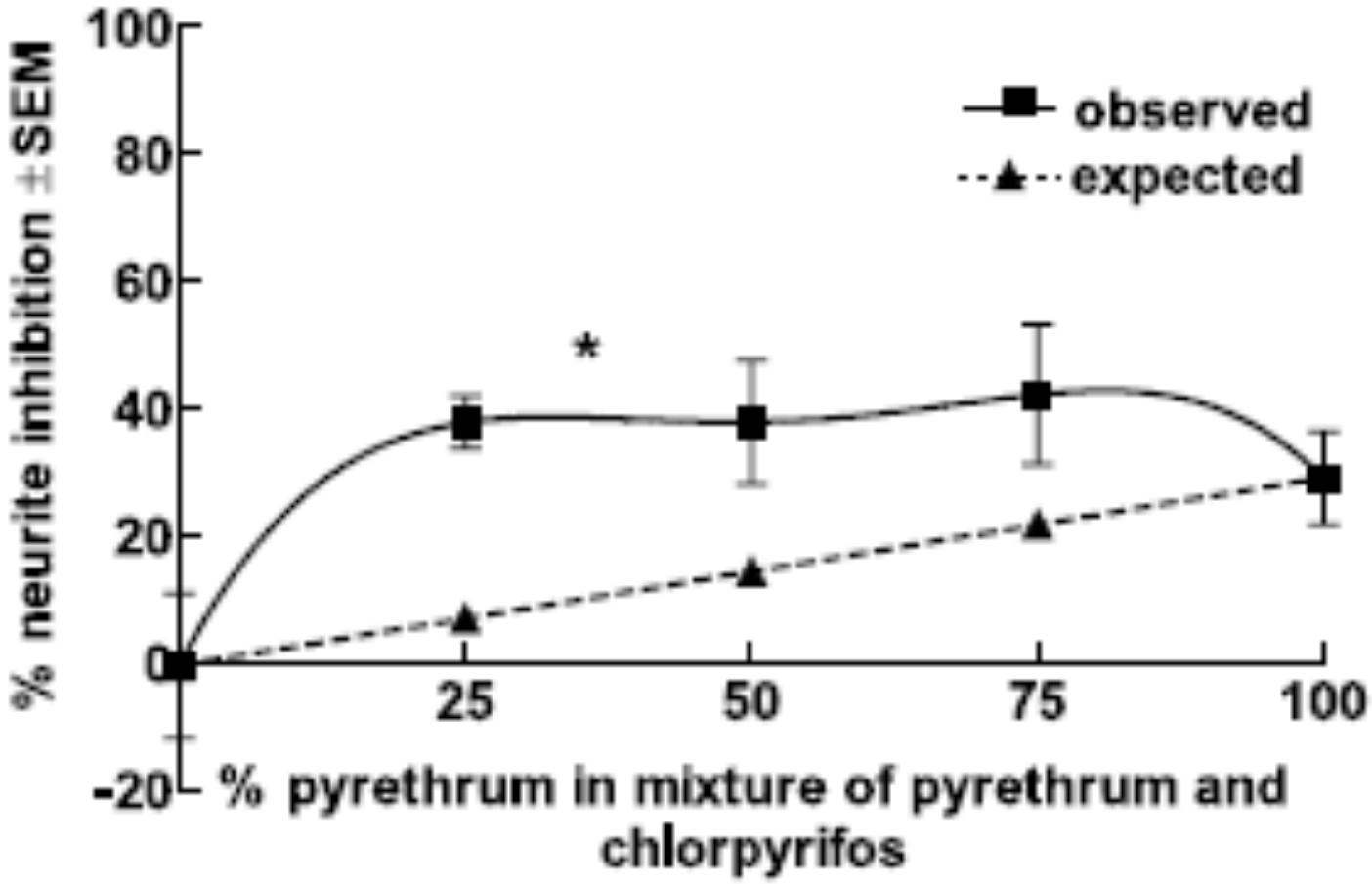
% neurite inhibition ±SEM
100
80
60
40
20
0
-20
*
observed
expected
25
50
75
100
% pyrethrum in mixture of pyrethrum and chlorpyrifos

Available online at www.sciencedirect.com
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Toxicology 185 (2003) 67–78
TOXICOLOGY
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The effects of acute pesticide exposure on neuroblastoma cells chronically exposed to diazinon

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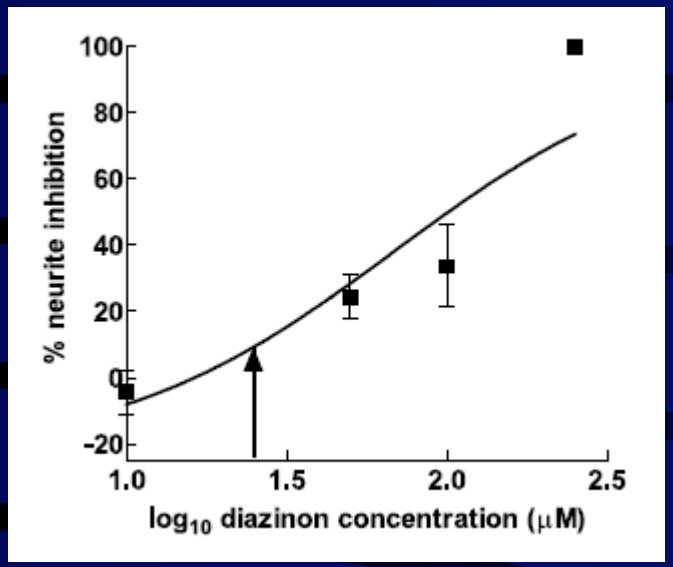
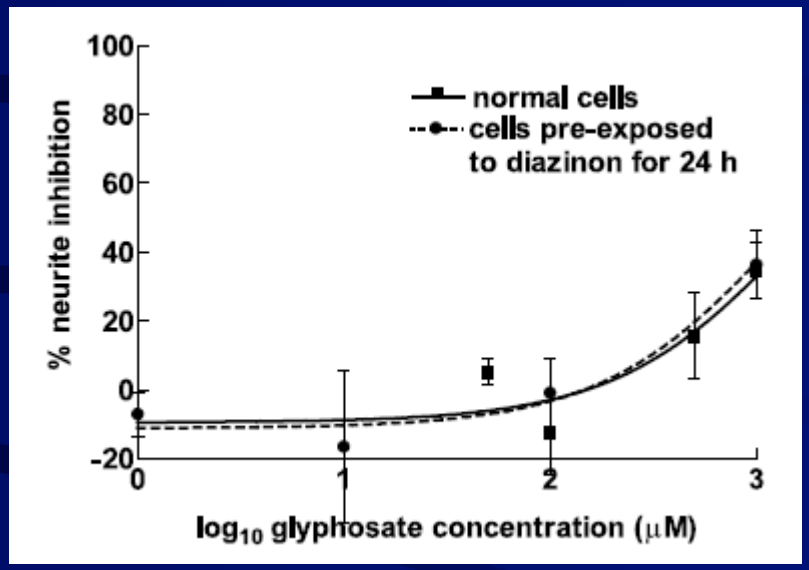
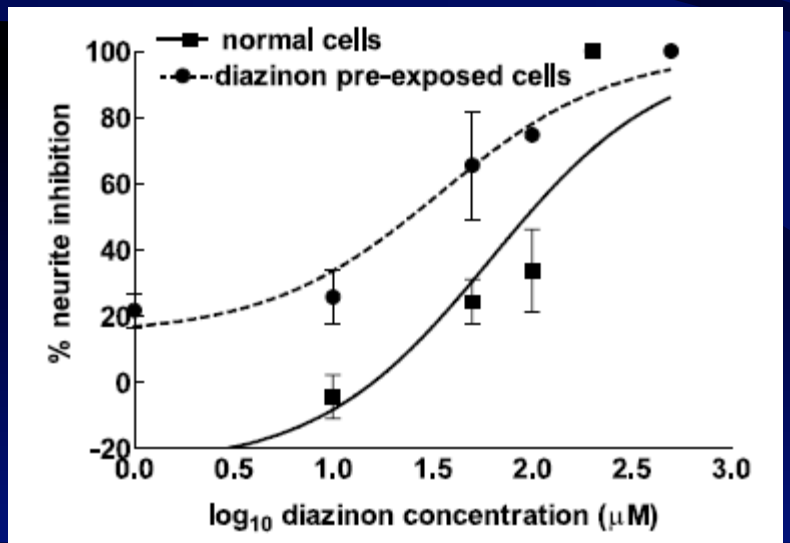
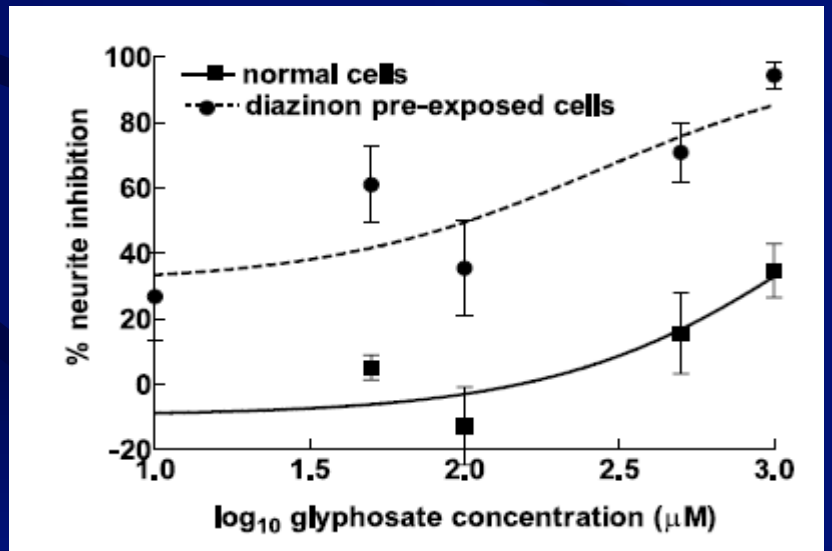
25 μM diazinon for 8 weeks





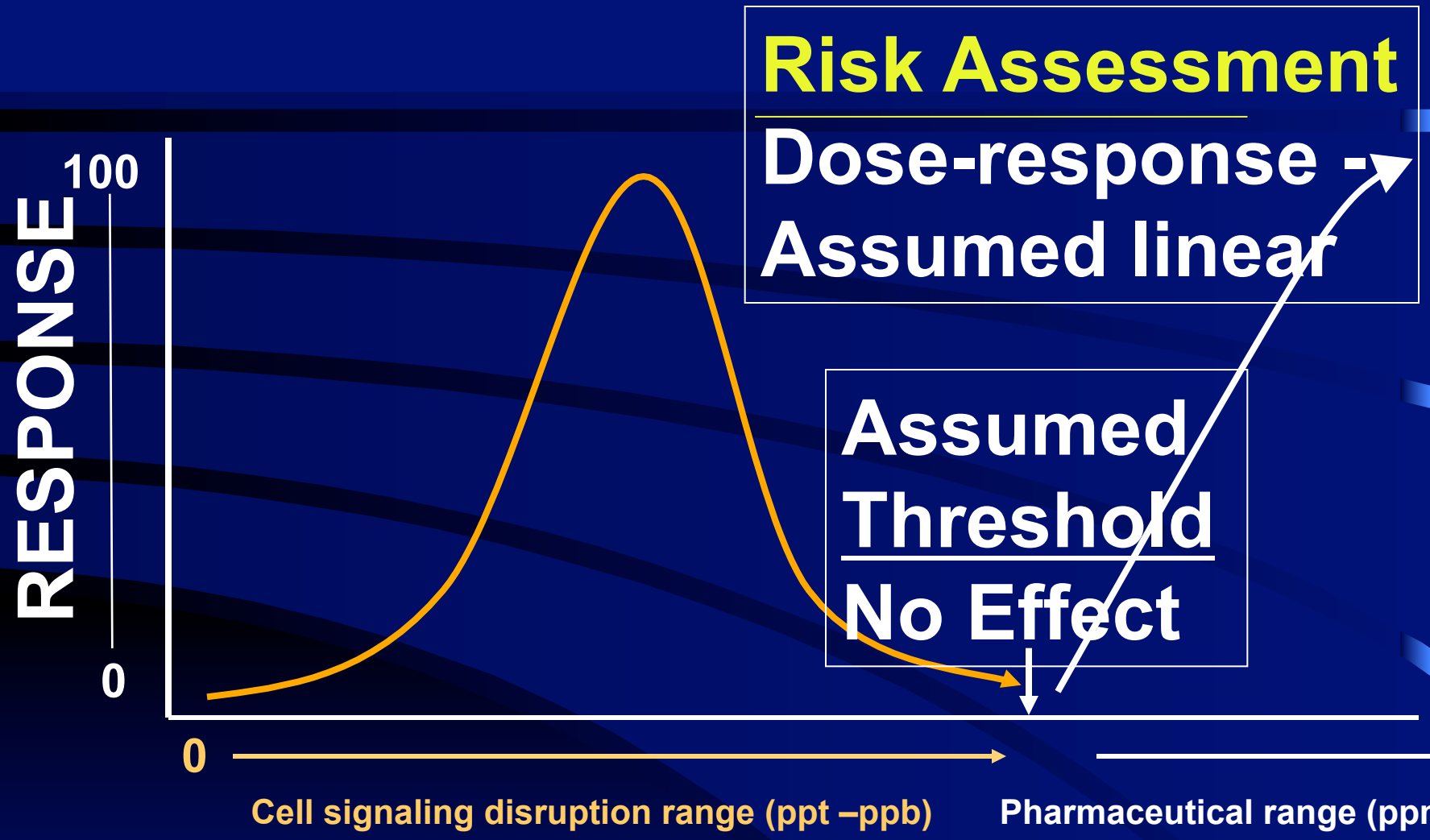




The low dose OP scenario

- Protracted periods of exposure (thousands of hours) to very low doses
- OPs are very ‘avid’ with respect to a large number of biomolecules
- Therefore the fact that concentrations may be low does not mean that nothing is happening

INVERTED-U DOSE-RESPONSE CURVE FOR CELL SIGNALLING DISRUPTORS



Seattle Tower (Dr R Pleus)

- Volume of Seattle Tower = 1,699,767 cu ft = 48,132,041 litres

-Crew member with 20,000 hours cumulative service, breathing at 10 litres per minute, will consume

-10 x 60 x 20,000 = 12,000,000 litres of cabin air

-¼ of the volume of the Seattle Tower

Functional consequences of repeated organophosphate exposure: Potential non-cholinergic mechanisms.

A.V. Terry

Pharmacology & Therapeutics 134 (2012) 355–365

The purpose of this review is to discuss several non-cholinesterase targets of OPs that might affect such fundamental processes and includes cytoskeletal and motor proteins involved in axonal transport, neurotrophins and their receptors, and mitochondria (especially their morphology and movement in axons).

Conclusions

- Classical regulatory toxicology cannot address cabin air quality questions
- Passengers and crew are exposed to a complex mixture of chemicals, usually at low dose, and any toxic effects will be the result of that exposure
- A precautionary minimisation/removal of such exposures is a tractable approach

Albert Einstein

- *"A clever man solves a problem – a wise man avoids it"*