



WORKING FOR A HEALTHY FUTURE

# Combined exposures to dangerous substances: toxicology and beyond

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*Chemical substances at work: facing up to the challenges*  
*2<sup>nd</sup> and 3<sup>rd</sup> March 2009*

# Summary...

- A toxicologists view of combined exposure
- Combined in space and time
- Independent exposures and additive risks
- An example of exposure to pesticides
- Public concern about exposure to mixtures
- Problems in understanding the effects of mixtures when you don't know the causal factor

# Regulations...

- Regulation of chemicals generally done on an individual basis but workers often exposed to several chemicals:
    - at once or
    - within a short period of time
  - Workers may also be exposed by different routes:
    - inhalation
    - dermal absorption
    - ingestion
- ...but regulatory action is mostly control of inhalation exposure
- For some substances exposure metric based on mixture, e.g. rubber fume

# Toxicological combined action...

- Toxicologists generally talk about interaction in terms of substances being:
  - Simple dissimilar action (simple independent action)
  - Simple similar action (simple joint action, concentration/dose addition)
  - Interaction (e.g., synergism, potentiation, supra-additivity, antagonism, sub-additivity, inhibition)

Cassee FR, Sühnel J, Groten JP, Feron VJ (1999). Toxicology of chemical mixtures. In: General and Applied Toxicology, Vol. 1, edited by Ballantyne B, Marrs TC, Syversen T. London: Macmillan Reference, 303-319.

# Independent (Simple dissimilar action)

- The effects of the chemicals are the same as if they were in the absence of the others, i.e. they do not influence each other's action

$$R(x) = R(x_a) + R(x_b)$$

- This does not mean the effects of the mixture can be ignored

Factory A  
-substance X

Factory B  
-substance X  
-substance Y

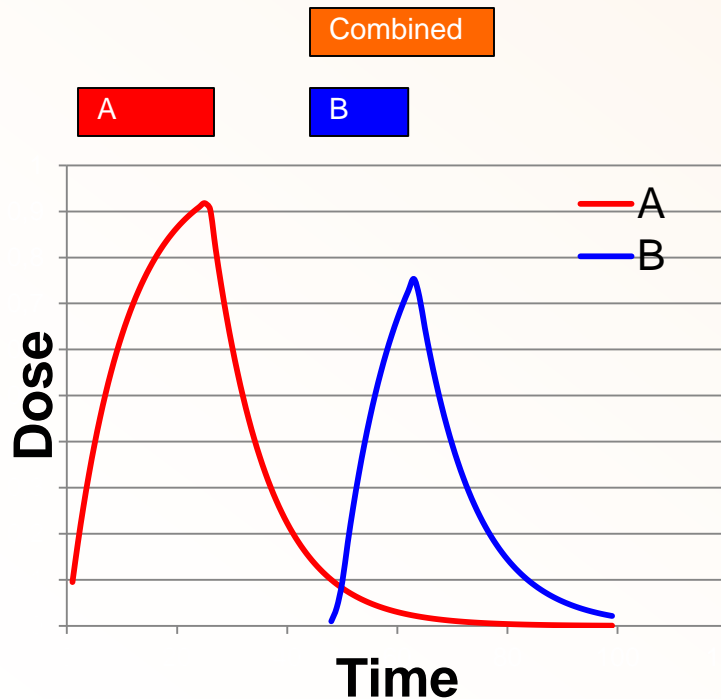
# Dose addition (Simple similar action)

- Individual compounds in a mixture share the same mechanism/mode of action for their the toxicological effects, and they differ only in their potencies
- The effect (or response) for the mixture is obtained by summing the doses of the individual compounds, after adjustment for differences in their potencies.

$$R(x) = R(x_a + x_b)$$

# An implication of dose addition...

- If some of the substances in a mixture have relatively long half-lives and the worker is sequentially exposed then the individual may be exposed to a mixture.



# Combined effects (Interaction)...

- The combined effects of two or more chemicals is either greater (synergistic, potentiating, supra-additive) or less (antagonistic, inhibitive, sub-additive, infra-additive) than that predicted on the basis of dose-addition
- Is this a practical possibility?



# A practical approach for dose addition...

- Estimate exposure (usually systemic exposure) to each substances as a fraction of with the OEL agreed for that substance. If the sum of the fractions is  $\leq 1$  then exposure of the operator is acceptable
- Derive effect-specific OELs using available data and repeat above
- Collect more data on exposure and/or toxicity data

# Committee on Toxicity...

Committee on \_\_\_\_\_  
**TOXICITY**

Committee on Toxicity of Chemicals in Food,  
Consumer Products and the Environment

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Risk Assessment of Mixtures of Pesticides  
and Similar Substances

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<http://cot.food.gov.uk/cotwg/wigramp/wigrampfinalreport>

# Pesticide mixtures...

## Organophosphates

Azamethiphos

Chlorpyrifos

Dichlorvos

Dimethoate

Ethoprophos

Fosthiazate

Malathion

Pirimiphos-methyl

Tolclofos-methyl

## Carbamates

Methiocarb

Oxamyl

Pirimicarb

Thiodicarb

Bendiocarb

Benfuracarb

Aldicarb

# Occupational exposure scenarios...

Average number of farms sprayed per year

<b>Region</b>	<b>Contractor</b>	<b>Employee</b>	<b>Owner/tenant</b>
East Midlands	13	4	1
Eastern	21	2	2
London & South East	18	2	2
North East	18	1	1
North West	4	1	1
Scotland	27	2	2
South West	28	2	2
Wales	37	1	1
West Midlands	31	2	1
Yorkshire & the Humber	34	1	2

# Operator exposure...

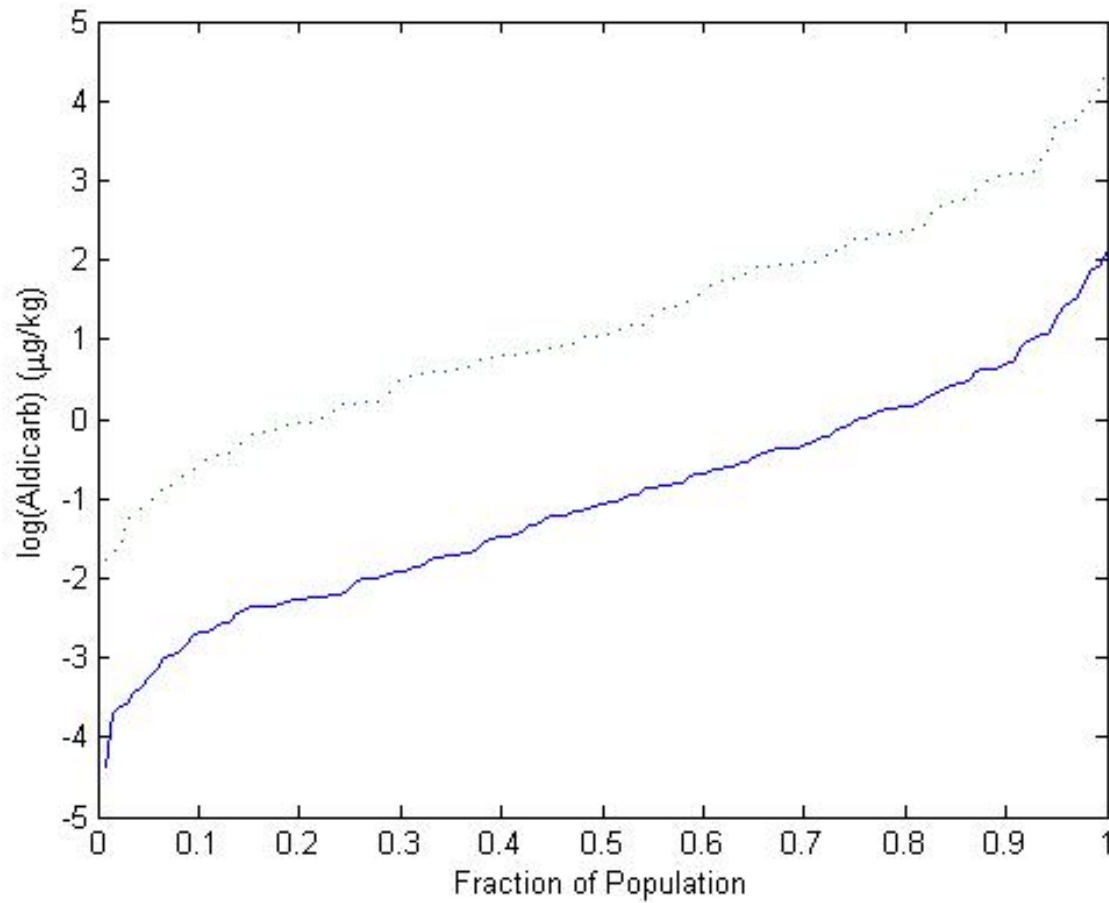
Based on EUROPOEM

Dermal exposure (mg/kg active substance)

	Hand held		Other	
	ADE	AHE	ADE	AHE
Minimum	0.06	0.01	0.0001	0.0002
Median	1.82	0.09	0.03	0.02
Maximum	1364.80	71.51	2.11	18.59

Used Monte Carlo modelling

# Aldicarb for farmers



# Farmers internal dose ( $\mu\text{g}/\text{kg}$ )

	Adjusted ADI dose	Average dose		Maximum dose	
		50 <sup>th</sup>	90 <sup>th</sup>	50 <sup>th</sup>	90 <sup>th</sup>
Aldicarb	10.4	0.087	4.335	11.158	113.100
Chlorpyrifos	20.4	0.022	0.836	1.076	46.591
Methiocarb	15.2	0.021	0.832	1.367	44.036
Pirimicarb	57.0	0.117	3.220	7.300	242.900

# Index of mixture...

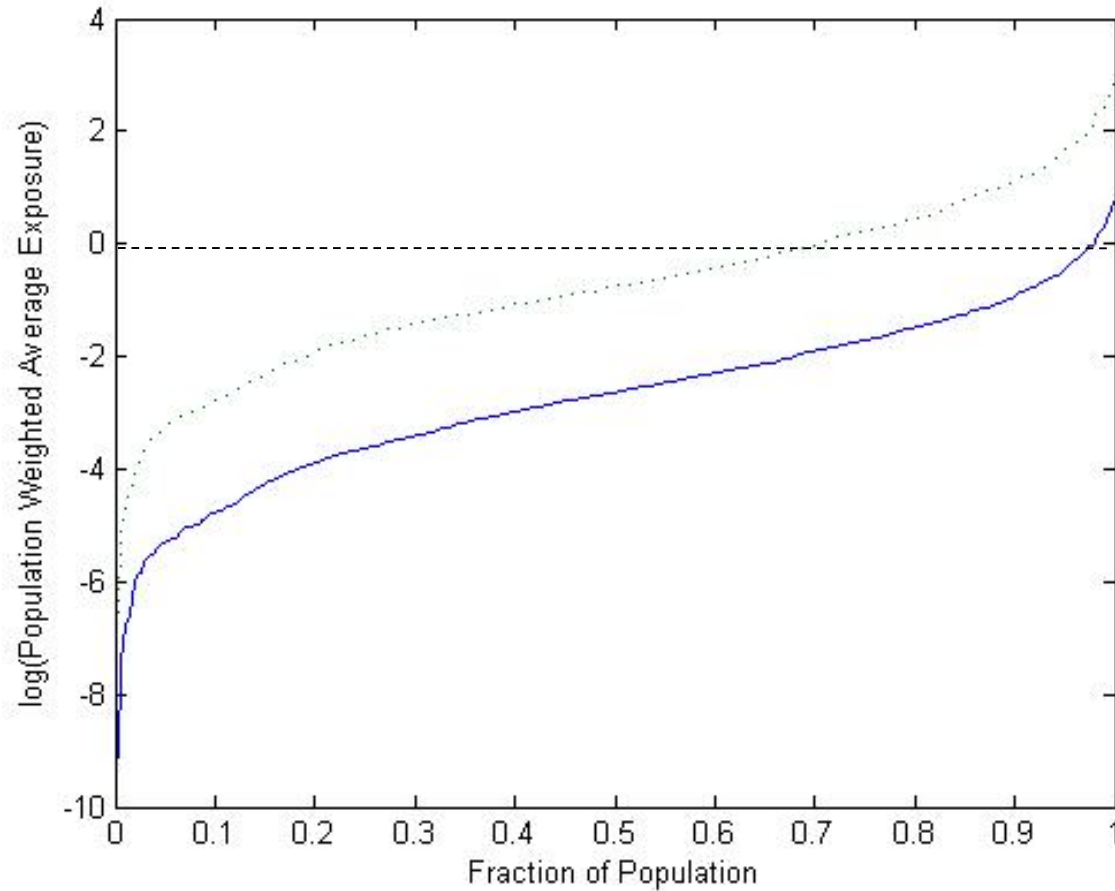
$$IDX = \sum_{k=1}^N C_k / ADI_k$$

If the value of IDX is greater than unity it suggests that the aggregate dose is greater than the overall ADI

ADI adjusted to reflect internal dose



# Farmers...





## Chemical cocktail blamed for soaring breast cancer rate

By FIONA McRAE  
Last updated at 00:01 18 October 2008

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Cocktails of gender-bending chemicals, found in everyday products from CD cases to babies' bottles, may be to blame for soaring rates of breast cancer, scientists have warned.

Experts fear the chemicals, used in pesticides, cosmetics, electrical goods and plastics, have the power to trigger the cancer which claims the lives of more than 1,000 British women a month.

The warning follows official figures which show the number of cases of breast cancer has almost doubled in a generation.

Almost 37,000 women in England and Wales were diagnosed with the disease in 2004 - 10 per cent more than in the previous year and 80 per cent more than in 1971. Less than half of cases can be explained by genetics and lifestyle factors such as diet, leading to fears manmade chemicals may also play a part.

A report by the World Wildlife Fund points the finger at synthetic oestrogens - common chemicals with structures similar to that of the female sex hormone oestrogen. Oestrogen, a key ingredient of the contraceptive pill and hormone replacement therapy, is already thought to fuel breast cancer, sparking fears manmade chemicals with a similar structure or action may have the same effect.

Among the chief suspects is bisphenol A.



© Rex Features

**Breast cancer: The number of cases has almost doubled in just a generation**

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The Beckhams write to Jade as her publicist says doctors have been unable to control her pain



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Girls Aloud singer still managed to look glamorous on climb



# Toxic Airlines...



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A Fact Not Fiction Films Production

# Georgina Downs - UK Pesticides Campaign - Home Page

## Pesticide Exposures for People in Agricultural Areas

*"People move to the countryside thinking it will be a healthy environment to bring up their children and do not know about the dangers and risks inherent in the spraying of poisonous chemicals on surrounding fields, until they themselves suffer adverse effects on their health"*

Georgina Downs



**NEW** - Georgina nominated in the categories Campaigner of the Year and Grass Roots Campaigner at Observer's Ethical Awards 2009 - To support Georgina and the UK Pesticides Campaign click [here to add your vote](#)

**NEW** - See Georgina's article regarding her High Court victory in the February 2009 edition of the Ecologist magazine - Adobe PDF

**NEW** - UK Government's arrogance and contempt for rural residents continues as DEFRA to appeal High Court ruling - Adobe PDF

Historic Victory for Georgina in her Landmark High Court Action as Government Policy on Pesticides is Ruled Unlawful

Georgina named a "Woman of the Year"

Georgina wins the Observer's Secret Pioneers poll

Georgina nominated in new Inspiration Awards for Women - To

photo by Ayia Akdemir



# Parkinson's disease...

## Environmental risk factors for Parkinson's disease and parkinsonism

**Table 3** Adjusted results† (all cases vs controls)

	OR (95% CI)
Ever used tobacco containing product‡	0.50 (0.42 to 0.60)
Ever consumed beer, wine or spirits regularly	1.01 (0.83 to 1.23)
House with water supply from river or well‡§	1.18 (0.97 to 1.43)
Ever been knocked unconscious‡	1.57 (1.29 to 1.91)
Knocked unconscious:	
Once vs never	1.35 (1.09 to 1.68)
More than once¶ vs never	2.53 (1.78 to 3.59)
Ever had a general anaesthetic for an operation	0.81 (0.67 to 0.98)
Ever been treated by doctor after exposure to gas/ smoke	0.99 (0.49 to 1.20)
Average annual intensity of exposure	
Solvents:	
Low exposure* vs no exposure	1.17 (0.92 to 1.50)
High exposure* vs no exposure	0.88 (0.69 to 1.12)
Pesticides:	
Low exposure* vs no exposure	1.13 (0.82 to 1.57)
High exposure* vs no exposure	1.41 (1.06 to 1.88)
Iron:	
Low exposure* vs no exposure	1.11 (0.79 to 1.56)
High exposure* vs no exposure	1.14 (0.82 to 1.59)

*Dick, et al. , (2007) Environmental risk factors for Parkinson's disease and parkinsonism: the Geoparkinson. Occup. Environ. Med.; 64: 666-672.*

# Summary...

- Regulations generally don't deal well with combined exposure
- Terminology should be clear and advice practicable
- Pressure groups are concerned about a “cocktail effect”
- Understanding the effects of combined exposure is difficult