

Assessing exposure to pesticides for epidemiological studies

John Cherrie

Summary...

- Pesticides are designed to be biologically active
- Usage is complex and mostly in small (poorly regulated) operations
- Many different “actives”
- Active compounds have changed over time
- Evidence for causation of cancer and neurodegenerative disease
- Exposure assessment methods need to be improved

Benefits and risks...

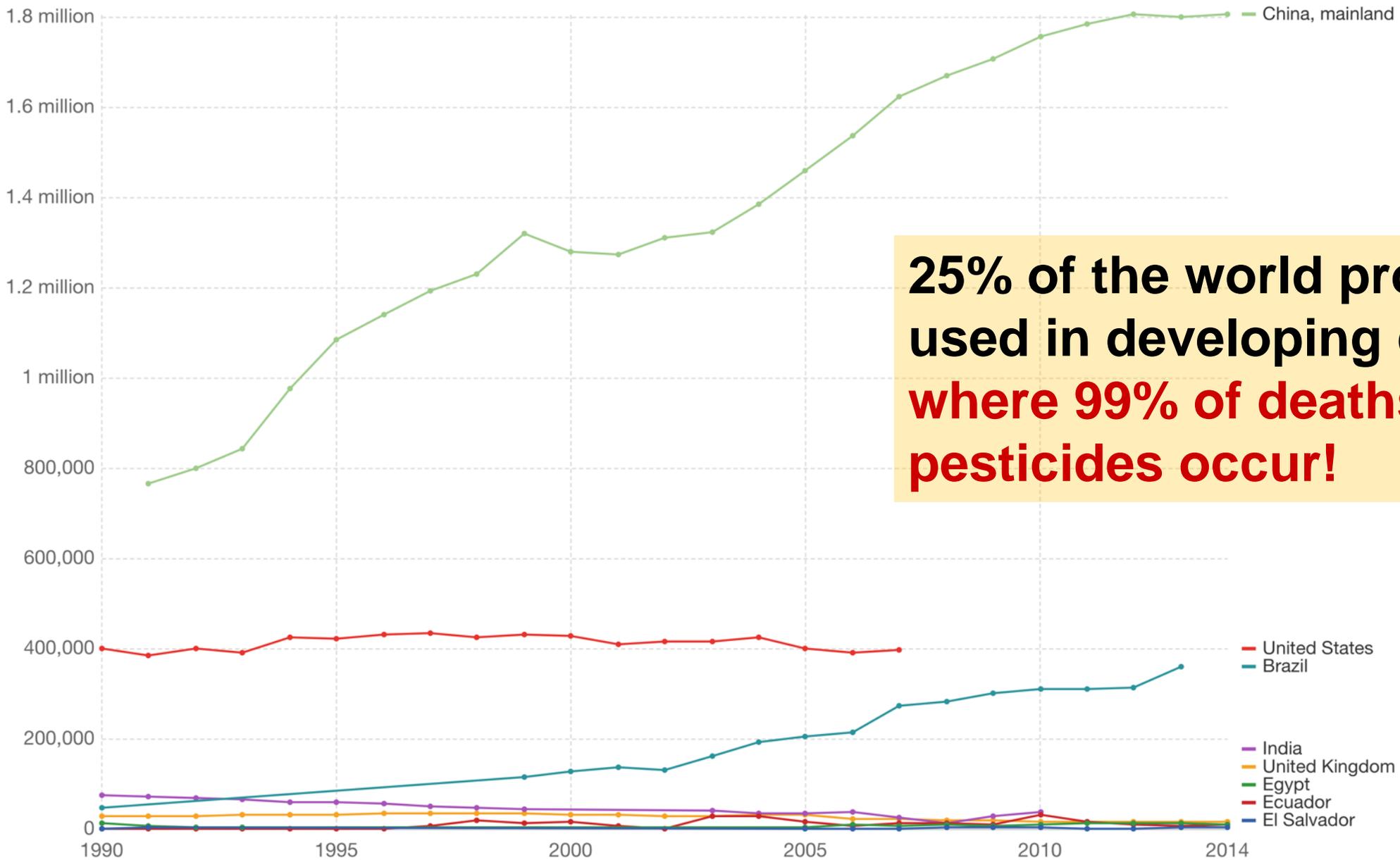
Food preservation
Disease control
Crop protection

Toxic to humans
Damage to environment
and ecosystems



Pesticide use, tonnes

Total pesticide use by country, measured in tonnes of pesticide consumption per year.



25% of the world production used in developing countries... where 99% of deaths due to pesticides occur!

Source: UN Food and Agricultural Organization (FAO)

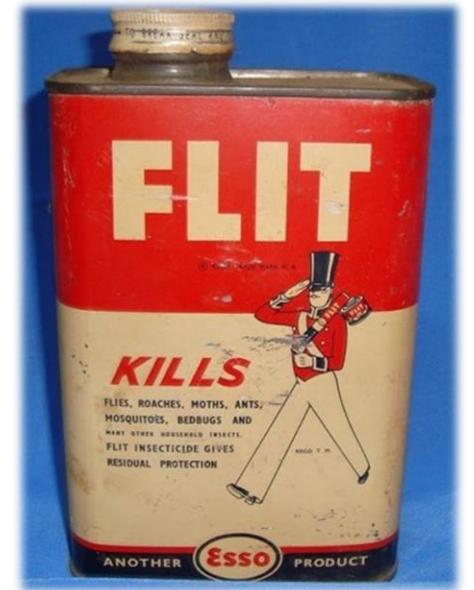
Uses and chemicals...

- **INSECTICIDES:** Pyrethroids, Organophosphates, Carbamates, Organochlorine, Manganese compounds
- **FUNGICIDES:** Thiocarbamates, Dithiocarbamates, Cupric salts, Tiabendazoles, Triazoles, Dicarboximides, Dinitrophenoles, Organotin compounds
- **HERBICIDES:** Bipyridyls, Chlorophenoxy, Glyphosate, Acetanilides, Triazines

Operations often involve Mixing/Loading + Application

Types of products...

- Pesticides used in different settings:
 - Agricultural
 - Veterinary
 - Domestic
 - Institutional
- Formulations: liquid, gel, paste, chalk, powder, granules, pellets, baits...
- Concentrations: from 2% to 80% of active ingredient
- Containers: glass, plastic or metal flasks, bottles, drums, traps, plastic bags or paper bags....



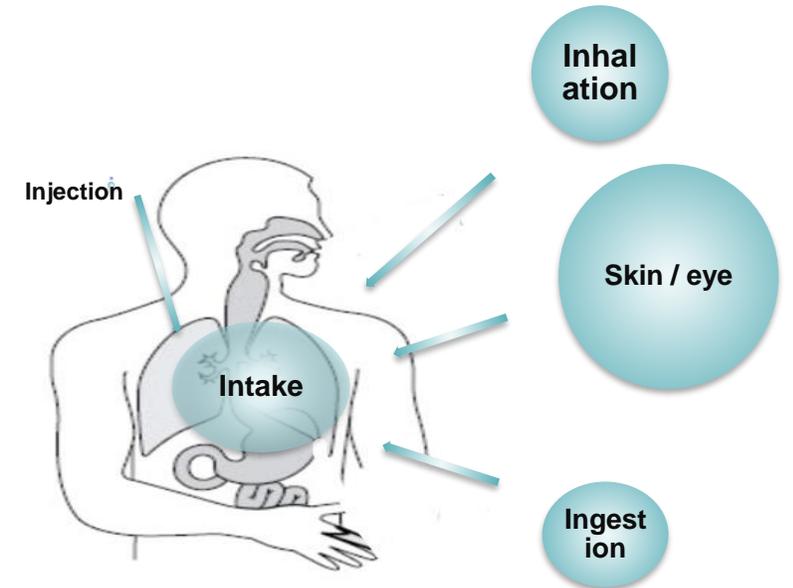
Persistence and bio-concentration

- Compounds with low water solubility and are lipophilic
- Resist degradation in the environment and accumulate in the food-chain
- May concentrate in marine animals

Aldrin, Dieldrin,
Chlordane, DDT, Endrin,
Heptachlor, Mirex,
Toxaphene

Toxicokinetics...

- Routes of Absorption: Dermal, ocular, ingestion, inhalation, injection
- Biotransformation into inactive or more active metabolites
- Distribution and storage: Fat soluble pesticides are stored in adipose tissue
- Elimination: Urinary excretion, biliary / faecal excretion, excretion in milk
- Uptake through skin is dependant on the concentration

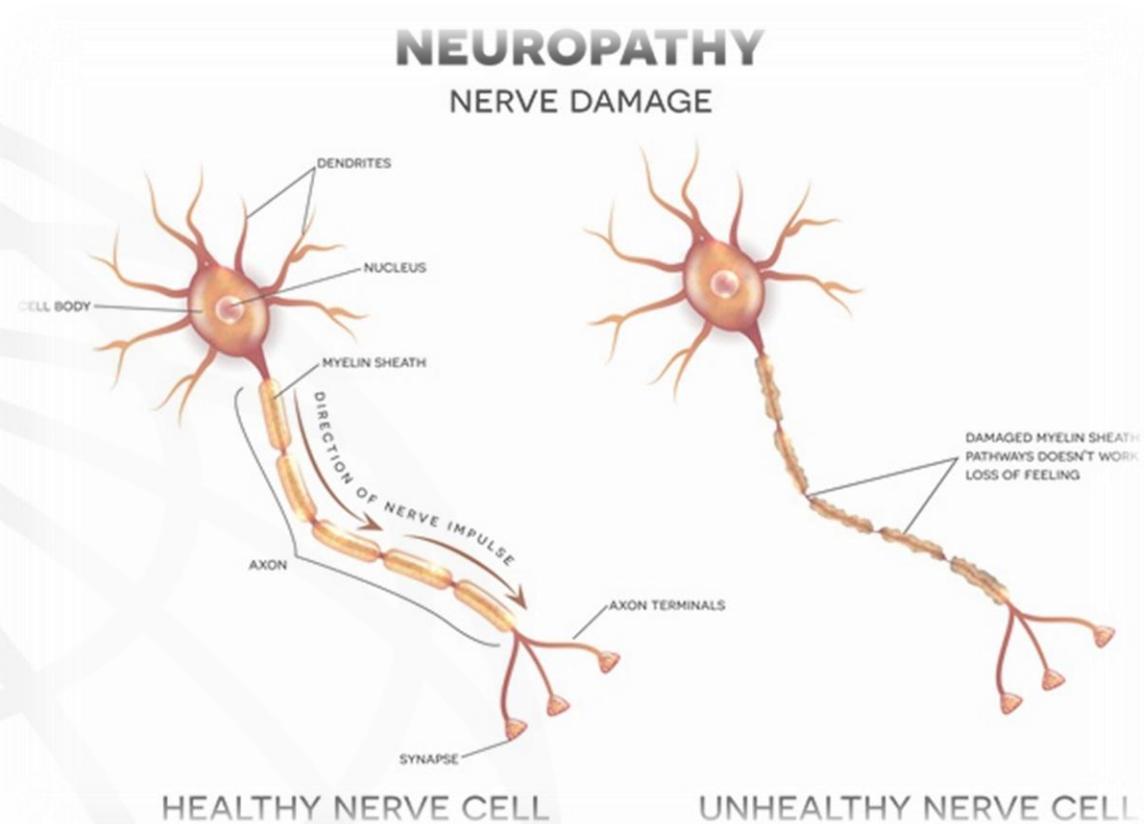


Pesticide epidemiology...

- Because pesticides are variably used in a diverse range of situations it is difficult to retrospectively assess exposure
 - No good records
 - No exposure measurements
- Great reliance on recall of subjects
- Exposure often non-specific, e.g. “any pesticide” or “any herbicide”

Chronic neurological effects...

- Memory and concentration problems
- Unusual fatigue
- Irritability and depression
- Visual difficulties
- Delayed polyneuropathy



Neurodegenerative disease...

- Epidemiological studies show strong association between Parkinson's Disease (PD) and the fungicide maneb and the herbicide paraquat
- Associations with the organochlorine dieldrin and organophosphates (OPs) less strong
- Overall association with 'pesticides'

AGRICAN...

- Very large prospective study of agricultural workers in France
- Self-reported PD and history of lifetime exposure to 13 crops and 5 types of animals and pesticide
- Exposure was assessed with the crop-exposure matrix PESTIMAT
 - Assignment based on sources about pesticide registration, sales and recommended use
 - Specific to active ingredient
 - Assesses frequency, probability and intensity
 - Time (1950-2010)

AGRICAN...

- Pesticide use associated with an increased risk of PD in all types of activities (OR = 1.31 cattle to 1.79 peas)
- Authors consider results supports an association of PD with dithiocarbamate fungicides, rotenone and the herbicides diquat and paraquat
- However, most ORs are not significantly increased

Cancers...

- Pesticide exposure associated with cancers of the lung, prostate and lymphatic and haematopoietic system
- Many pesticides are not mutagenic
- No active ingredient, other than arsenic, has been classified as a definite human carcinogen

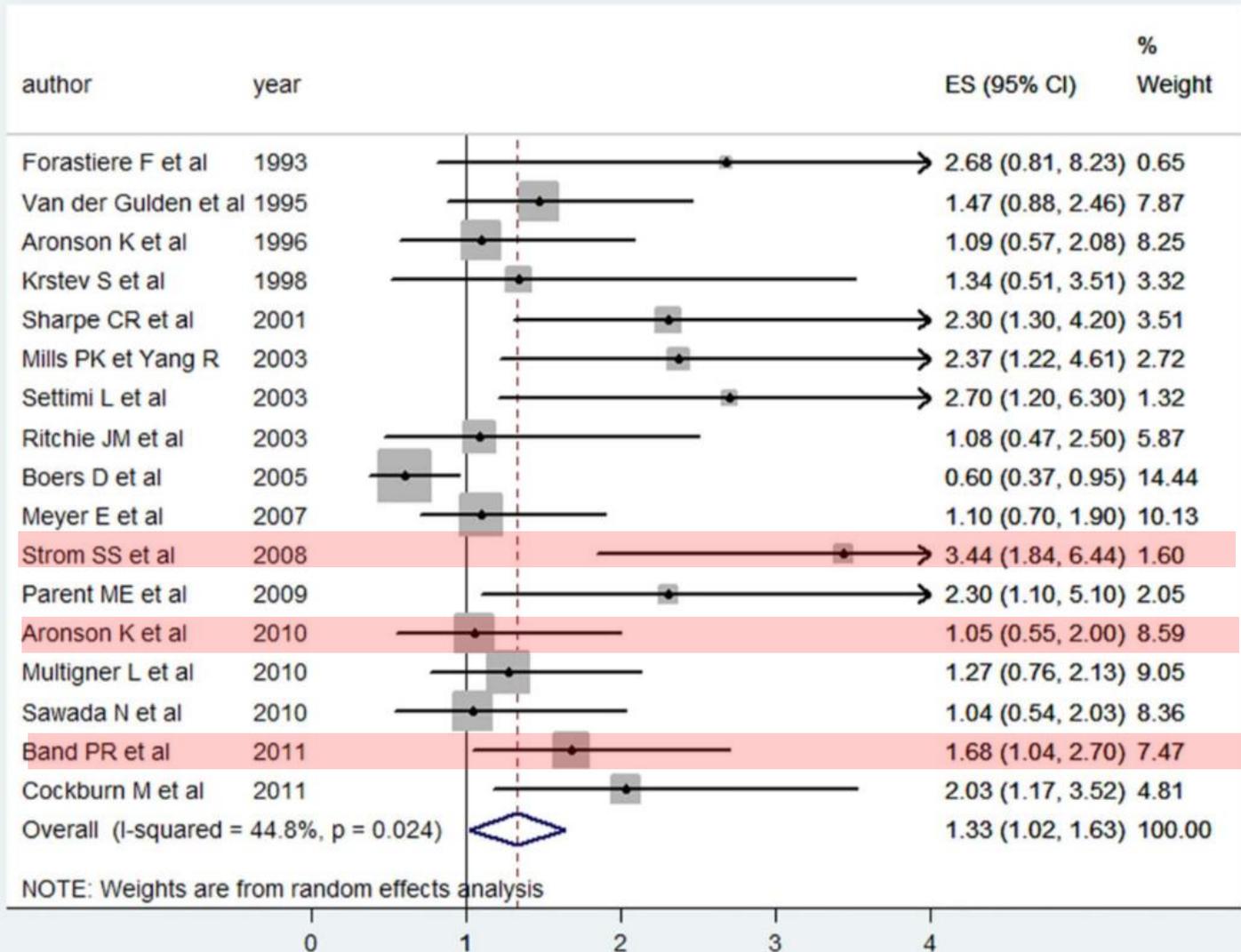
Prostate cancer (PC)...

- Lewis-Mikhael *et al* carried out a systematic review and meta-analysis
- Data heterogeneous and provides inconsistent results
- In the Agricultural Health Study
 - increased PC risk among the highly exposed applicators with a family history of PC
- The pooled OR for high exposure, it was 1.33 (1.02 to 1.63)

Prostate cancer (PC)...

High exposure
to pesticide

Case-control
studies



Aronson *et al*

- Plasma organochlorine levels and prostate cancer risk
 - 13 organochlorine pesticide biomarkers in blood
 - Long half-lives – 10 to 50 years
- Population-based case-control study
- >70% of patients had detectable levels of nine PCB congeners and seven pesticides
 - Only around 10% of subjects reported occupational pesticide exposure
- No evidence of any increased risk

Storm *et al*

- Prostate Cancer in Mexican-Americans: Identification of Risk Factors
- Population-based case-control study with JEM
 - Exposure to agrichemicals (fertilizers, pesticides, herbicides)
 - Four levels: none (0), low (1), medium (2), and high (3)

Variable	Multivariable ^a	
	OR (95% CI)	P-value
First-degree family history of prostate cancer		
No	1.00	
Yes	1.81 (0.86–3.78)	0.12
Agrichemical exposure ^b		
None	1.00	
Low/medium	1.01 (0.53–1.93)	0.97
High	3.44 (1.84–6.44)	<0.001 P-trend = 0.001
Occupational physical activity		
None/low	1.00	
Moderate/high	0.46 (0.28–0.77)	0.003

Bond *et al*

- Prostate cancer risk and exposure to pesticides in British Columbia farmers
- JEM with three axes: chemical agent, type of work, time
 - chemical agent axis includes chemical, biological, and selected physical exposures
 - type-of-work axis presents combinations of various factors: region, crop, task, and job title
- Assessed 290 different chemical agents; of these, approximately 180 were pesticides
- For high exposure DDT OR=1.68 (1.04–2.70), simazine OR=1.89 (1.08–3.33) lindane OR=2.02 (1.15–3.55)

Newcastle-Ottawa Scale...

1) Ascertainment of exposure

- a) secure record (e.g. surgical records) ☆
- b) structured interview where blind to case/control status ☆
- c) interview not blinded to case/control status
- d) written self report or medical record only
- e) no description

2) Same method of ascertainment for cases and controls ☆

3) Non-Response rate

- a) same rate for both groups ☆
- b) non respondents described
- c) rate different and no designation

Study quality...

- Lewis-Mikhael *et al* assessed study and exposure assessment quality using the Newcastle-Ottawa Scale

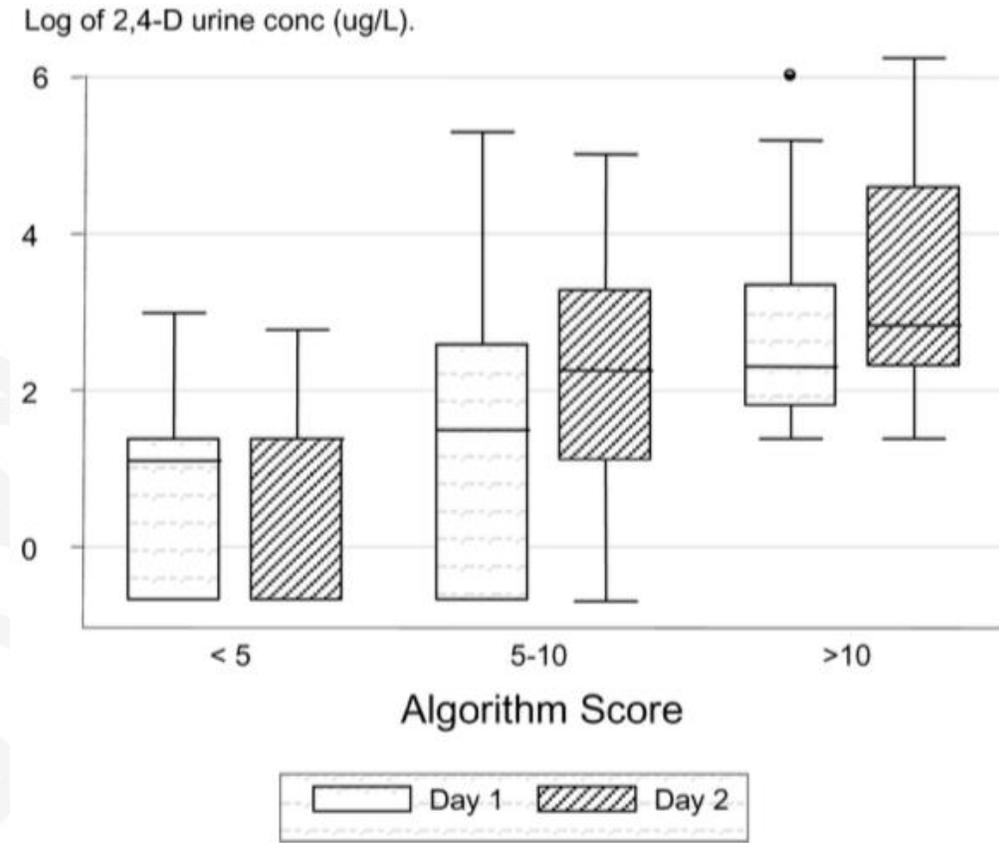
Grouping	Studies included in the analysis	Number of studies	Pooled OR	CI (95%)
Overall quality of the studies according to NOS	High quality	4	0.88	0.53 to 1.23
	Medium quality	11	1.43	1.12 to 1.75
	Low quality	2	2.09	0.97 to 3.21
Exposure assessment quality (NOS)	3 Stars	5	0.85	0.57 to 1.14
	2 Stars	8	1.42	1.06 to 1.77
	1 Star	4	2.19	1.38 to 3.00
Methodology adopted for assessment of pesticide exposure	Measuring serum level of pesticides	4	1.12	0.74 to 1.50
	Expert judgement	3	0.90	0.29 to 1.51
	Mainly depended on JEM	2	2.22	0.63 to 3.81
	Self-reporting	4	1.34	0.91 to 1.77
	Group-level exposure assessment*	4	2.24	1.36 to 3.11

JEMs...

- Carles *et al* review
 - Eight generic JEMs that only provide broad pesticide exposure groups
 - Eight specific matrices for agricultural cohorts that generally provide exposure to active ingredients
- They recommended:
 - Considering gender in the design of JEMs
 - Updating necessary
 - Assess specific actives
 - Specific jobs
 - Intensity estimates should be validated
 - Include incidental exposure, e.g. re-entry tasks

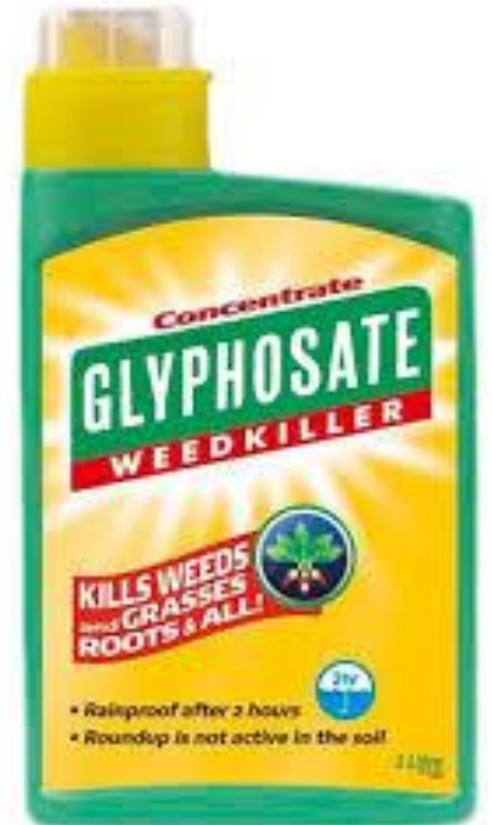
Algorithms...

- $E = (MIX + APPLY + REPAIR).PPE$
- Each factor assigned a score dependant on the circumstances, e.g. MIX = 0, 3, or 9 depending on how often the applicator mixes pesticides prior to applying
- Validated in a biomonitoring study
- PPE usage important



Glyphosate and cancer...

- In 2015 IARC concluded that glyphosate was a probable human carcinogen
 - Sufficient evidence from animal studies
 - Limited evidence in humans (non- Hodgkin lymphoma)
 - Genotoxicity and oxidative stress mechanism identified
- The results have been controversial

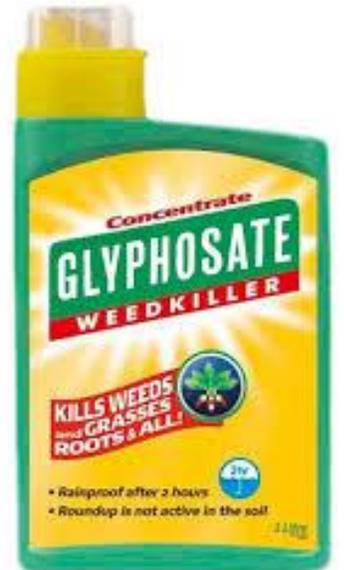


Glyphosate and cancer...

- EFSA: 'there is very limited evidence for an association between glyphosate-based formulations and NHL'
 - They classified the case-control epidemiology as 'unreliable'
 - No evidence of a risk in the Agricultural Health Study
 - No consistent evidence in animals
 - Disputed the mechanistic evidence based on unpublished (proprietary) data

Glyphosate and cancer...

- Overall, the evidence is equivocal
- Decision is, to some extent, a matter of judgement
- Further scientific evidence is really needed to come to a more decisive conclusion



IMPRESS...



- A new project to improve exposure assessment methodologies for epidemiological studies on pesticides
- Funded by European Crop Protection Association
- Tasks...
 - Use previously collected exposure data from existing epi studies and historical records
 - Assess current exposure (using biomonitoring) in various populations to examine performance of EA approaches
 - Compare and contrast performance of EA methods within existing epi studies

IMPRESS outputs...

- Validation of an accepted and adaptable semi-quantitative individual-based assessment method against measured levels of urinary pesticide metabolites in a range of settings
- Comparison of reliability and performance of several grouped- and individual-based assessment methods



Summary...

- Epidemiological studies of workers exposed to pesticides are difficult to undertake
- General move to specific JEMs or CEMs, and algorithm-based metrics
- Need to validate the approaches used