

Assessing exposure to pesticides for epidemiological studies

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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...



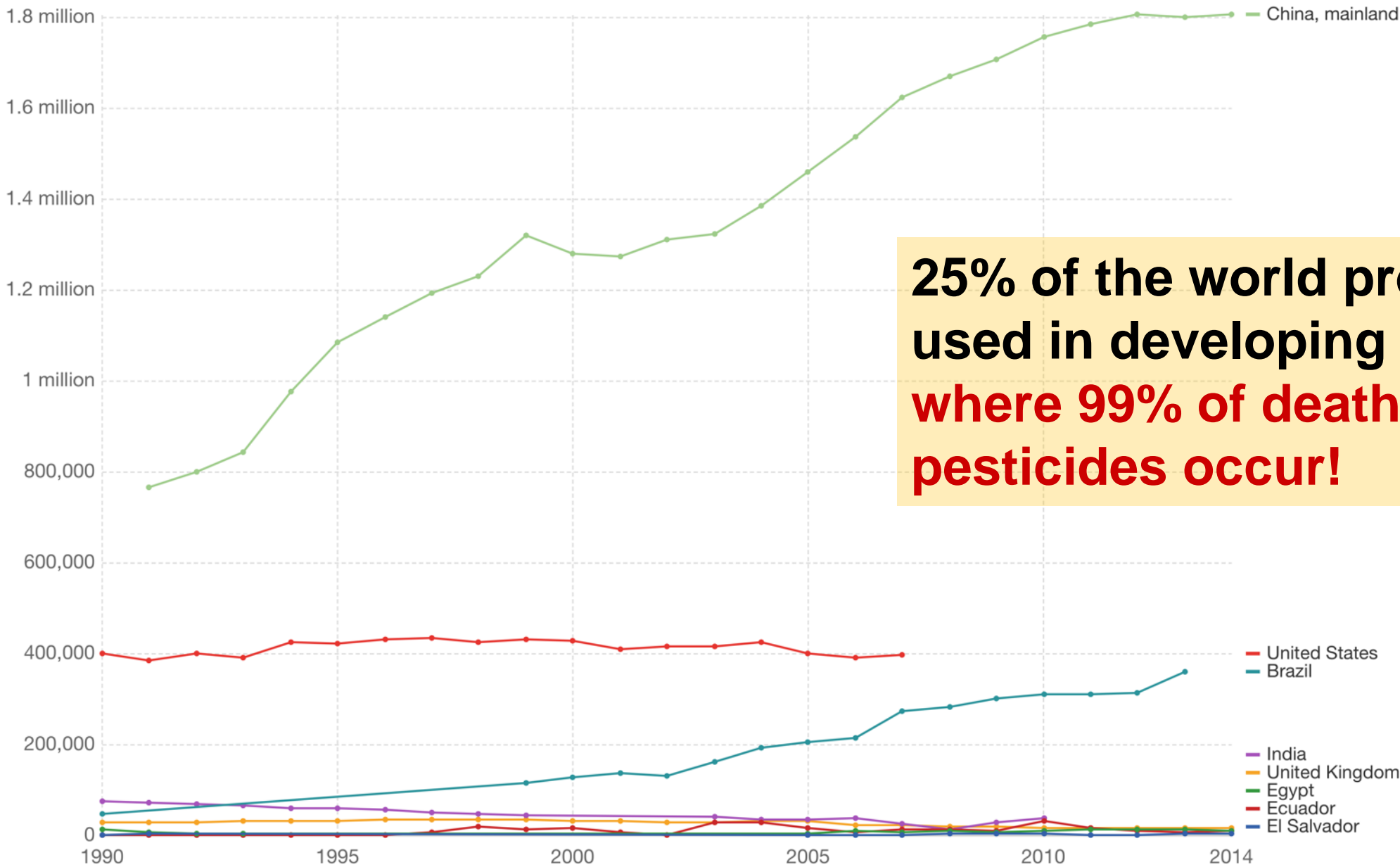
**Food preservation
Disease control
Crop protection**

**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!

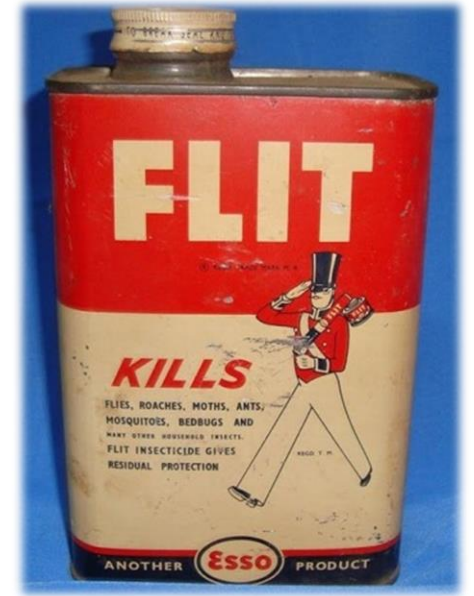
Uses and chemicals...

- **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....



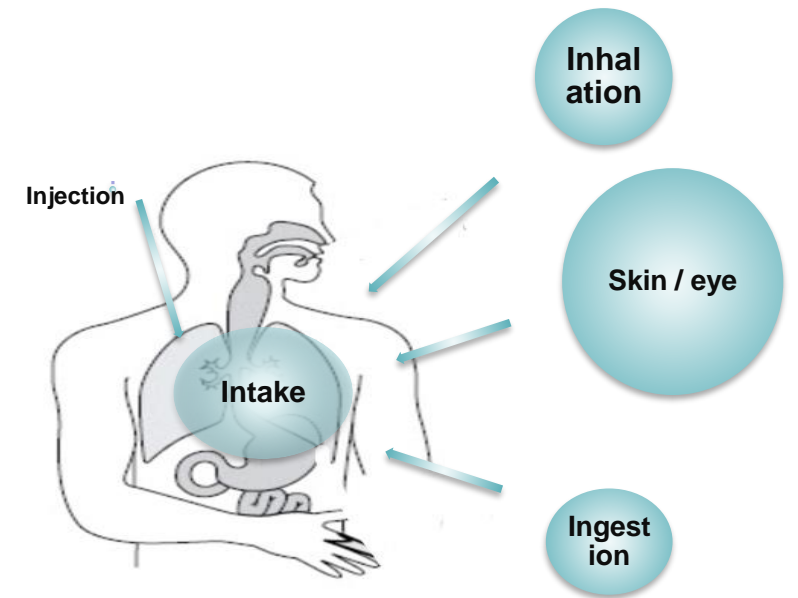
Persistence and bio-concentration

- 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

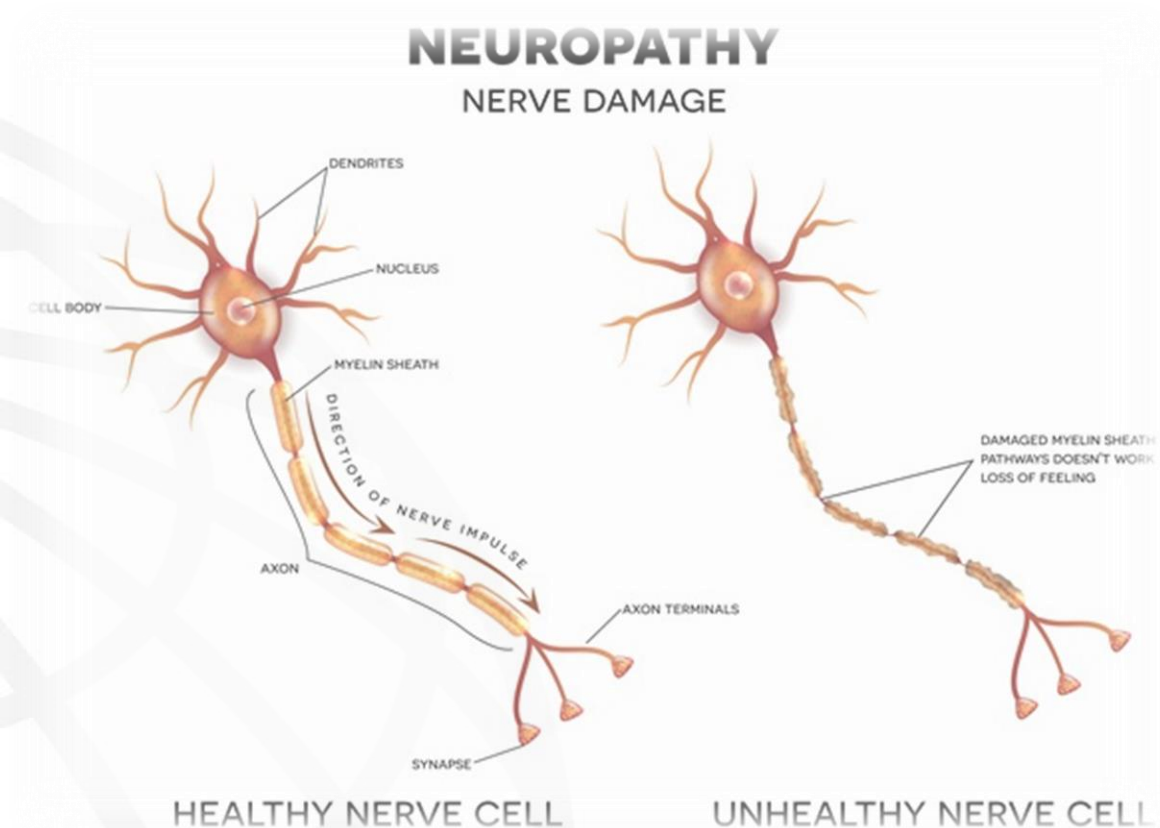


Pesticide epidemiology...

- 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

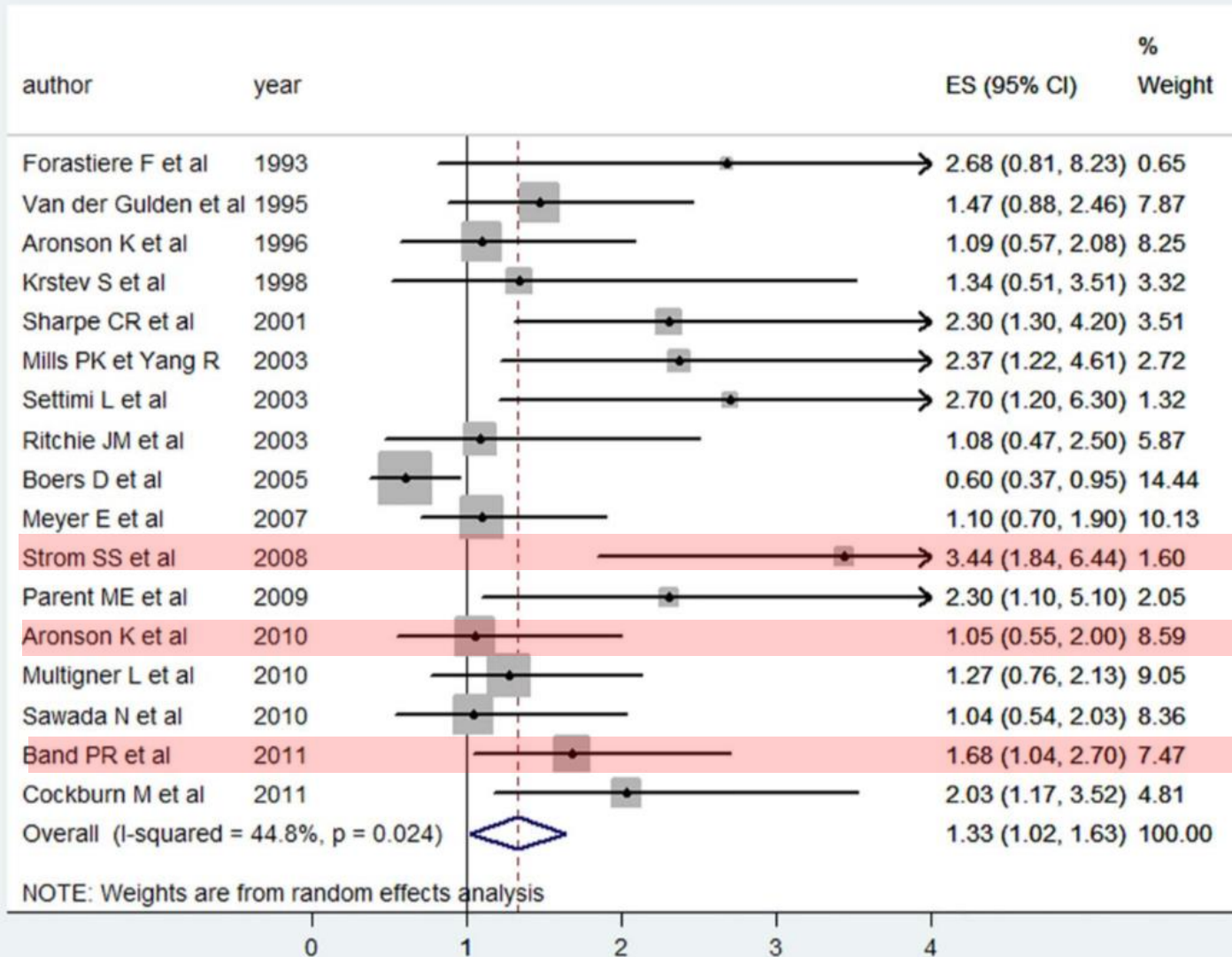
Prostate cancer (PC)...

- 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

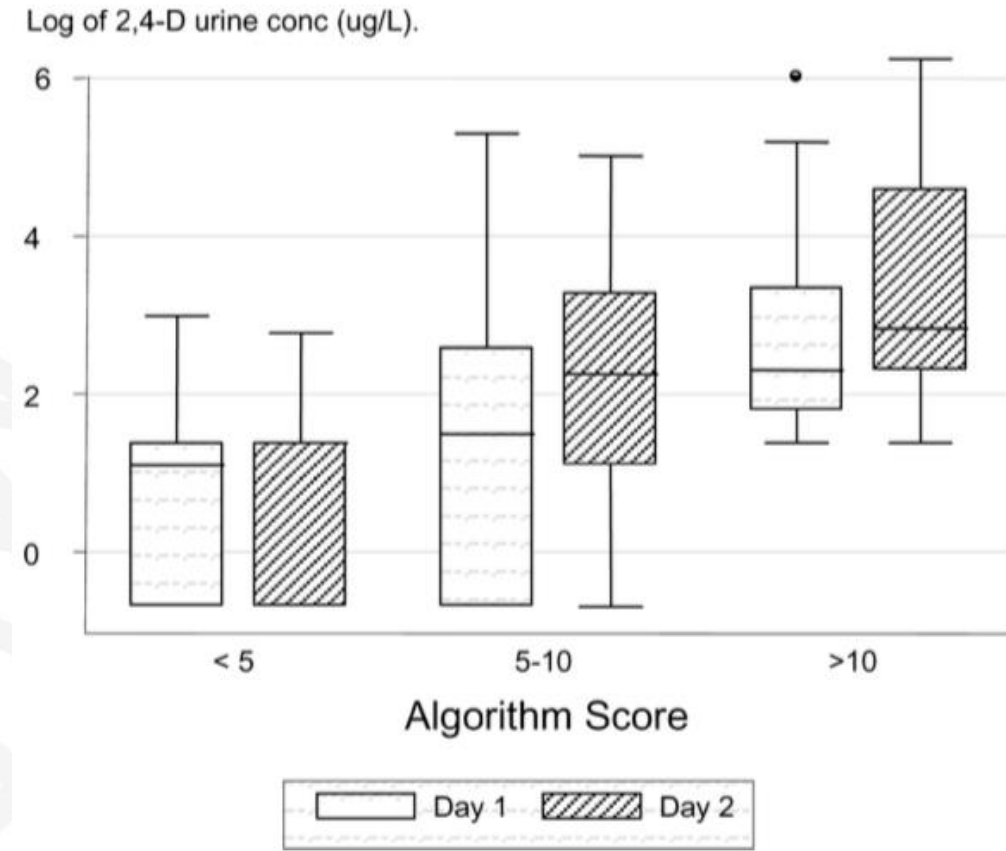
Grouping	Studies included in the analysis	Number of studies	Pooled OR	CI (95%)
Overall quality of the studies according to NOS	High quality	4	0.88	0.53 to 1.23
	Medium quality	11	1.43	1.12 to 1.75
	Low quality	2	2.09	0.97 to 3.21
Exposure assessment quality (NOS)	3 Stars	5	0.85	0.57 to 1.14
	2 Stars	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