



IARC Evaluations of Pesticides & Cancer Epidemiological Evidence

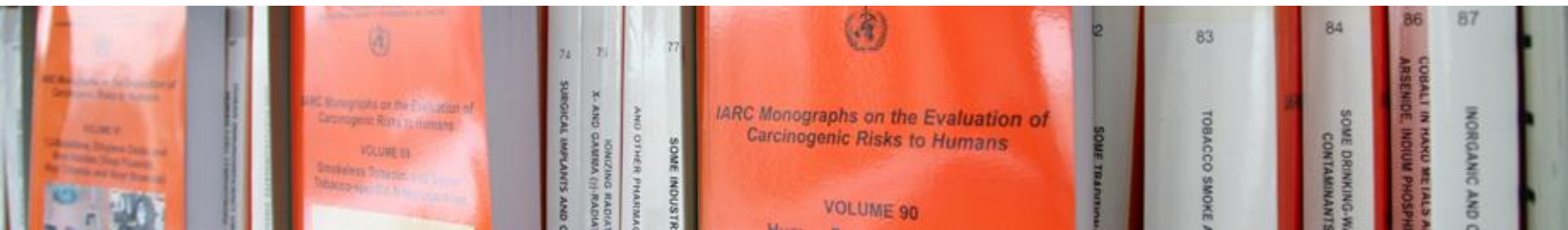
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The IARC Monographs

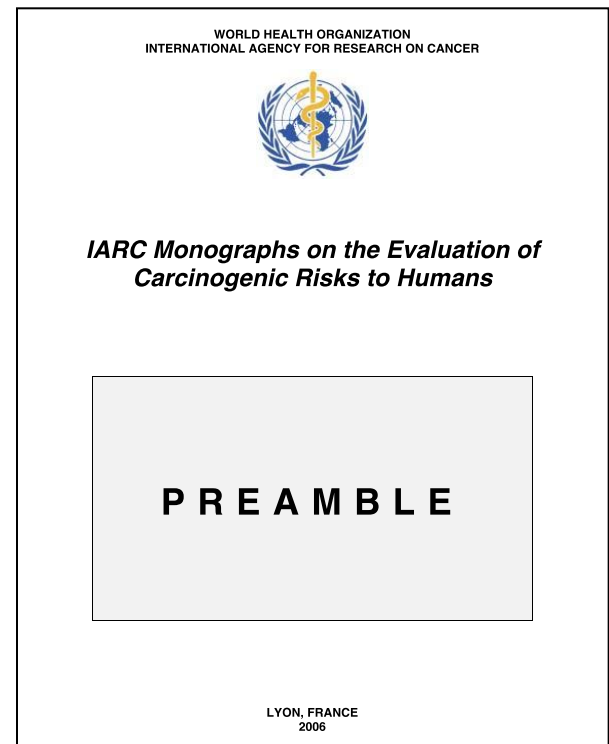
(<http://monographs.iarc.fr/indexfr.php>)

- “The Encyclopedia of Carcinogens”
- Evaluate factors capable of causing cancer in humans
 - Environmental & occupational exposures
 - Chemical, physical & biologic agents
 - Drugs, foods, & personal habits
- More than 950 agents evaluated since 1971
 - 118 carcinogenic to humans (as of October 2015)
 - >330 probably or possibly carcinogenic
- National & international health agencies use the Monographs
 - To identify carcinogens
 - To support prevention or regulation



What makes the IARC Monographs process unique?

- Systematic reviews of human, experimental, and mechanistic data
- Consensus evaluations by the world's leading experts, free from conflicts of interest
- A public guidance document
 - Procedures for participant selection, conflict of interest & meeting conduct
 - Criteria for evaluation of evidence
 - Decision process for overall evaluation



Evaluating human data

Cancer in humans

— Preamble Part B, Section 6(a)

Cancer in experimental animals

Mechanistic and other relevant data

- *Sufficient evidence*

Causal relationship has been established

Chance, bias, and confounding could be ruled out with reasonable confidence

- *Limited evidence*

Causal interpretation is credible

Chance, bias, or confounding could not be ruled out

- *Inadequate evidence*

Studies permit no conclusion about a causal association

Integrating Human and Animal Evidence

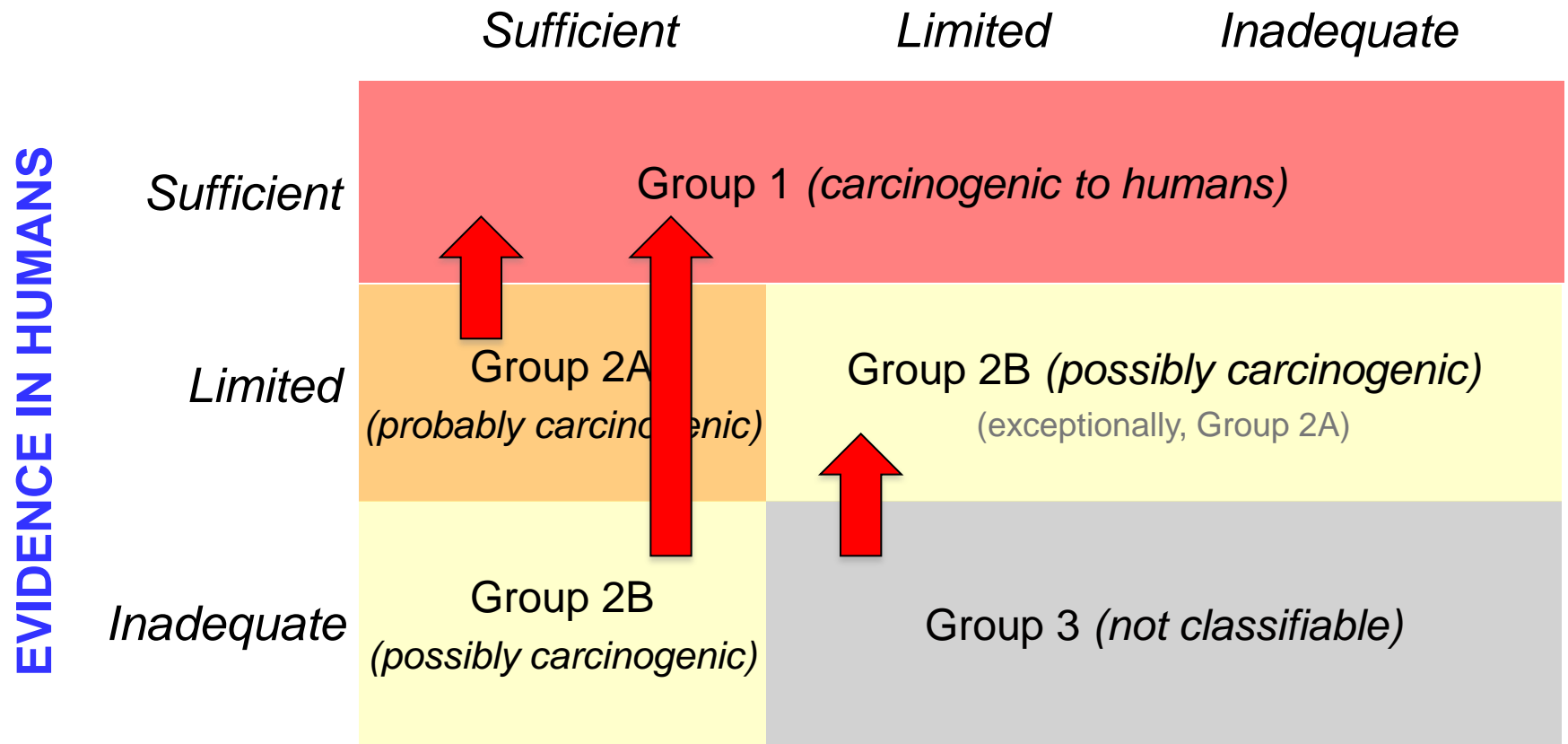
EVIDENCE IN EXPERIMENTAL ANIMALS

EVIDENCE IN HUMANS

	<i>Sufficient</i>	<i>Limited</i>	<i>Inadequate</i>
<i>Sufficient</i>	Group 1 (<i>carcinogenic to humans</i>)		
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Mechanistic Modifications - when human data are less than sufficient

EVIDENCE IN EXPERIMENTAL ANIMALS

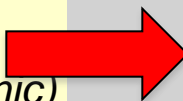


Strong supporting evidence in exposed humans

Mechanistic Modifications - when human data are less than sufficient

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**Strong evidence: mechanism in animals
DOES NOT operate in humans**

Prior IARC Evaluations of Pesticides

75 pesticides and pesticide classes were evaluated 1971-2014.

Classification	Number	Details
Group 1	1	Arsenic and arsenical compounds, including pesticides (1980, 2012)
Group 2A	4	Occupational exposure in spraying non-arsenical insecticides (1991) & 3 others upgraded from 2B
Group 2B	21	
Group 3	49	Includes 2 downgraded from 2B

Implication: Human data were inadequate for most pesticides evaluated

Challenges in Evaluating Epidemiologic Data on Pesticides and Cancer

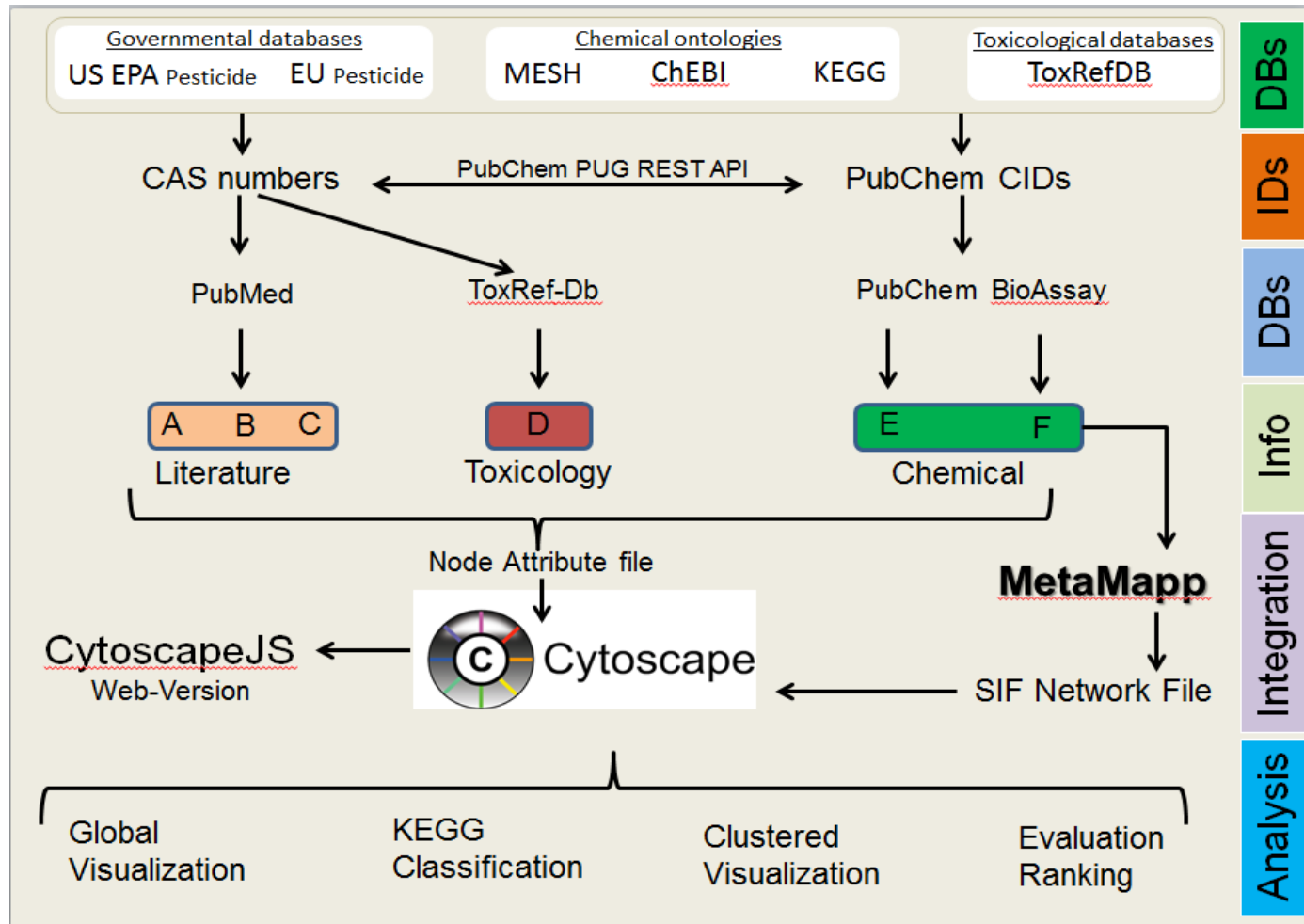
- Small numbers
 - Low prevalence of significant exposure
 - Rare endpoints
- Need for data on specific pesticides
- Need for quantitative exposure data
- Importance of establishing dose-response
- Exposure to multiple agents
- Potential for nonlinear effects (e.g., non-genotoxic mechanisms)

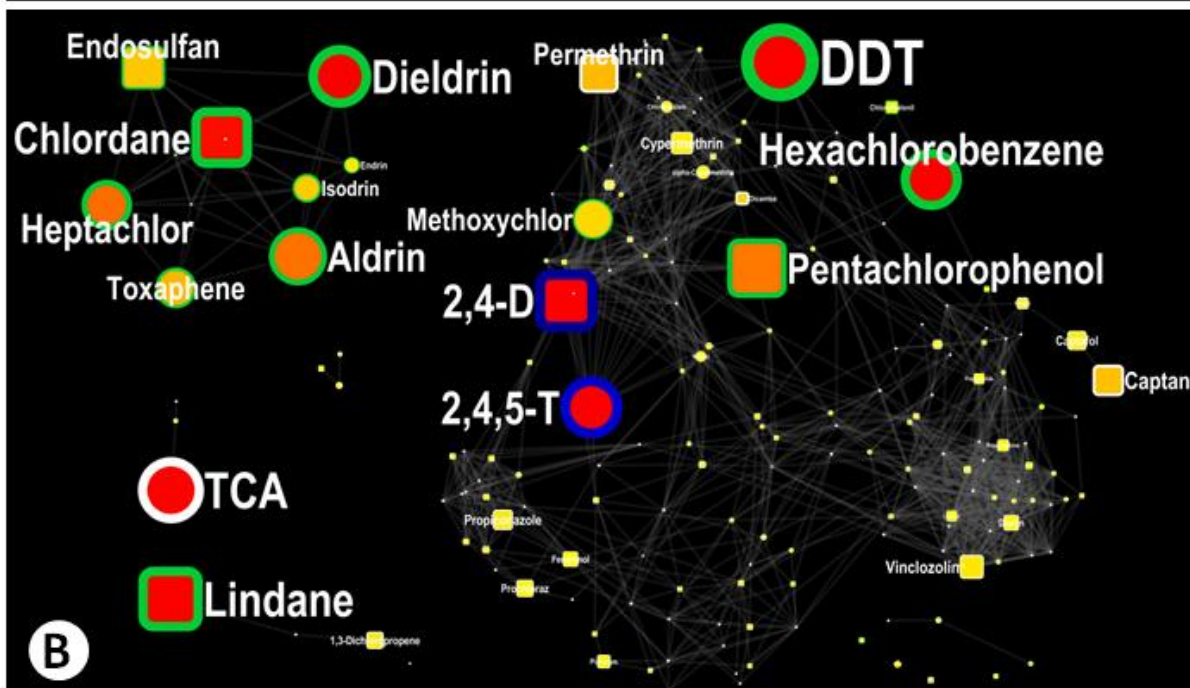
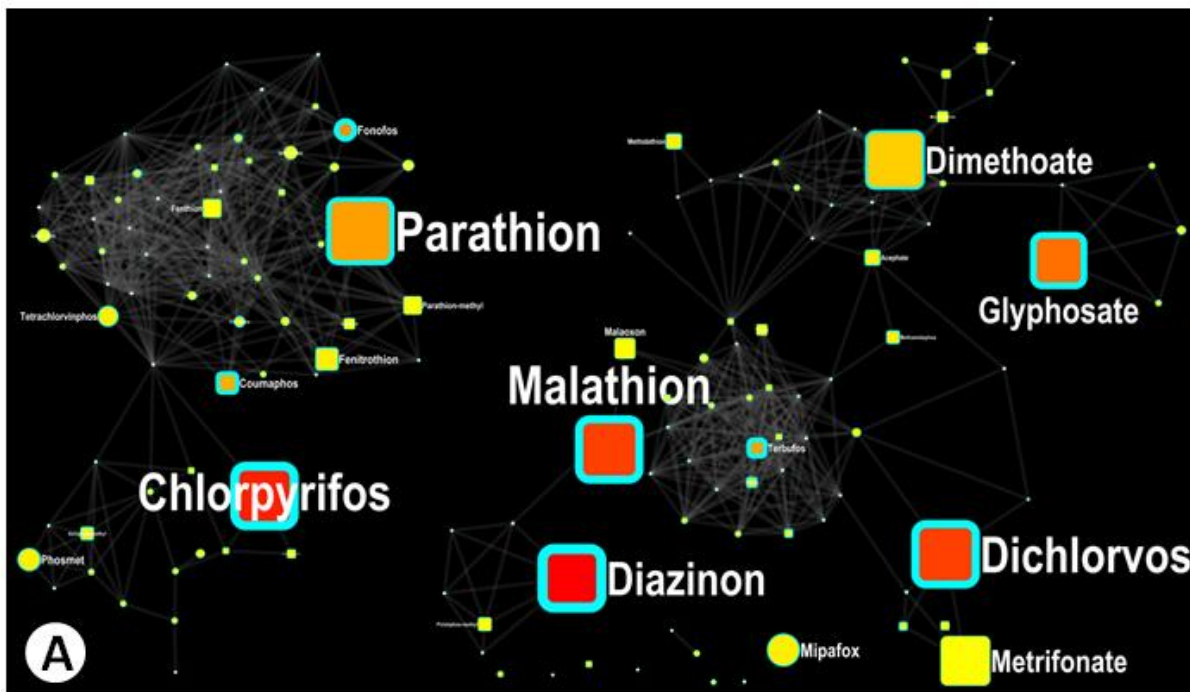
Selecting Pesticides for Evaluation - 2014 Advisory Group on Priorities

Recommendation	Pesticide class	Priority*	Prior evaluation
<u>Malathion</u>	OP insecticide	High	1987, Group 3
<u>Diazinon</u>	OP insecticide	High	None
<u>Lindane</u>	OC insecticide		1987, 2B (HCCH)
<u>Permethrin</u>	Pyrethroid insecticide	High	1991, Group 3
<u>Pendimethalin</u>	Dinitroaniline herbicide	High	None
<u>Carbaryl</u>	Carbamate insecticide	High	1987, Group 3
DDT	OC insecticide	Medium	1991, Group 2B
2,4,6- trichlorophenol, pentachlorophenol, <u>Hexachlorobenzene</u>	OC insecticide	Medium	1999, Group 2B (PCPs)
<u>Fonofos, terbufos,</u> <u>chlorpyrifos</u>	OP insecticide	Medium	None
Glyphosate	OP herbicide	Medium	None
Atrazine	Triazine herbicide	Medium	1999, Group 3
EPTC	Thiocarbamate herbicide	Medium	None
Biphenyl	Fungicide	Medium	None

High priority based on widespread global use, data from new epidemiologic studies, cancer bioassays or high throughput screening

Selecting Pesticides for Evaluation - A Novel Approach Using Chemoinformatics





Visualization

A. Organophosphates and other pesticides with at least 1 phosphorous atom

B. Organochlorines and other pesticides with more than 2 chlorine atoms

Node size is proportional to number of papers; colour indicates number of epidemiology papers (red=largest numbers)

OP & OC Pesticides Selected for Evaluation

Name	Rank	PubMed cancer hits	PubMed human cancer hits	Existing IARC (year)	Other classifications	Usage notes
Parathion	1	42	6	3 (87)	EPA Group C	Restricted
Malathion	2	40	12	3 (87)	EPA Suggestive	High
Diazinon	5	30	16	-	EPA Not likely	High
Glyphosate	7	21	9	-	EPA Group C (1985), Group E (1991), HPV	High
TCVP	13	6	1	3 (87)	US EPA Likely	Active
DDT	1	494	190	2B (91)	POP, RoC-RA	Restricted
Lindane	2	189	51	2B (87)	POP, RoC-RA; EPA Suggestive	Active
2,4-D	1	145	84	2B (91)	HPV	Active

Lindane (Vol 113) – Cancer in Humans

- Non-Hodgkin lymphoma
 - RR 2.5 (1.4-4.4) for High use in US AHS (p-trend 0.004)
 - Significant association with number of sheep “dipped” by Icelandic sheep farmers
 - Significant associations with self-reported lindane use in case control studies in the US Midwest (OR 1.5) and Canada (OR 2.06)
 - Inconsistent associations with lindane biomarkers (β HCH) in blood
- **Conclusion:** *Sufficient evidence for NHL*

Overall Evaluation – Lindane: *Group 1*

EVIDENCE IN EXPERIMENTAL ANIMALS

Sufficient

Limited

Inadequate

EVIDENCE IN HUMANS

Sufficient

Group 1 (*carcinogenic to humans*)

Limited

Group 2A
(*probably carcinogenic*)

Group 2B (*possibly carcinogenic*)
(exceptionally, Group 2A)

Inadequate

Group 2B
(*possibly carcinogenic*)

Group 3 (*not classifiable*)

Glyphosate (Vol 112) – Cancer in Humans

Key epidemiology studies for Non-Hodgkin Lymphoma (NHL):

US, Canadian and Swedish case-control studies

- Positive association that persisted after adjustment for other pesticides

Agricultural Health Study (US)

- No additional support for association, but results do not contradict other studies

Conclusion: *Limited evidence of carcinogenicity in humans (NHL)*

Positive association observed, causal interpretation is credible;

Chance, bias and confounding could not be ruled out with reasonable confidence

Glyphosate – Other Evidence

- Cancer in animals
 - *Sufficient evidence* for carcinogenicity of glyphosate in feeding studies of rat & mice
 - Renal tubule adenomas+carcinomas & haemangiosarcomas in mice
 - Pancreatic islet cell adenoma in rats
- Mechanistic evidence
 - *Strong evidence* for genotoxicity & oxidative stress that can operate in humans

Overall Evaluation – Glyphosate: *Group 2A*

EVIDENCE IN EXPERIMENTAL ANIMALS

EVIDENCE IN HUMANS

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DDT (Vol 113) – Cancer in Humans

- Rich database (>100 studies) on several cancers
- **Liver cancer**
 - HCC associated with DDT measured in blood in 2 cohort studies & 1 case-control study in China (RRs \approx 3-4)
 - No association with occupational DDT exposure in Sardinian malaria control workers (RR \approx 1)
- **Testicular cancer**
 - Positive associations with DDT in blood in 2 cohort studies & 2 small case-control studies (post-diagnosis samples)
 - No association in 1 large case-control study
 - Inconsistent in 2 studies of maternal exposure

DDT – Cancer in Humans 2

- **Non-Hodgkin lymphoma** (>30 studies)
 - RR 1.7 (1.1-2.6) in US AHS for high use (p-trend 0.02)
 - Null for NHL mortality in Sardinian DDT sprayers
 - Inconsistent associations in studies using DDT or DDE biomarkers and case-control studies using self-report or expert assessment
- **Breast cancer** (>40 studies)
 - No clear association with DDT or DDE in blood or adipose tissue

Evolution of evidence on breast cancer & DDE in blood and adipose tissue, 1993-2001 (Lopez-Cervantes et al., 2004)

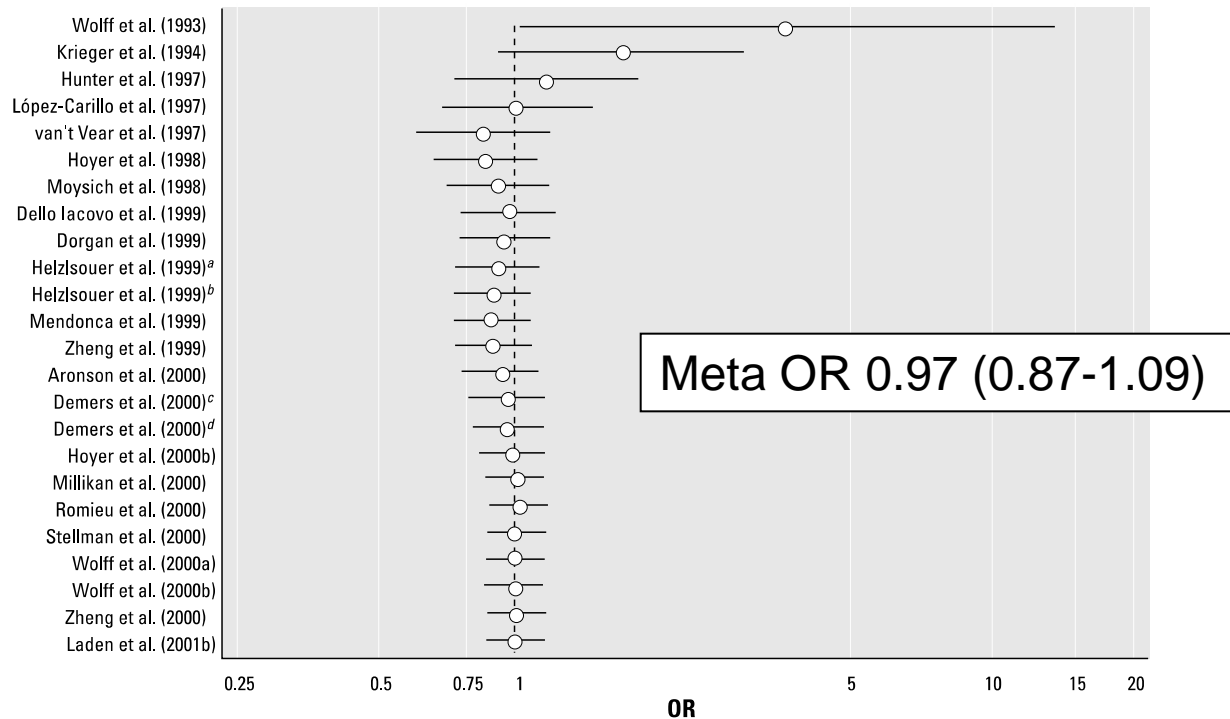


Figure 1. Accumulated meta-analysis; summary OR = 0.97 (95% CI, 0.87–1.09).

^aBiologic samples taken in 1974. ^bBiologic samples taken in 1989. ^cControls are population based. ^dControls are clinical based.

Conclusions - Cancer in humans

Limited evidence for liver & testis cancer & NHL

Inadequate evidence for breast cancer

DDT – Other Evidence

- Cancer in animals
 - *Sufficient evidence* for carcinogenicity of DDT, DDE and DDD in feeding studies of rats, mice & hamsters
 - Increased liver tumours & lymphoma in mice
 - Increased liver tumours in rats
- Mechanistic evidence
 - *Strong evidence* for immunosuppression, oxidative stress & androgen/oestrogen receptor-mediated effects

Overall Evaluation – DDT: *Group 2A*

EVIDENCE IN EXPERIMENTAL ANIMALS

EVIDENCE IN HUMANS

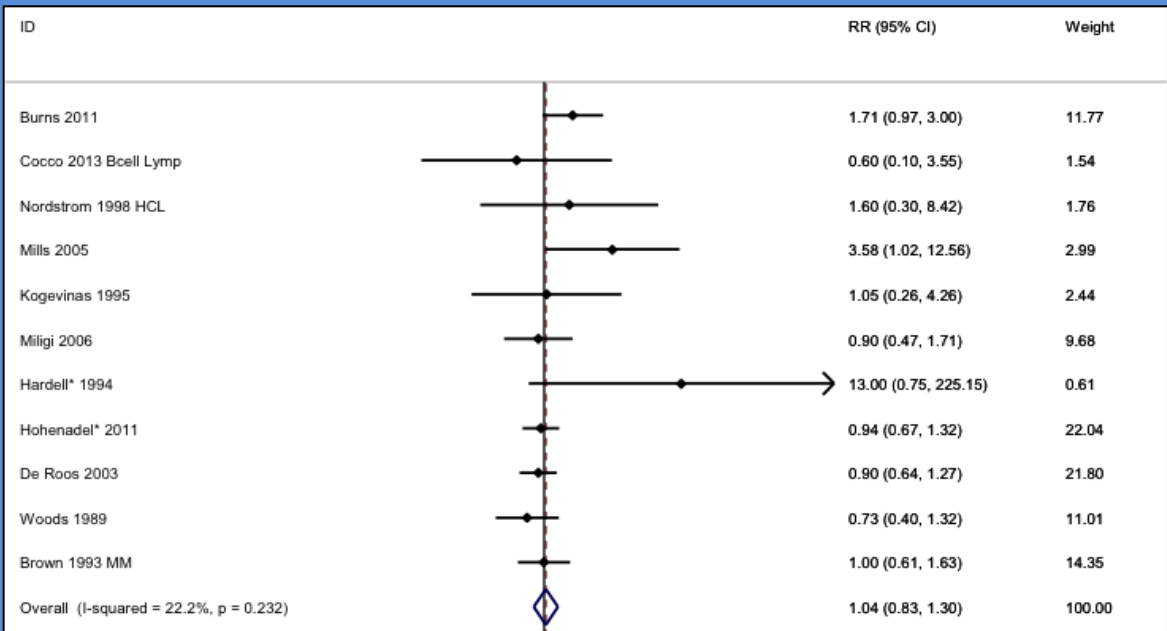
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2,4-D – Cancer in Humans

- Complex, challenging database:
 - Occupational cohort studies: pesticide manufacturing workers, sprayers, farm & forestry workers, military personnel (Vietnam war)
 - Population-based case-control studies
- Some studies judged uninformative about 2,4-D:
 - Only exposure to “phenoxy herbicides” as a class assessed
 - Potential for dioxin contamination

2,4-D – Cancer in Humans

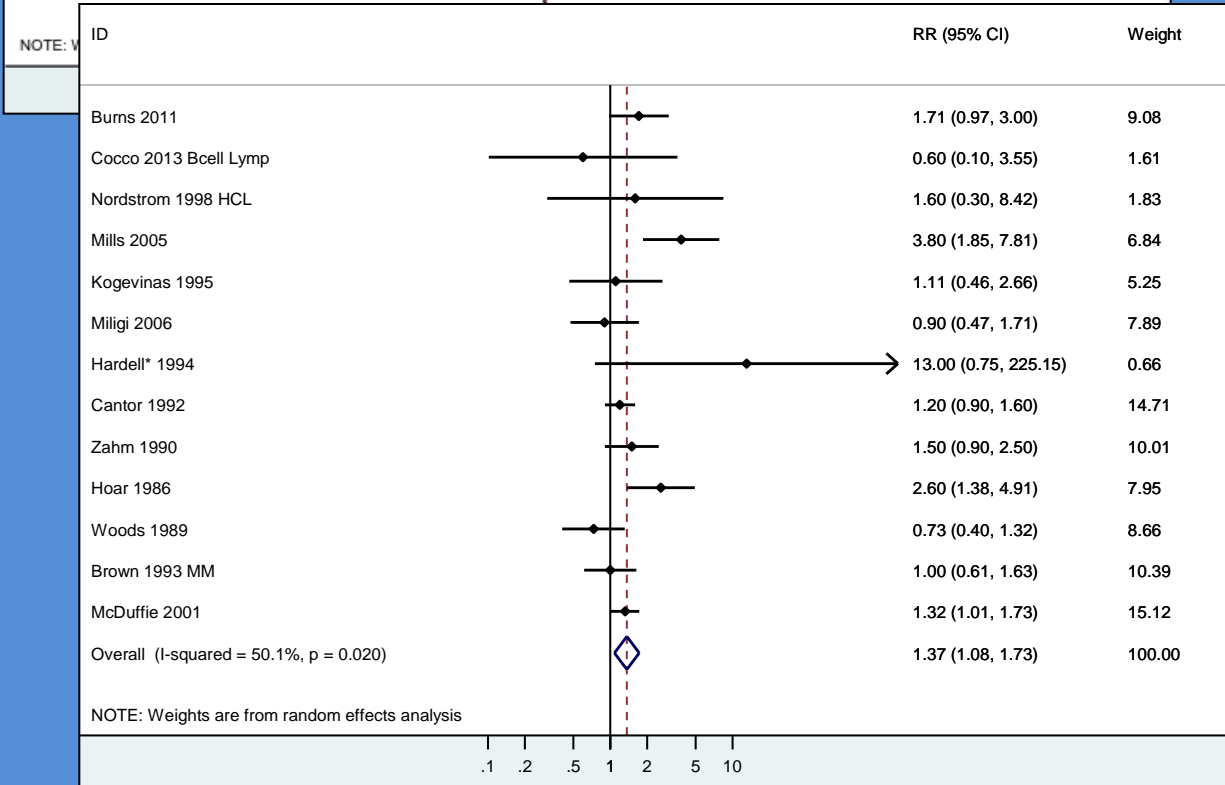
- Non-Hodgkin lymphoma (>10 studies)
 - Increased risk in California farmworker cohort
 - No excess risk overall in 2 cohorts of herbicide manufacturing workers, but RR = 2.2 in highest exposure category in one study (USA)
 - Positive associations in 4 population case-control studies (US, Canada & Sweden) with dose-response in 2;
 - Four others essentially null
 - No association in published meta-analysis or updated meta-analysis by the Working Group (RR 1.04), but results were sensitive to studies adjusted for multiple pesticides



Forest plots of RR for NHL and 2,4-D

Top: most adjusted estimates

Bottom: least adjusted estimates



2,4-D – Cancer in Humans 2

- Soft tissue sarcoma (3 studies)
 - Strong association in an international cohort study of manufacturing workers
 - No association in 2 US case-control studies
- Other cancers (breast, prostate, melanoma, brain)
 - Few studies & inconsistent findings
- **Conclusion:** *Inadequate evidence*

2,4-D – Other Evidence

- Cancer in animals
 - *Limited evidence* from injection & feeding studies in rats & mice
- Mechanistic evidence
 - *Strong evidence* for oxidative stress
 - *Moderate evidence* for immunosuppression

Overall Evaluation – DDT: *Group 2A*

EVIDENCE IN EXPERIMENTAL ANIMALS

Sufficient

Limited

Inadequate

Sufficient

Group 1 (*carcinogenic to humans*)

Limited

Group 2A
(*probably carcinogenic*)

Group 2B (*possibly carcinogenic*)

Inadequate

Group 2B
(*possibly carcinogenic*)

Group 3 (*not classifiable*)
(exceptionally, Group 2B)

EVIDENCE IN HUMANS

Overall Results - 8 Pesticides, Vol 112 & 113

Pesticide	Volume	Previous IARC Category	Current IARC Category
Lindane	113	2B (as part of class)	Group 1
Glyphosate	112	-	Group 2A
Malathion	112	3	Group 2A
Diazinon	112	-	Group 2A
DDT	113	Group 2B	Group 2A
Tetrachlorvinphos	112	3	Group 2B
Parathion	112	3	Group 2B
2,4-D	113	2B (as part of class)	Group 2B

Results & Observations

- **Results**
 - 1 new Group 1 agent
 - 4 new Group 2A agents: 2 upgraded, 2 classified first time
 - 3 new Group 2B agents: upgraded or classified separately
- Epidemiologic literature on pesticides has grown significantly but “further research is needed”
 - Uncertain value of pesticide biomarkers
 - Improving exposure assessment is essential
 - Multiple pesticide exposures pose problems for analysis and interpretation