IARC Evaluation of the Carcinogenicity of Pesticides: 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
  - 114 carcinogenic to humans (as of October 2014)
  - >330 probably or possibly carcinogenic
- National & international health agencies use the Monographs
  - To identify carcinogens
  - To support prevention or regulation
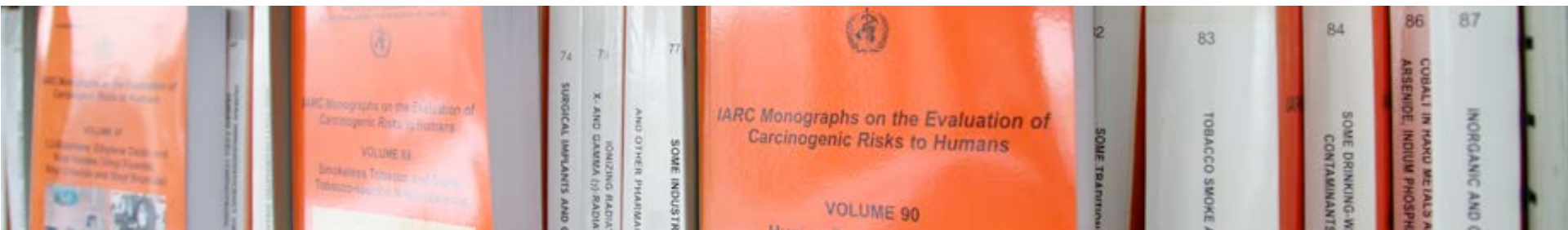
Cancer Hazard Assessment based on 3 lines of evidence
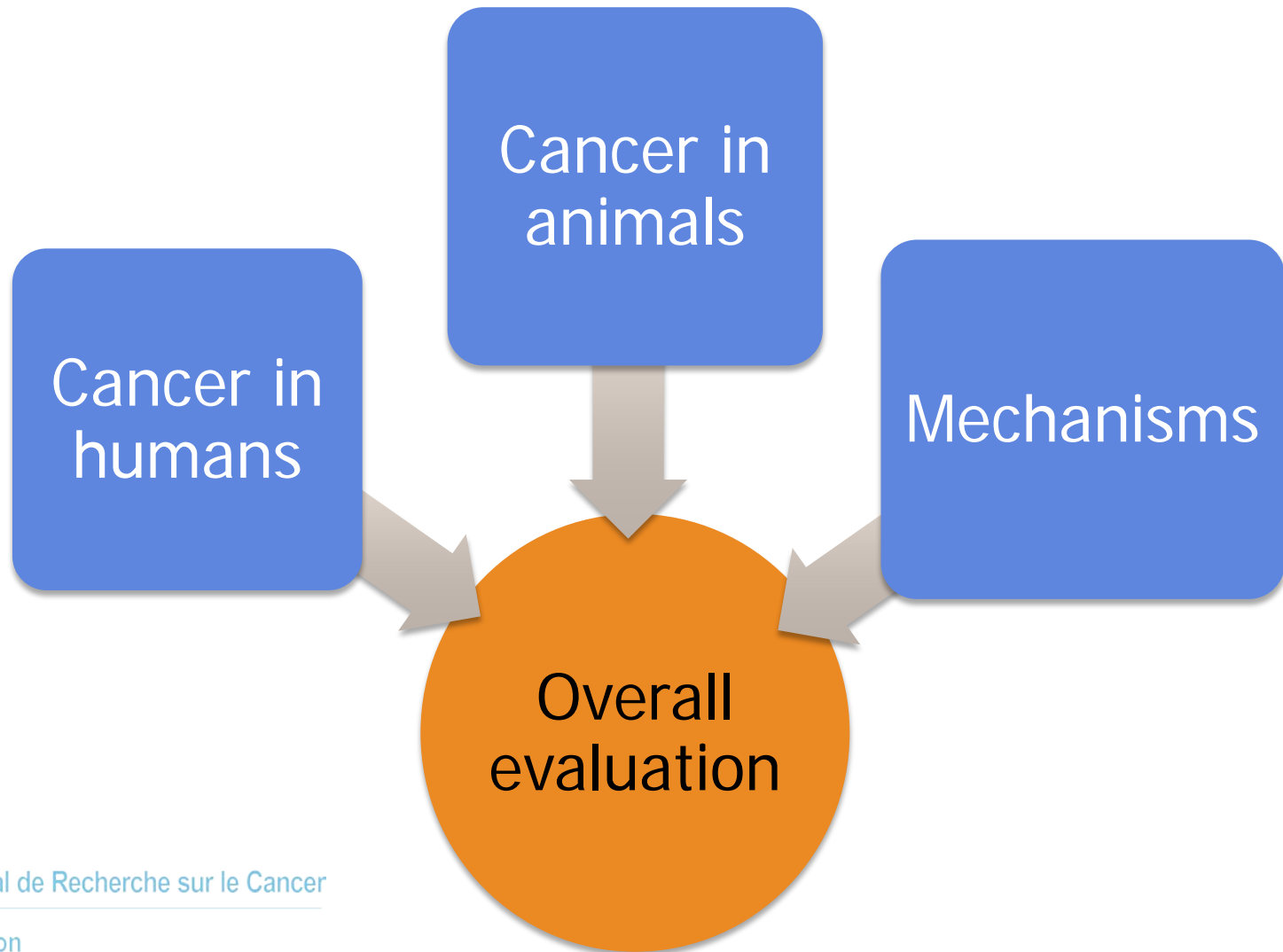
Evaluating human data

Cancer in humans	Cancer in experimental animals	Mechanistic and other relevant data
— Preamble Part B, Section 6(a)		

|	
☐ *Sufficient evidence*	Causal relationship has been <u>established</u> Chance, bias, and confounding <u>could be ruled out with reasonable confidence</u>
☐ *Limited evidence*	Causal interpretation is <u>credible</u> Chance, bias, or confounding <u>could not be ruled out</u>
☐ *Inadequate evidence*	Studies permit <u>no conclusion</u> about a causal association
☐ *Evidence suggesting lack of carcinogenicity*	Several adequate studies covering the full range of exposure levels are mutually consistent in not showing a positive association at any observed level of exposure Conclusion is limited to cancer sites and conditions studied

Integrating Human and Animal Evidence

EVIDENCE IN EXPERIMENTAL ANIMALS

EVIDENCE IN HUMANS	*Sufficient*	*Limited*	*Inadequate*
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)*	

Mechanistic Modifications -
when human data are less than sufficient

EVIDENCE IN EXPERIMENTAL ANIMALS

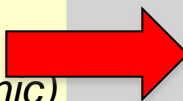|	*Sufficient*	*Limited*	*Inadequate*
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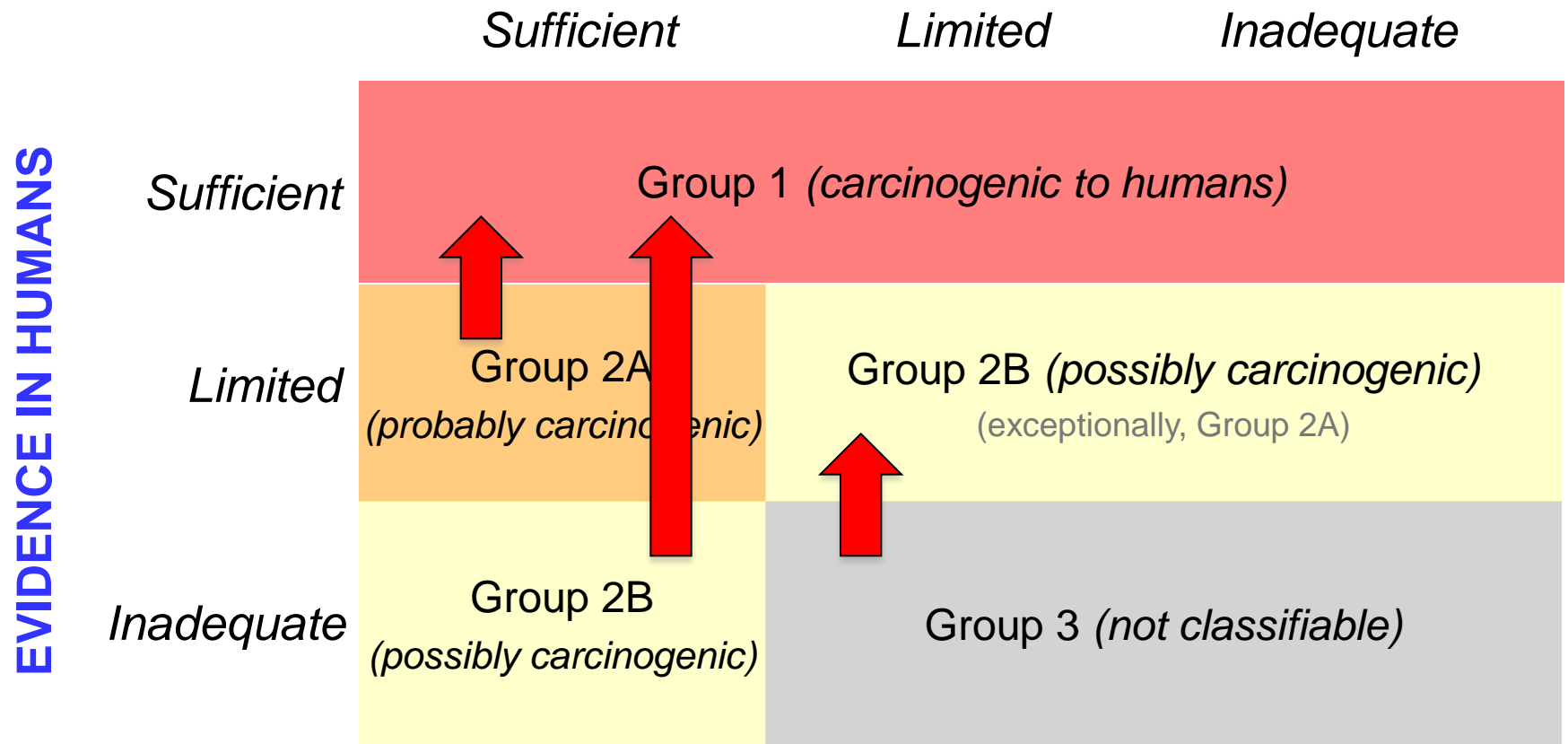
Strong supporting evidence in exposed humans

Mechanistic Modifications -
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EVIDENCE IN HUMANS

International Agency for Rese...

World Health Organization

Strong evidence: mechanism in animals DOES NOT operate in humans

Prior IARC Evaluations of Pesticides

75 pesticides and pesticide classes have been evaluated 1971-2014.

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

Implication: Human data are inadequate for most pesticides evaluated to date.

Selecting Pesticides for Future Evaluation: 2014 Advisory Group on Priorities

| Recommendation	Pesticide class	Priority*	Prior evaluation
Malathion	OP insecticide	High	1987, Group 3
Diazinon	OP insecticide	High	None
Lindane	OC insecticide		1987, 2B (HCCH)
Permethrin	Pyrethroid insecticide	High	1991, Group 3
Pendimethalin	Dinotroaniline herbicide	High	None
Carbaryl	Carbamate insecticide	High	1987, Group 3
DDT	OC insecticide	Medium	1991, Group 2B
2,4,6-trichlorphenol, pentachlorophenol,	OC insecticide	Medium	1999, Group 2B (PCPs)
Hexachlorobenzene	OC insecticide	Medium	2001, Group 2B (HCB)
Fonofos, terbufos, chlorpyrifos	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

A Novel Approach Using Chemoinformatics
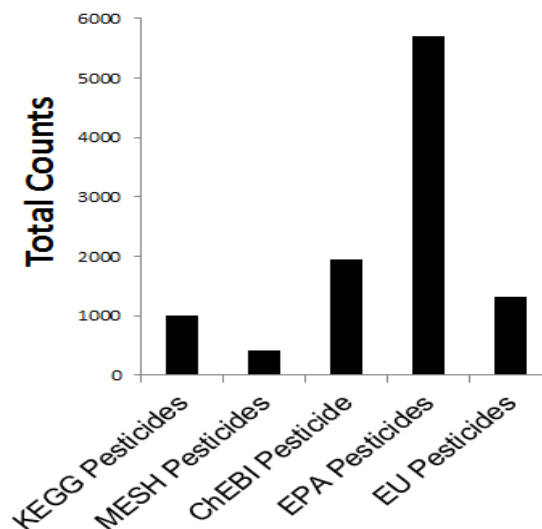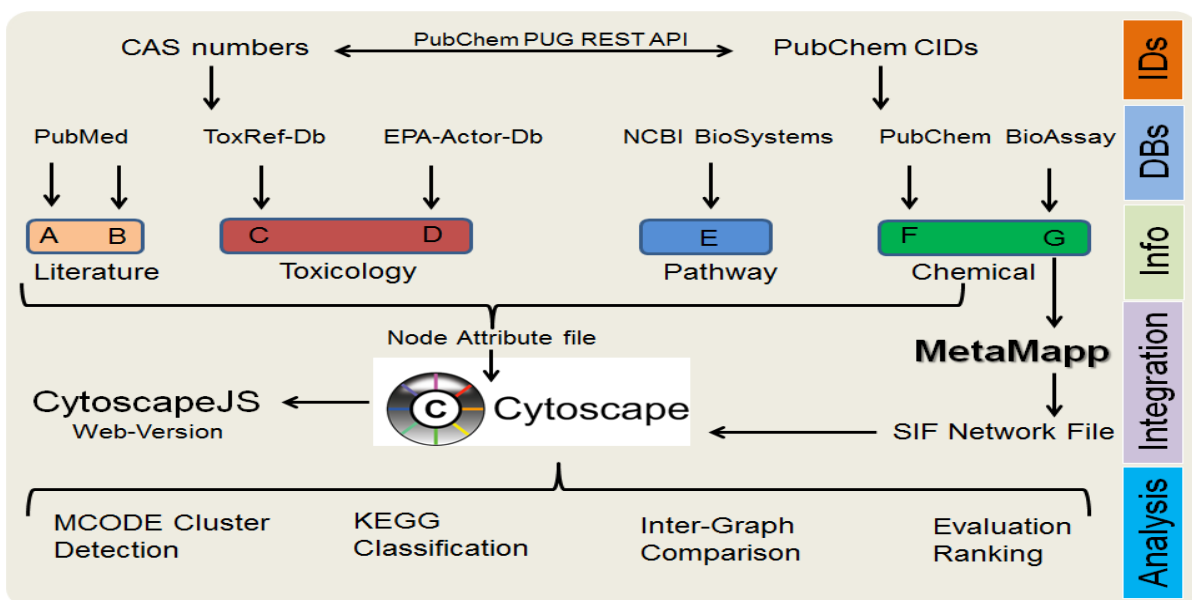
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Cancer and Pesticides animal studies paper count	NCBI Eutils	cas numbers AND top three synonyms AND pesticide* AND cancer AND animals[mesh] AND hasabstract[text]
Active BioAssys counts	PubChem PUG	pubchem.ncbi.nlm.nih.gov/rest/pug/compound/cid/XXX/aids/JSON?aids_type=active (XXX is PubChem Compounds identifier for the compound)
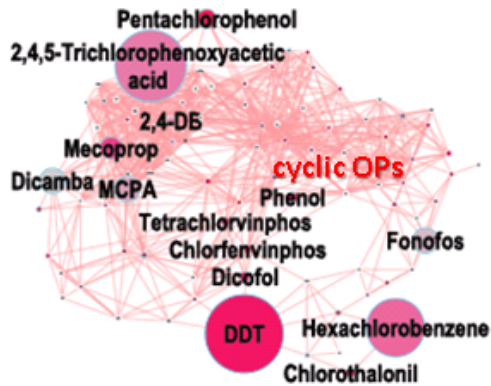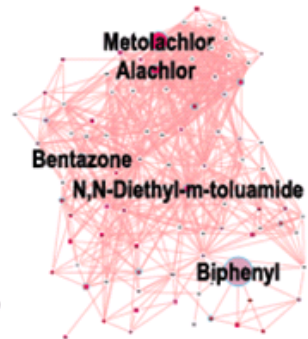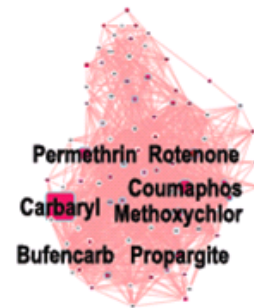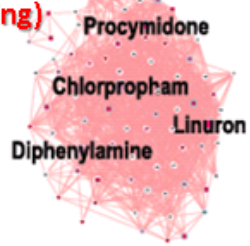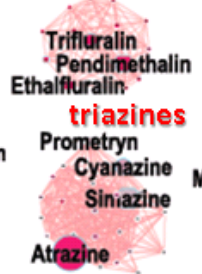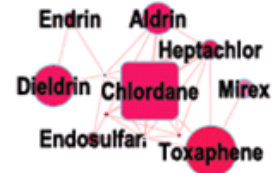
Top 10 Pesticides Identified by the Chemoinformatics Approach

Name	PubChem CID	Class	PubMed Cancer EPI	PubMed All	PubChem Bioassay	Notes
DDT	3036	OC	39	355	35	POP/ED/SCRC
2,4,5-T	1480	Auxins	20	129	4	SCRC
Chlordane	5993	OC	16	89	31	SCRC
Hexachlorobenzene	8370	OC	16	137	5	ED/SCRC
Lindane	727	OC	15	216	29	POP/ED/SCRC
Toxaphene	5284469	OC	14	47	87	POP/SCRC
Dieldrin	969491	OC	11	137	40	POP/SCRC
Malathion	4004	OP	10	46	17	
Atrazine	2256	Triazine	9	83	9	HPV
Aldrin	61103	OC	8	60	16	POP/SCRC

POP = Persistent Organic Pollutant
HPV = High production volume chemical
ED = Suspected endocrine-disrupting activity
SCRC = Listed under Stockholm and/or Rotterdam convention

International Agency for Research on Cancer

World Health Organization

Upcoming IARC Evaluations of Pesticides

IARC MONOGRAPHS - MEETINGS

Upcoming Meetings

Meeting 112:   Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos (3-10 March 2015)

Preliminary List of Agents
Call for Data (closing date 3 February 2015)
Call for Experts (closing date 30 July 2014)
Request for Observer Status (closing date 3 November 2014)
WHO Declaration of Interests for this volume
Instructions for Authors
Preliminary List of Participants

Meeting 113:   Some Organochlorine Insecticides and Some Chlorphenoxy Herbicides (2-9 June 2015)

Preliminary List of Agents
Call for Data (closing date 2 May 2015)
Call for Experts (closing date 10 October 2014)
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International Agency for R

World Health Organization

Epidemiologic Data Available for Evaluation: IARC Monographs 112 & 113

Agent	Total Studies	Cohort	Case-Control
DDT	114	77	33
2,4-D	57	28	29
Malathion	27	7	20
Lindane	24	5	19
Diazinon	21	9	12
Glyphosate	16	5	10
Parathion	9	5	4
Tetrachlorvinphos	4	1	3

The Epidemiologic Database on Pesticides
Literature tree for DDT
IARC Monograph 113
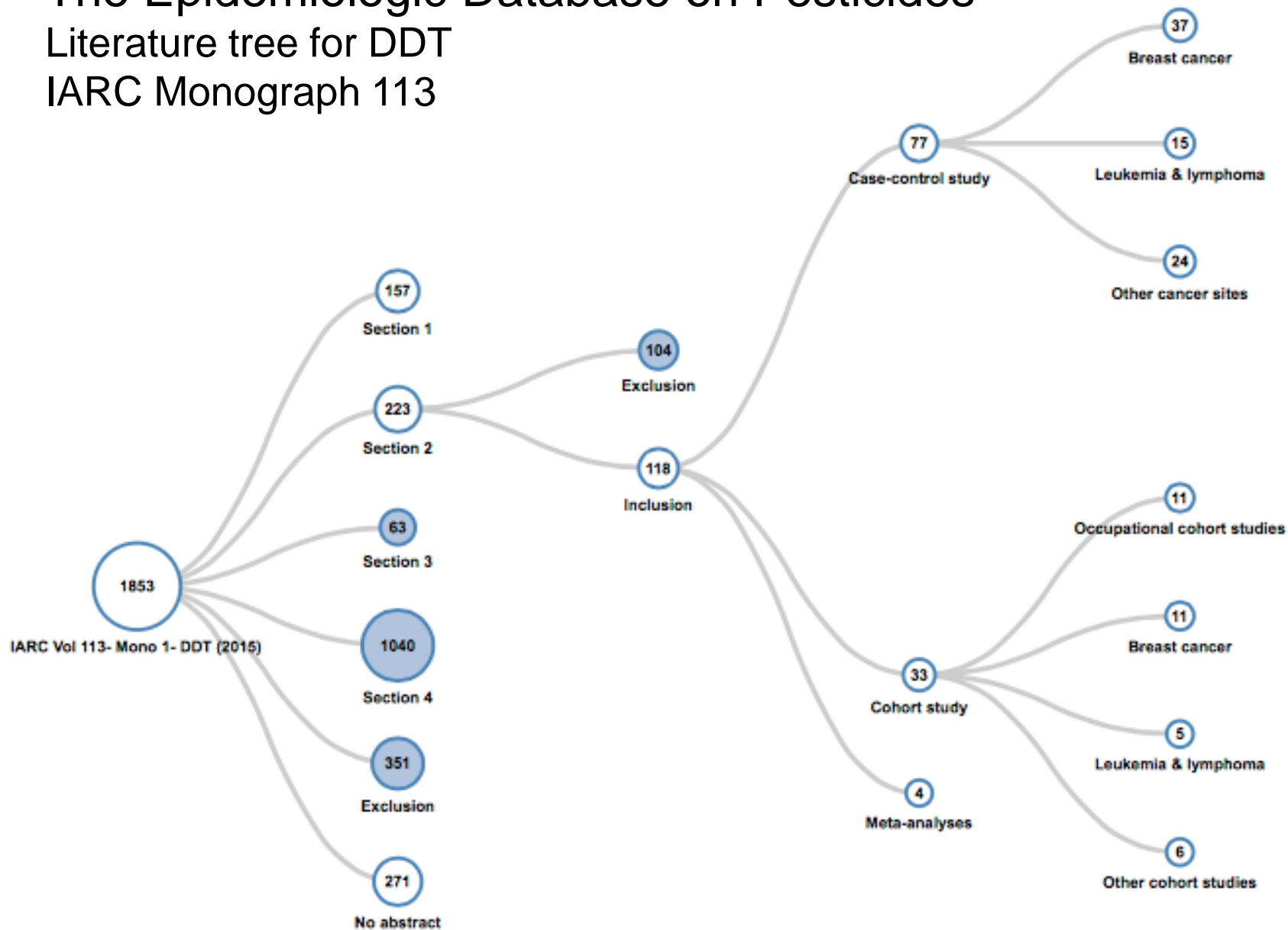
Challenges in Evaluating Epidemiologic Data on Pesticides and Cancer

- Need for data on specific pesticides

- Exposure to multiple agents

- Small numbers

    - Low prevalence of significant exposure

    - Rare endpoints

- Need for quantitative exposure data

- Importance of establishing dose-response

- Potential for nonlinear effects (e.g., non-genotoxic mechanisms)

Challenges in Epidemiologic Research on Pesticides (and Cancer)

- Finding appropriate study populations
  - Large numbers exposed at low levels or small numbers exposed at high(er) levels

- Exposure assessment
  - Assessment of individual pesticides
  - Objective exposure measures
  - Quantitative exposure estimation
  - Estimating historical exposures
  - Biomarkers for less persistent compounds

General Features of Studies That Are More Likely to Contribute to Sufficient Evidence

- Cohort & case-control studies
- Clear presentation of methods & results
- Focused on the exposure of interest
- High-quality exposure assessment
  - Quantitative estimates
- Control of important confounders
- High-quality analysis
  - Internal comparisons
  - Thorough exposure-response assessment
  - Consideration of latency

Conclusions

- Human data are *inadequate* for most pesticides evaluated by IARC to date

- Numerous pesticides can be prioritised for evaluation or re-evaluation

- Hazard identification and risk assessment need *more* and *better* epidemiologic data

- Especially :
  - Studies with adequate sample size
  - Quantitative exposure data
  - Exposure-response data