Clinical Teratology: In Bed With The Devil?

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In Bed With The Devil

- We will never know how many babies have been saved by teratology studies done in animals, *in vitro* or *in silico.*

In Bed With The Devil

- The only way we ever know that an exposure is teratogenic in humans is to recognize that it causes birth defects in babies.

In Bed With The Devil

- Clinical teratology research is all about recognizing when we have harmed babies as quickly and as effectively as possible.

In Bed With The Devil

- Clinical teratology counselling depends on learning from our own failures.

Kinds of Human Data

- Case reports
- Clinical series
- Pregnancy registries
- Cohort studies
- Case-control studies
- Record linkage studies

Case Reports

- Where the recognition of many human teratogenic exposures starts
- Get no respect because most associations observed are much more likely to be coincidental than causal

Clinical Series

- How most exposures that are teratogenic in humans and all teratogenic syndromes have been recognized

Clinical Series

- Most are epidemiological nightmares
  - Biased ascertainment
  - No appropriate comparison group
  - Cannot be used to provide quantitative estimate of risk

Pregnancy Registries

- Clinical series of outcomes among women who have taken a particular drug or drugs during pregnancy
- Natural approach for post-marketing surveillance of prescription drugs

Pregnancy Registries

- Best used to look for major effects; insensitive to more subtle or rare effects
- Collection of high-quality outcome data difficult (but critical)

Pregnancy Registries

- Subject to problems of all clinical series
  - Ascertainment bias in spades if not prospective
  - Often inappropriately compared to rigorously collected birth defects registry data

Cohort Studies

- Compare frequency of birth defects among children born to women treated or not treated with an agent during pregnancy

Cohort Studies

- Can estimate risk and statistical significance
- Can assess many different outcomes simultaneously
- Two flavours:
  - Birth cohorts
  - Exposure cohorts

Birth Cohort Studies

- Insensitive to rare exposures and outcomes
- Quality of exposure and outcome (birth defect diagnosis) data critical
- Very big, very expensive, and infrequently done

Exposure Cohort Studies

- Use existing TIS infrastructure
- Efficient for uncommon exposures
- Exposure and outcome data of varying quality
- Often underpowered for robust conclusions

Quality of Information on Birth Defects

- Rasmussen et al. *Am J Hum Genet* 46:478, 1990: 4929 mothers of infants with major congenital anomalies and 3029 mothers of normal infants

Quality of Information on Birth Defects

- "Did [your child] have a health problem at birth or a birth defect that was diagnosed in the first year of life?"

Quality of Information on Birth Defects

- Sensitivity (case mothers responding “yes”) = 61%
- PPV (mothers responding “yes” whose baby had a major birth defect) = 47%

Power

The chance of finding an association that really exists

Power Depends On

- Sample size
- Frequency of outcome
- Strength of association between treatment and outcome

Power Depends On

- How exposure is defined
  - Drug or class
  - Dose (amount, route, duration)
  - Timing of exposure
- How adverse outcome is defined

80% Power: 100 Births

Unexposed	Exposed	RR
3.0%	15.4%	5.1
1.0%	11.5%	11.5
0.1%	9.5%	95.0

α = 0.05, 1 control per case, 2 tails

80% Power: 250 Births

Unexposed	Exposed	RR
3.0%	9.4%	3.1
1.0%	6.0%	6.0
0.1%	4.1%	40.6

α = 0.05, 1 control per case, 2 tails

Case-Control Studies

- Compare frequency of maternal treatment during pregnancy among children with or without birth defects

Case-Control Studies

- Can estimate risk and statistical significance
- Quality of exposure and outcome (birth defect diagnosis) data critical

Case-Control Studies

- Insensitive to rare exposures
- Can only be used to look for association with birth defects present in cases

What Teratogenic Effects Should We Look For?

- Congenital anomalies (structural)
  - Major anomalies
  - Multiple anomalies
  - Minor anomalies

Congenital Anomalies

- Teratogens do not affect all congenital anomalies
- Unlikely:
  - Monogenic disorders (inherited)
  - New dominant mutations
  - Chromosomal abnormalities

Congenital Anomalies

- Teratogenic exposures usually produce characteristic patterns of congenital anomalies.

Characteristic Patterns of Anomalies

- Not standard ICD-10 classifications
- Not restricted to an anatomic system
- Minor anomalies often most characteristic

What Teratogenic Effects Should We Look For?

- Birth weight
- Birth length
- Head circumference
- Growth during childhood

What Teratogenic Effects Should We Look For?

- Premature delivery
- Spontaneous abortion
- Late fetal death/ stillbirth
- Infant death
- Death in later childhood

What Teratogenic Effects Should We Look For?

- Functional defects
  - Mental retardation
  - Deafness
  - Blindness
  - Autism
  - Others

What Teratogenic Effects Should We Look For?

- Transplacental carcinogenesis
- Other adult-onset diseases
- Second-generation reproductive effects

Case-Control Studies

- Can provide excellent power for rare outcomes
  - Greatest strength
  - Greatest weakness

Statistical significance
and
clinical significance
are not the same thing.

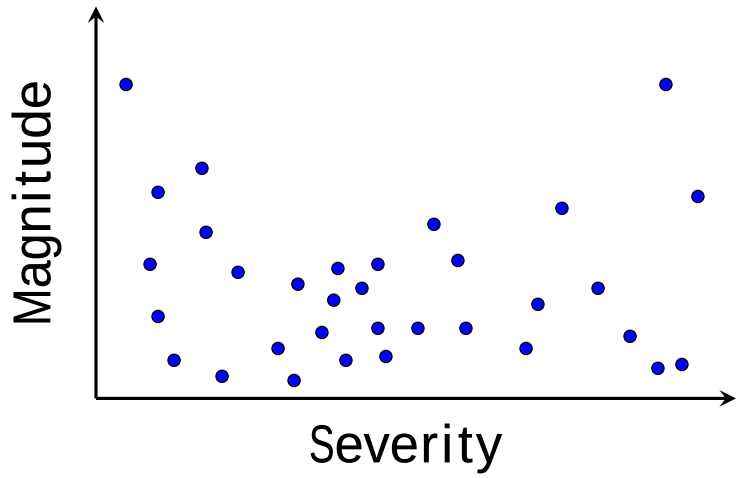
Statistical Significance

- An expression of how likely an association is to have occurred by chance alone
- What gets a paper published in the *New England Journal of Medicine*

Clinical Significance

- What matters to a pregnant woman and her physician.
  - Can I take this medicine if I am pregnant?
  - Should I consider an abortion?
  - Do I need prenatal diagnosis?

Two Dimensions of Risk



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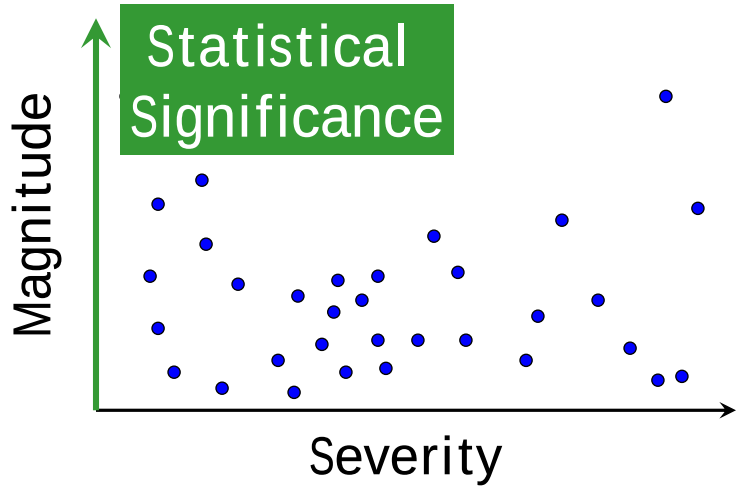

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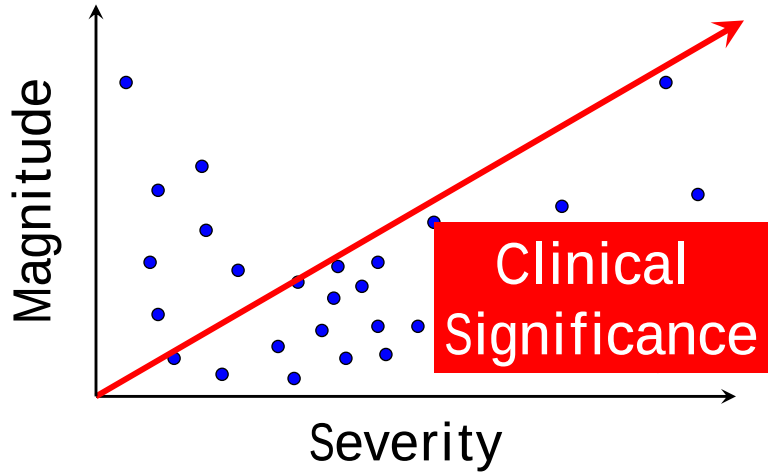

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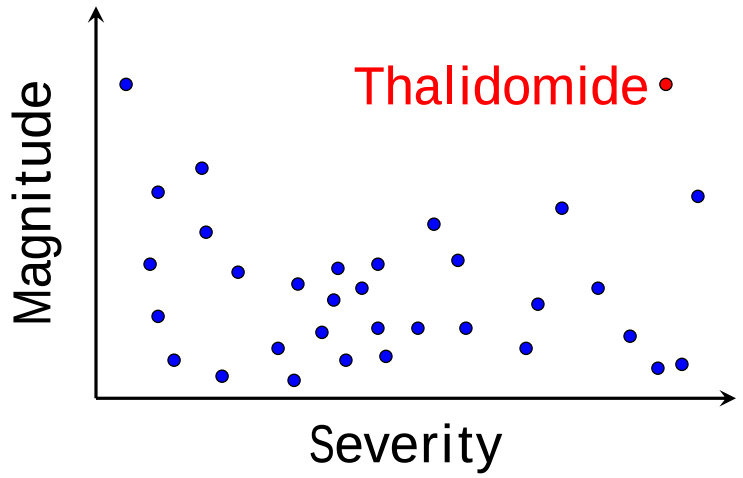

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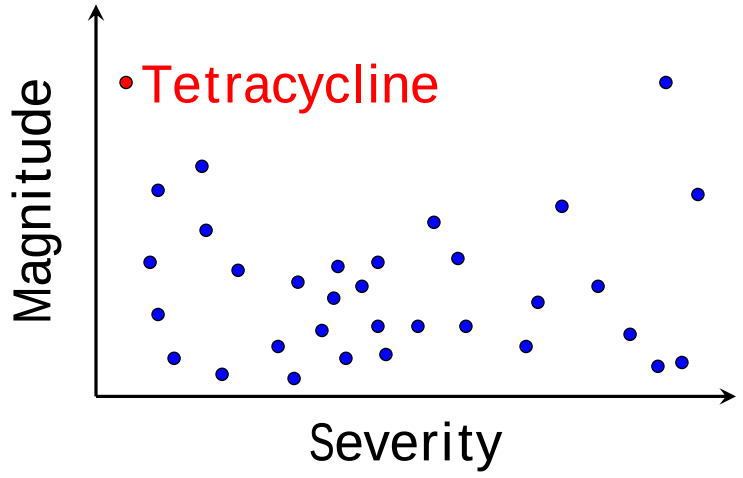

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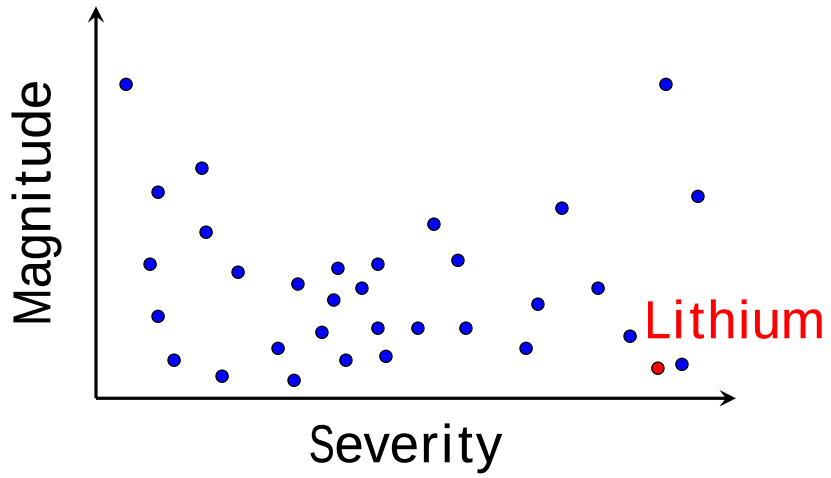


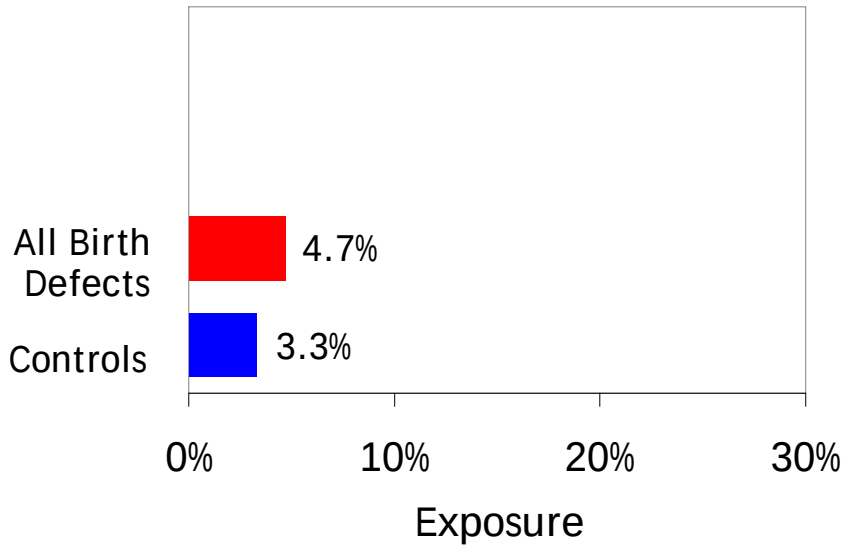
Statistical Significance

- Is easiest to demonstrate in a subgroup with the most "effective" exposure and/or most characteristic outcome
  - Multiple anticonvulsant therapy
  - Toxic methyl-Hg exposure
  - Attempted abortion with misoprostil

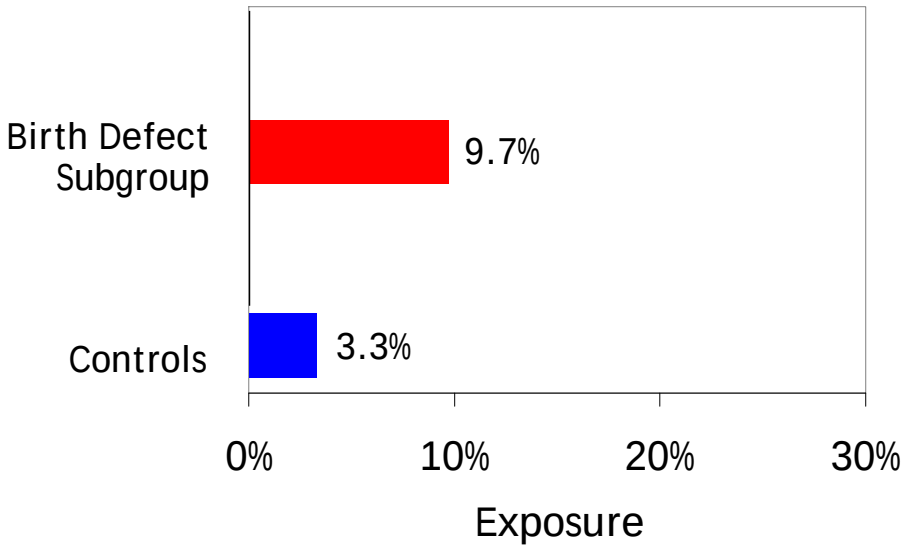
Subgroup Analysis

- In the real world, we usually do not know which birth defects will occur in excess
- Generally look broadly first (e.g., at all birth defects), then more narrowly (e.g., by kind of birth defect)

Subgroup Analysis



Subgroup Analysis



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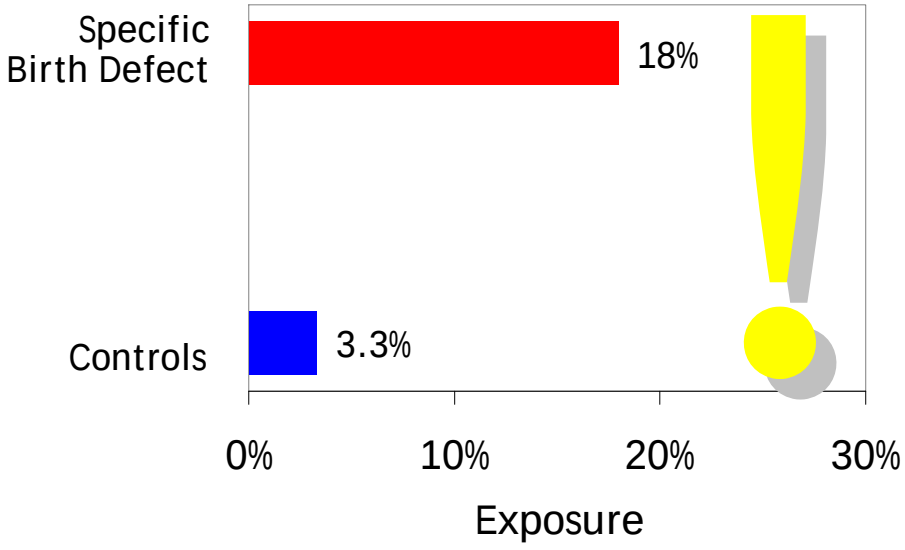

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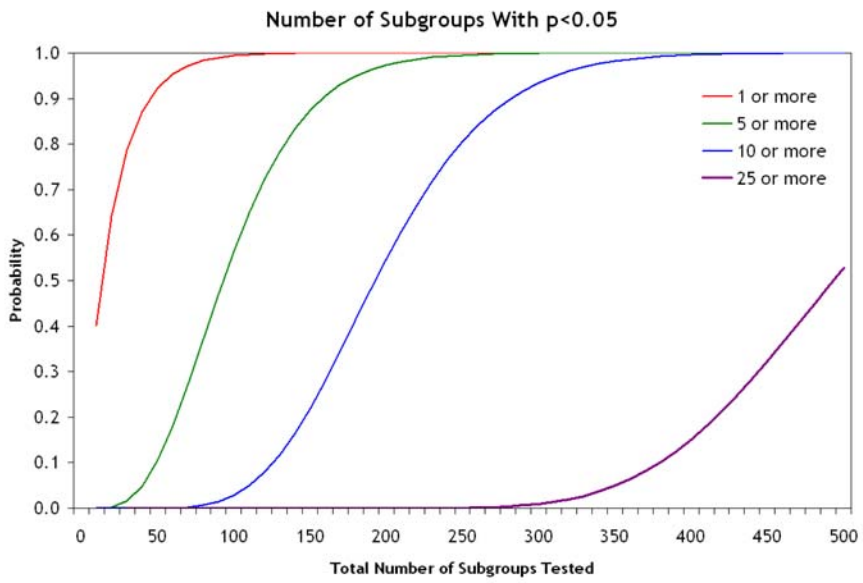


Subgroup Analysis

"Selective reporting of *post hoc* subgroup observations, which are generated by the data rather than tested by them, is analogous to betting on a horse after watching the race."

Rothwell: Lancet 365:176, 2005

Record Linkage Studies

- Use existing records or databases to identify both exposures and outcomes
- May be analyzed as cohort studies or case-control studies (or both)

Record Linkage Studies

- Often cost effective
- Information on potential confounders often limited
- Quality of exposure and/or outcome data may be poor

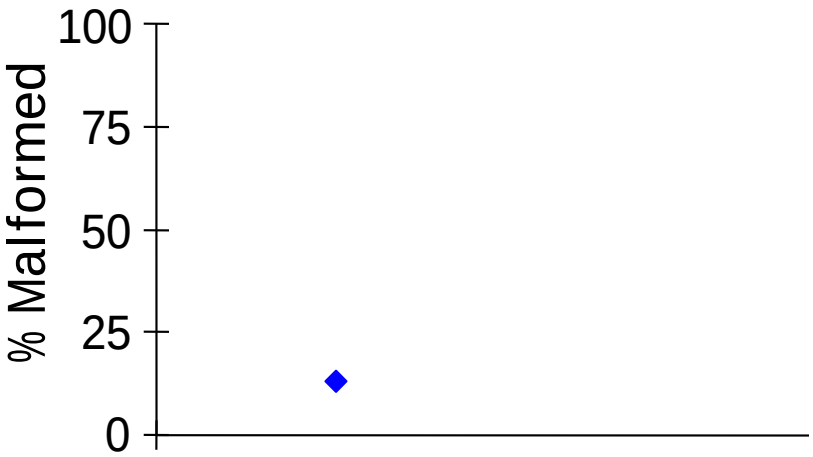
Uncertainty of the Risk Estimate

- Estimating teratogenic risk for an individual patient always requires extrapolation beyond the available data.

Uncertainty of the Risk Estimate

- The more you have to extrapolate, the greater the uncertainty.

Uncertainty of the Risk Estimate



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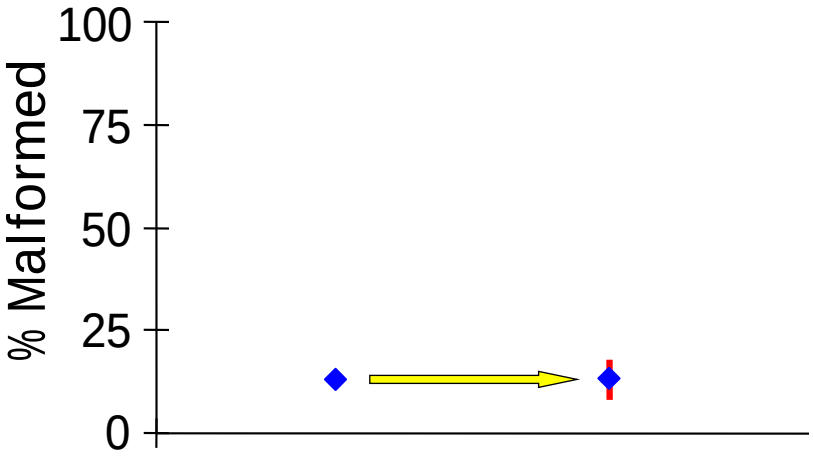

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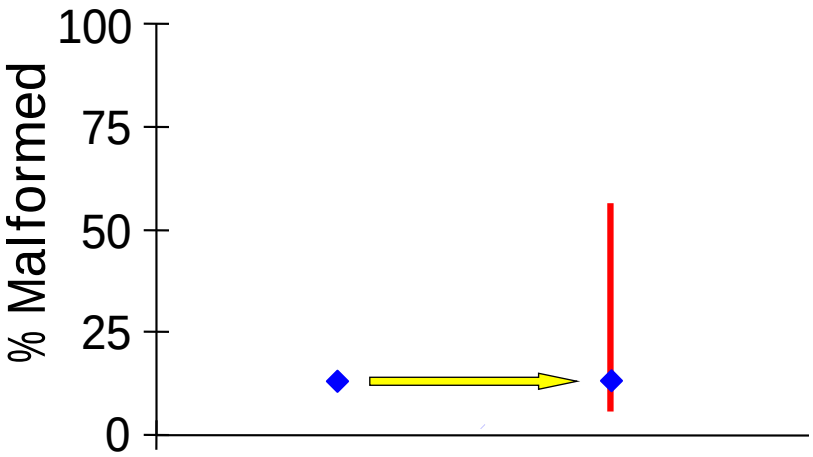

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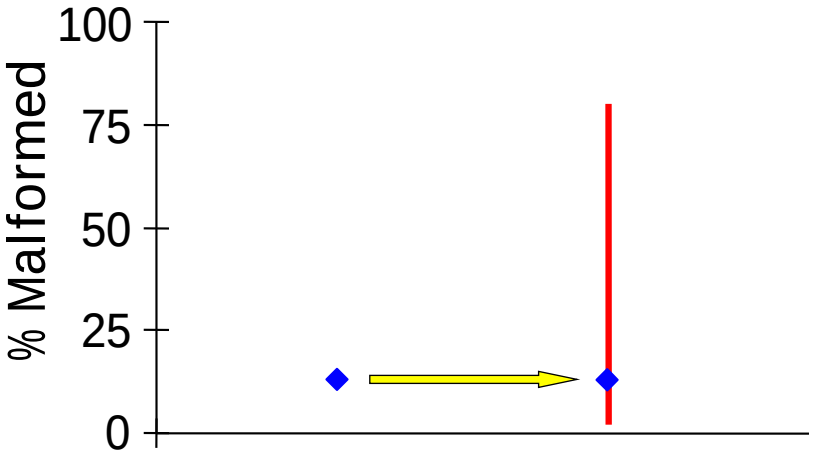


Reducing Uncertainty

- Consider all relevant data
- Weigh evidence on basis of quality, consistency and clinical relevance
- Integrate all available information into the clinical assessment

Interpreting Information from Multiple Studies

- Formal meta-analysis
- Expert consensus
- Flying by the seat of your pants

Formal Meta-analysis

- Systematic approach to identifying, evaluating, synthesizing and combining the results of relevant studies in a particular area

Formal Meta-analysis

- May permit quantitative conclusions that cannot be drawn from individual studies to emerge from multiple studies
- Effects of biases and limitations of individual studies can be assessed

Formal Meta-analysis

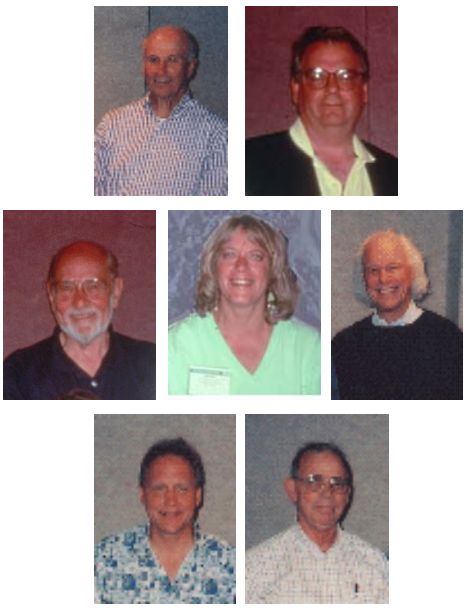
- "Statistical alchemy for the 21st century"
  …Alvan Feinstein
  - Garbage in, garbage out
  - Mixing apples and oranges
  - The file drawer problem

Expert Consensus

- Can simultaneously evaluate studies of different types, sizes, and quality, including non-epidemiological studies

Expert Consensus

- Consensus is qualitative, not rigorously quantitative
- Consensus depends on who is making it



TERIS

The Teratogen Information System

Flying by the Seat of Your Pants

- Quality depends on who is doing the flying
- Can be done quickly and cheaply (often not well)
- Difficult and time consuming to do well

The Problem

Clinical teratologists and epidemiologists speak different languages and dance to different tunes.

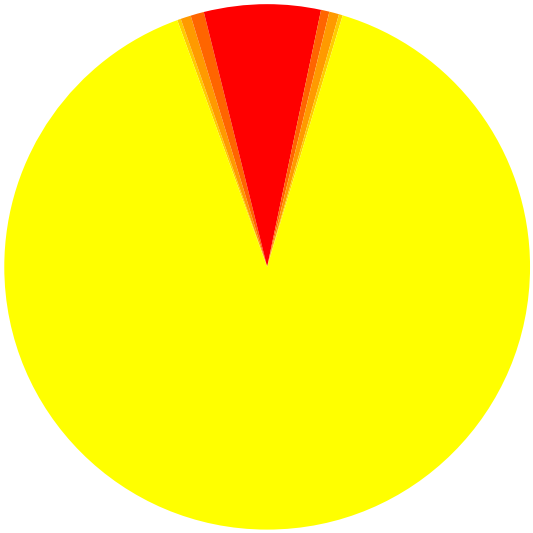
Clinical Teratologists Like

- Lots of data
- Statements of absolute risk
- No “ifs”, “ands” or “buts”
- Good news (no adverse effect)

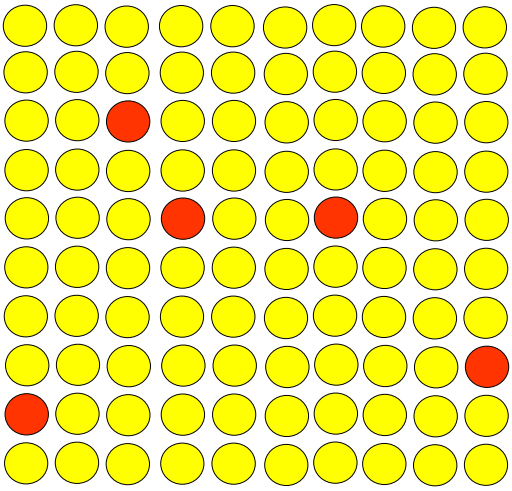
Epidemiologists Like

- Novel problems (no data)
- Statements of relative risk
- Consideration of possible bias, interaction and effect modification (“ifs”, “ands” and “buts”)
- Bad news (large effects)

The Epidemiologist's World



The Clinical Teratologist's World



Uncertainty of the Risk Estimate

- Uncertainty is greatest when no information on the teratogenic risk is available

Lack of Knowledge Is a Problem

- Many teratogenic risks remain unrecognized
- Babies and their mothers are being harmed unnecessarily

Lack of Knowledge Is a Problem

- Pregnant women may be advised or choose to terminate their pregnancies to avoid risk

Lack of Knowledge Is a Problem

- Pregnant women may not receive treatments that benefit their own health or that of the fetus

Lack of Knowledge Is a Problem

- Teratogenic risk of 468 drugs approved 1980-2000 evaluated by TERIS expert Advisory Board
- Risk undetermined for 427 (91.2%) of treatments

Lo & Friedman, Obstet Gynecol 100:465-73, 2002

Not Using the Knowledge We Have Is Also a Problem

- Many preventable birth defects continue to occur

Prevention of Teratogenic Exposures

- Physician information and education
- Public education
- Regulation
- Folic acid fortification / supplementation

Prevention of Teratogenic Exposures

- Immunization
  - Rubella
  - Varicella
- Recognition of affected child
  - Recurrent exposure
  - Genetic predisposition

Prevention of Teratogenic Exposures

- We can't prevent teratogenic exposures until we know what they are.
- We don't know what exposures are teratogenic in humans until babies have been harmed.

How Should We Look For Teratogenic Effects?

- Case reports
- Clinical series
- Pregnancy registries
- Cohort studies
- Case-control studies
- Record linkage studies

If You Are in Bed
With The Devil…

Make The Most of It!