

# The limits of scientific expertise for public decision-making.



## The case of Toxicology

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Presentation based on Christina Rudén's thesis: Rudén, C. (2002) "From Data to Decision. A case study of controversies in cancer risk assessment" Karolinska University Press, Stockholm, Sweden.  
IDDR, Paris Dec 3-4, 2002



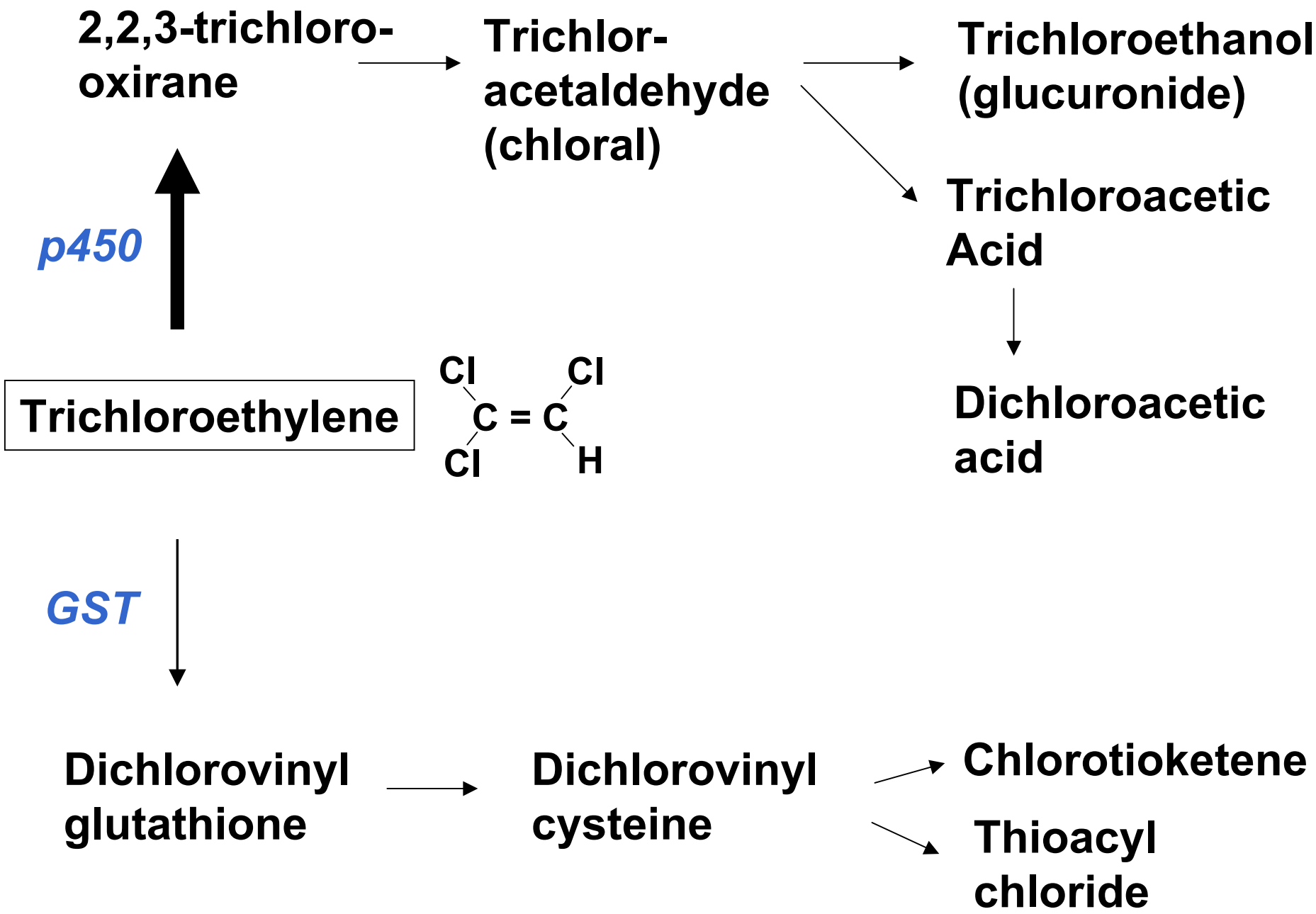
# The trichloroethylene case study

- A detailed comparison of 29 carcinogen risk assessments made of trichloroethylene in Europe and North America from 1973 to 2001.



# Main questions

- Why do risk assessors come to different conclusions?
- How are primary scientific data used for risk assessment purposes?
- How is scientific uncertainty handled in the risk assessment process?



# Cancer Risk Assessment Index (CRAI)

- |                                  |       |
|----------------------------------|-------|
| (1) Data from animal experiments | - / + |
| (2) Human data (epidemiology)    | - / + |
| (3) Human cancer risk            | - / + |



All trichloroethylene risk assessments belonged to one of four groups:

- - -

+ - -

+ - +

+ + +

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+ - -

+ - +

+ + +

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**NIOSH** (-73)

**IARC** (-76)

**NIOSH** (-78)

**IMM/SNV**

**HSE** (-82)

**IARC** (-79)

**Nord.EG** (-79)

(-90)

**VROM** (-84)

**AMI/CG** (-81)

**US EPA** (-85)

**IARC** (-95)

**ACGIH** (-89)

**WHO** (-85)

**IMM/SNV** (-86)

**DFG** (-96)

**ACGIH** (-92)

**IARC** (-87)

**US EPA** (-88)

**MAK** (-96)

**ACGIH** (-96)

**CEC** (-90)

**ATSDR/EPA** (-89)

**AMI** (-91)

**Can.EPA** (-93)

**GDCh** (-94)

**OECD/EU** (-96)

**ECETOC** (-94)

**ATSDR** (-97)

**HSIA** (-96)



# Hypotheses

- Data availability (time dependent)
- Data selection
- Interpretation of individual study results
- Evaluation of study quality
- Methods for species extrapolation
- Policy considerations

# Data availability

- - -

+ - -

+ - +

+++

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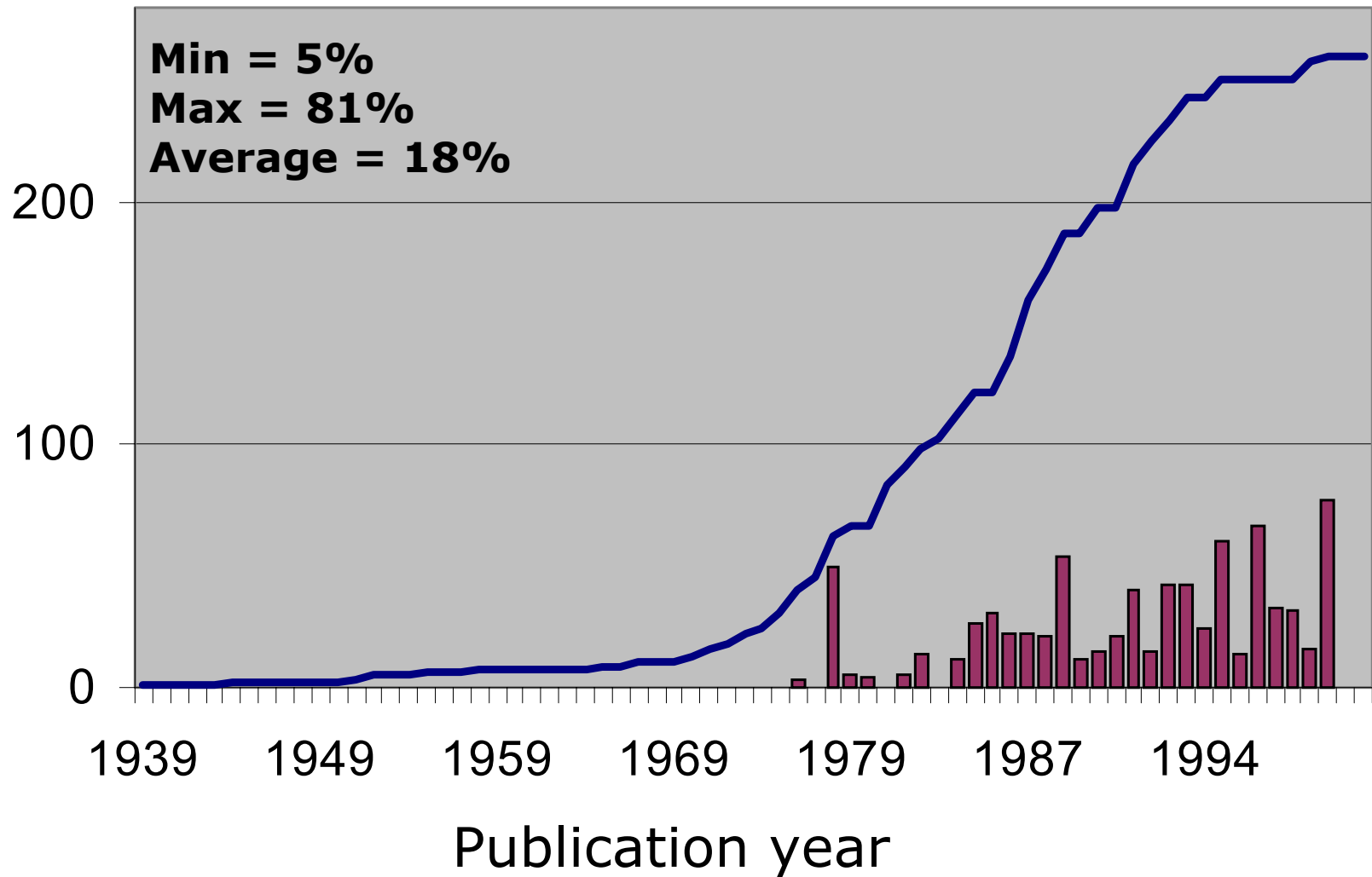
**ECETOC** (-94)

**ATSDR** (-97)

**HSIA** (-96)

# Data selection

Number of available primary references



# Interpretation of results

(The NTP example)

NTP (1983) 1990:

"...epichlorohydrin free trichloroethylene caused renal tubular-cell neoplasms in male 344/N rats, produced toxic nephrosis in both sexes, and shortened the survival time of males. This experiment in male 344/N rats was considered to be inadequate to evaluate the presence or absence of a carcinogenic response to trichloroethylene..."  
(NTP Technical Report 243).

# Interpretation of results

(The NTP example)

■ IARC 1987 (+ - -)

The renal tumors are  
not mentioned.

■ IARC 1995 (++++)

”An increased  
incidence of renal  
tubular cell  
adenocarcinomas  
was seen in males...”

# Interpretation of results – statistics (The NTP example)

■ IMM 1986 (+ - +)

”A **marginal, non-significant** increase in renal tumors.”

■ IMM 1990 (++++)

”... a **dose-related** increase in tubular adenocarcinoma was noted...this increase was **statistically significant** based on the incidence in surviving animals...”

# Interpretation of results

(The Henschler et al. example)

- ”These results cannot be taken as a proof of a carcinogenic potential...nor can this be convincingly excluded.” (Henschler et al 1980)
- “...negative results in ... mice and in rats and hamsters.” (IARC 1987, p. 364)
  - “Histopathological examination...indicated increased age-adjusted incidences of lymphomas in treated female mice: 9/29 controls, 17/30 at the low dose ( $p < 0.001$ ) and 18/28 ( $p = 0.01$ ) at the high dose.” (IARC 1995, p.107)



# Species extrapolation

- Default assumption: Effects seen in experimental species are relevant to humans.
- Criteria for deviation: If "the mechanism of experimental tumor formation is clearly identified with good evidence that this process cannot be extrapolated to man", then the substance should not be classified as a carcinogen.



# The EU process for classification and labelling (1996-2000)

- Contradicting data
- Data obtained from non-validated methods
- How to handle lack of data



# Contradicting data

Study 1: According to OECD guidelines,  
i.p. route of exposure.  
(Negative)

Study 2: Not according to OECD guidelines,  
inhalation route of exposure.  
(Positive)



# Conclusions (1)

- Scientific uncertainty inherent in testing and risk assessment leads to a wide scope of (scientifically acceptable) interpretations of toxicological data.
- The scope of possible interpretation is usually not described in risk assessments.



# Conclusions (2)

- Controversies among risk assessors relates in many cases to policy-related issues. I.e. issues that cannot readily be resolved by further (toxicological) research.
- Important differences concern where to put the burden of proof and what degree of prudence is motivated in the assessment.



# Conclusions (3)

- Further efforts should be made to improve the analysis and reporting of scientific uncertainty in risk assessment.
- Policy-related issues should be more clearly demarcated from purely scientific questions.



# Available data (TCE):

- >9 large epidemiology studies
- 12 chronic/carcinogenicity experiments:
  - Six experiments in mice, five in rats and one in hamsters
- By oral, inhalation and dermal routes



# Conclusions (4)

- Even if a large data set is available, significant uncertainty about a substance's potential to cause harm may still remain.
- Besides further testing of (previously untested) substances, we also need new, science-based methods to do provisional (and prudent) risk assessments, on the basis of a limited amount of data.