NTP
National Toxicology Program

Learning, Memory, and Intelligence Effects

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Learning, Memory, and Intelligence Effects

Level of Evidence Conclusions

- **Animal Studies**
  - Initial time period (>24 hours to 7 days): Moderate level of evidence
  - Intermediate time period (8 days to 1 year): Moderate level of evidence
  - Extended time period (>1 year): Low level of evidence
- **Human Studies**
  - Initial time period (>24 hours to 7 days): Inadequate level of evidence
  - Intermediate time period (8 days to 1 year): Low level of evidence
  - Extended time period (>1 year): Moderate level of evidence

Learning, Memory, and Intelligence Effects

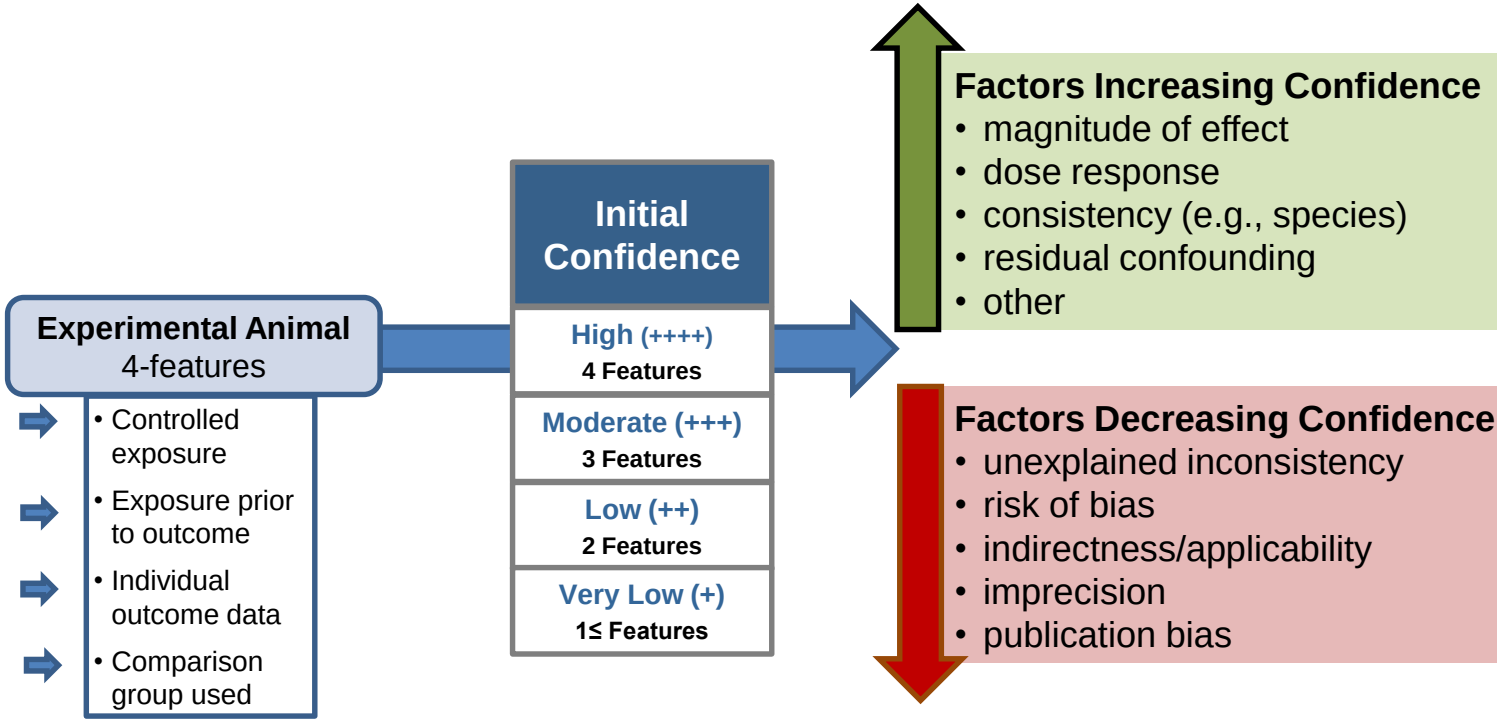
Animal Data

- Bodies of evidence
  - **Initial time period**: 7 studies
  - **Intermediate time period**: 7 studies
  - **Extended time period**: 2 studies
- Effects:
  - **Initial**: Effects on learning and memory
    - Evidence of impaired learning and memory in rats
    - Studies in monkeys were also available, but were limited in their ability to discern effects based on various concerns
  - **Intermediate**: Effects on learning and memory
    - Effects on learning and memory 2–6 weeks after exposure in rats
    - Studies in monkeys were also available, but were limited in their ability to discern effects based on various concerns
  - **Extended**: Inconsistencies in the two studies

Confidence Considerations to Support Level of Evidence

Animal – Learning, Memory, and Intelligence Effects

- **Initial and intermediate time periods:** 7 experimental animal studies
- **Extended time period:** 2 experimental animal studies



Confidence Considerations to Support Level of Evidence

Animal – Learning, Memory, and Intelligence Effects

- unexplained inconsistency
- risk of bias
- indirectness/applicability
- imprecision
- publication bias

- Factors that decreased confidence

All

- Risk of Bias (single study) ↓
  - Probably high for 1–3 key questions (a third with only 1)
  - Most studies probably high risk of bias for details not reported (NR) on multiple questions
  - Downgrades of 1 or 2 levels considered

Initial and Intermediate

- Imprecision ↓
  - Wide confidence intervals and large standard deviations

Extended

- Unexplained Inconsistency ↓

- Factors that increased confidence

Initial and Intermediate

- Dose Response ↑

- magnitude of effect
- dose response
- consistency (e.g., species)
- residual confounding
- other

Learning, Memory, and Intelligence Effects

Learning, Memory, and Intelligence Evidence Profile for Sarin										
INITIAL CONFIDENCE for each body of evidence (# of studies)	**Factors decreasing confidence** "---" if no concern; "↓" if serious concern to downgrade confidence					**Factors increasing confidence** "---" if not present; "↑" if sufficient to upgrade confidence				**FINAL CONFIDENCE RATING**
	Risk of Bias	Unexplained Inconsistency	Indirectness	Imprecision	Publication Bias	Large Magnitude	Dose Response	Residual Confounding	Consistency Species/Model	
Animal										
Initial period - Initial High (7 mammal studies)	↓	---	---	↓	---	---	↑	---	---	**Moderate**
Intermediate period – Initial High (7 mammal studies)	↓	---	---	↓	---	---	↑	---	---	**Moderate**
Extended period – Initial High (2 mammal studies)	↓	↓	---	---	---	---	---	---	---	**Low**

- **<u>Moderate Confidence</u>** that acute sarin exposure is associated with learning and memory effects in animals in the initial and intermediate time periods
- Consistent evidence of effects on learning and memory in rats through 6 weeks after exposure
- **Limitations:** risk-of-bias concerns, small sample size in some studies/groups, and heterogeneity of the data (tests used, outcomes measured, when the outcomes were measured, species tested, and method for administering sarin)

Learning, Memory, and Intelligence Effects

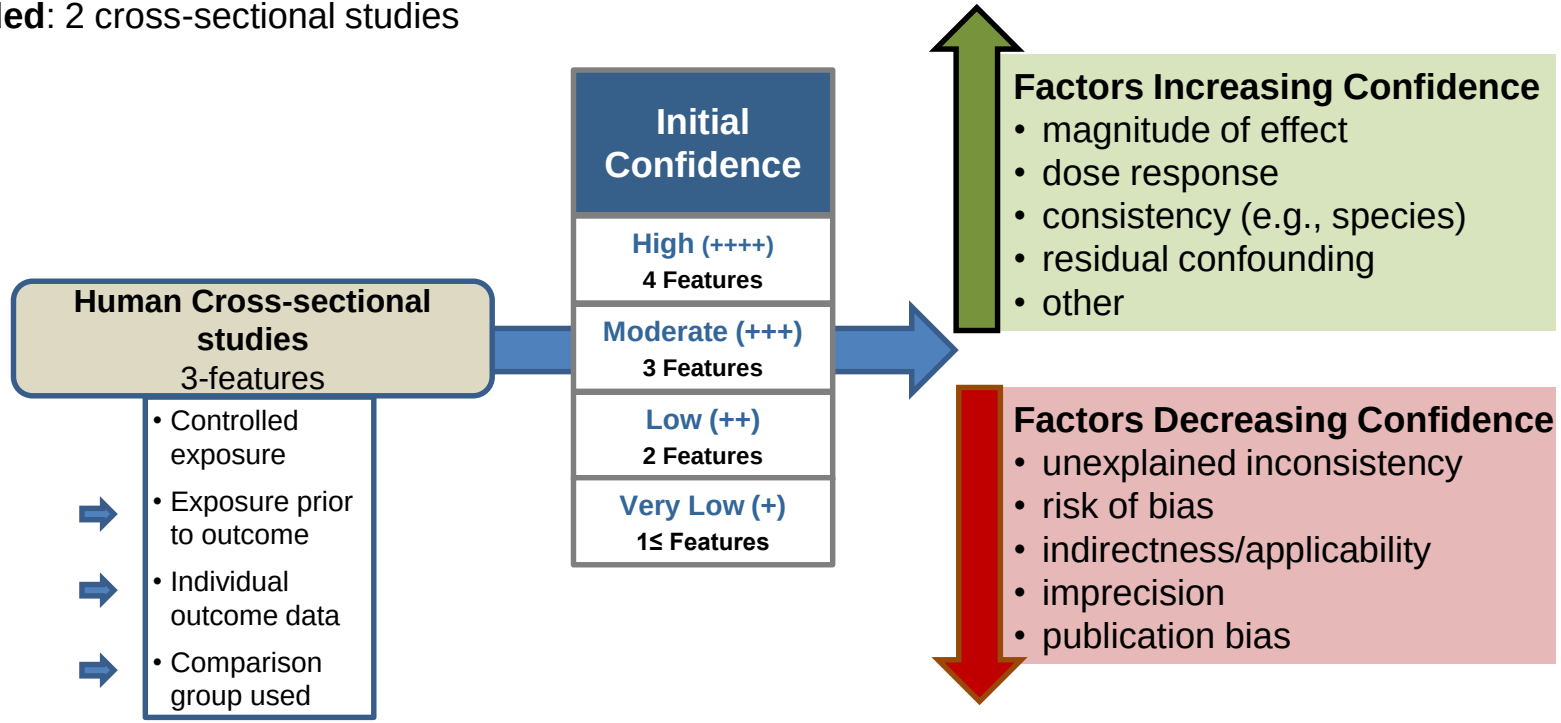
Human Data

- Bodies of evidence
  - **Initial time period**: No studies
  - **Intermediate time period**: 1 cross-sectional study; 2 case reports
  - **Extended time period**: 2 cross-sectional studies; 2 case series
- Effects
  - **Intermediate:** Some evidence of impaired memory
    - Lower digit symbol test scores
    - Self-reported memory issues
  - **Extended**: Some evidence of impaired memory
    - Decreased performance on memory function tests
    - Self-reported memory issues

Confidence Considerations to Support Level of Evidence

Confidence Conclusions Primarily Based on:

- **Initial:** No studies available
- **Intermediate**: 1 cross-sectional study and 2 case reports
- **Extended**: 2 cross-sectional studies



Confidence Considerations to Support Level of Evidence

Human – Learning, Memory, and Intelligence Effects

- Factors that decreased confidence

Intermediate

- Unexplained Inconsistency ↓
  - No ability to evaluate consistency – single study

Extended

- Risk of Bias (case series) ↓
  - Probably high for 1 or 2 key questions
  - Confounding: only considered probably high in one study
  - Outcome assessment: mainly due to lack of blinding of outcome assessors

- unexplained inconsistency
- risk of bias
- indirectness/applicability
- imprecision
- publication bias

- Factors that increased confidence
  - No changes for any factors for all 3 time periods

- magnitude of effect
- dose response
- consistency (e.g., species)
- residual confounding
- other

Learning, Memory, and Intelligence Effects

Learning, Memory, and Intelligence Evidence Profile for Sarin										
INITIAL CONFIDENCE for each body of evidence (# of studies)	**Factors decreasing confidence** "---" if no concern; "↓" if serious concern to downgrade confidence					**Factors increasing confidence** "---" if not present; "↑" if sufficient to upgrade confidence				**FINAL CONFIDENCE RATING**
	Risk of Bias	Unexplained Inconsistency	Indirectness	Imprecision	Publication Bias	Large Magnitude	Dose Response	Residual Confounding	Consistency Species/Model	
Human										
Initial period	No studies available									**No rating**
Intermediate period - Initial Moderate (1 cross-sectional study)	---	↓	---	---	---	---	---	---	---	**Low**
Intermediate period – Initial Low (2 case reports)	---	---	---	---	---	---	---	---	---	**Low**
Extended period – Initial Moderate (2 cross-sectional studies)	---	---	---	---	---	---	---	---	---	**Moderate**
Extended period – Initial Low (2 case series)	↓	---	---	---	---	---	---	---	---	**Very Low**

- **Moderate confidence** that acute sarin exposure is associated with effects on learning, memory, or intelligence years following acute exposure
- **Limitations**: few studies available, small number of subjects or case series with no control for comparison

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Questions?