

# Nervous System Morphological and Histological Effects

Robyn Blain, PhD

Health Sciences Division, ICF  
Contractor to the National Toxicology Program  
National Institute of Environmental Health Sciences



## 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): Inadequate 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): Inadequate level of evidence
- Extended time period (>1 year): Moderate level of evidence



## Animal Data

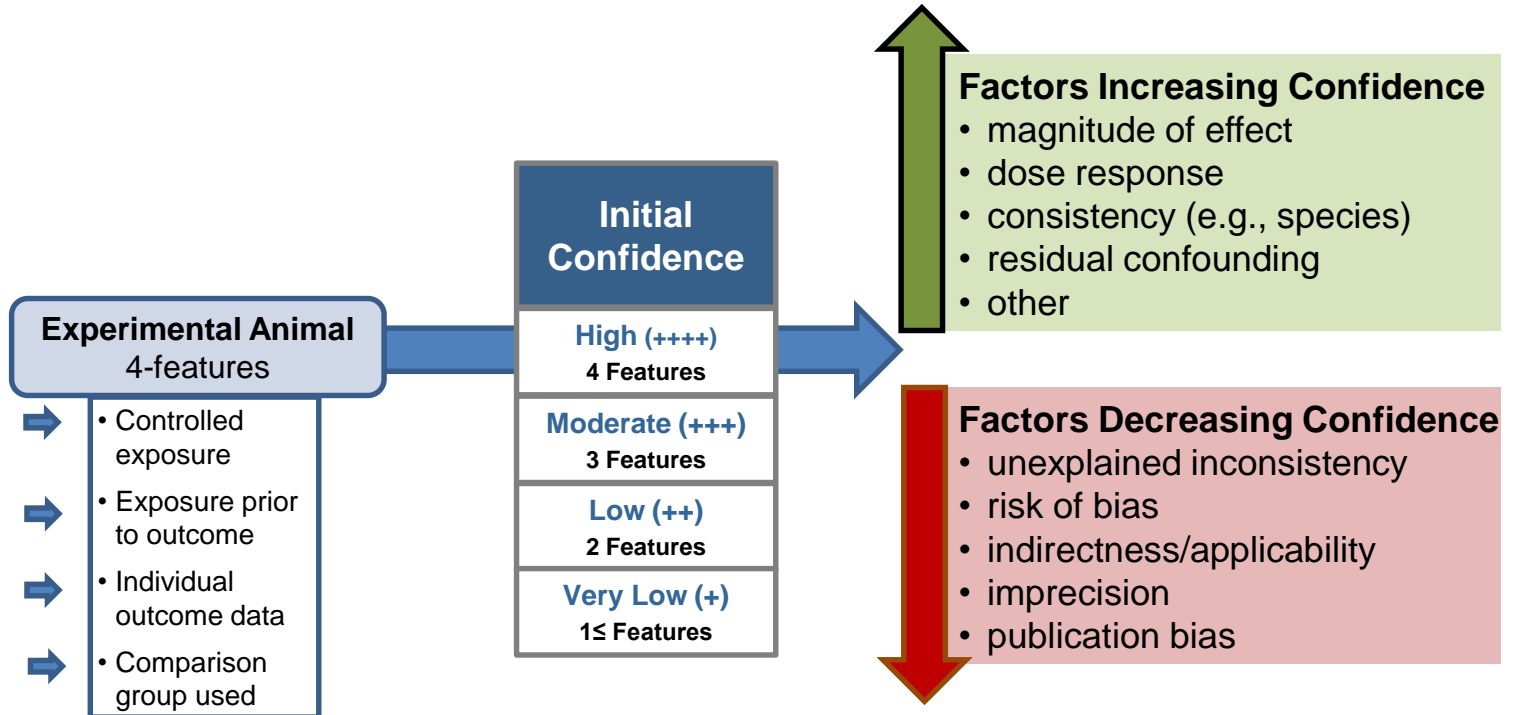
- Bodies of evidence
  - **Initial time period:** 4 studies
  - **Intermediate time period:** 3 studies
  - **Extended time period:** No studies
- Effects:
  - **Initial:** Brain damage reported in the first week
    - Different histopathological changes reported. Some examples include:
      - Brain damage
      - Cell death or necrotic cells in the piriform cortex and/or hippocampus
      - Neural degeneration
  - **Intermediate:** changes in brain histopathology through three months
    - Different histopathological changes reported. Some examples include:
      - Complete degeneration of the CA1 cell layer
      - Severe necrosis in the CA2 and CA3 regions
      - Severe neuronal necrosis



# Confidence Considerations to Support Level of Evidence

## Animal – Morphological and Histological Effects

- **Initial time period:** 4 experimental animal studies
- **Intermediate time period:** 3 experimental animal studies





# Confidence Considerations to Support Level of Evidence

## Animal – Morphological and Histological Effects


- Factors that decreased confidence


**Initial and Intermediate**

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

- Factors that increased confidence

- No changes for any factors for all 3 time periods

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

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



# Morphological and Histological Effects

Morphological and Histological Effects 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	
<i>Animal</i>										
<b>Initial period - Initial High</b> (4 mammal studies)	↓	---	---	---	---	---	---	---	---	<b>Moderate</b>
<b>Intermediate period – Initial High</b> (3 mammal studies)	↓	---	---	---	---	---	---	---	---	<b>Moderate</b>
<b>Extended period</b>	No studies available									<b>No rating</b>

- **Moderate Confidence** that acute sarin exposure is associated with nervous tissue effects in animals in the initial and intermediate time periods
- Consistent evidence of histological changes in the brain through 3 months
- **Limitations:** risk-of-bias concerns, small sample size for many studies or times, and heterogeneity of the data (lesions reported and method for administering sarin); also methods used to detect an effect are limited and may miss changes



## Human Data

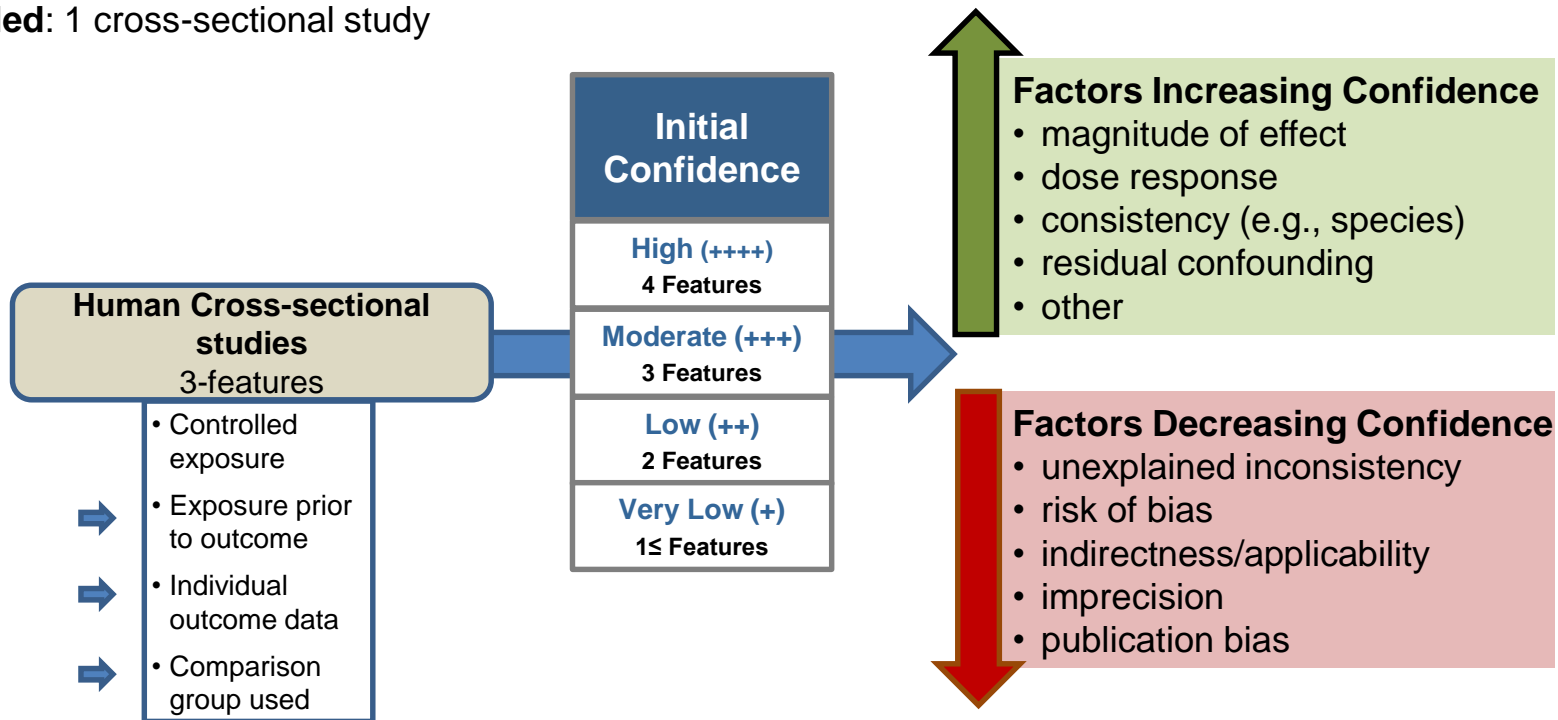
- Bodies of evidence
  - **Initial time period:** No studies
  - **Intermediate time period:** 1 case report
  - **Extended time period:** 1 cross-sectional study and 1 case report
- Effects
  - **Intermediate:** No changes in the standard MRI examination of the brain and spine at 8 months
  - **Extended:** Morphological changes in the brain years after exposure
    - Voxel-based morphometry demonstrated reduced regional gray matter volume in the right insular and temporal cortices with diffusion tensor MRI
    - Reduction in large and small myelinated fibers with preferential loss of large myelinated fibers of the sural nerve observed during autopsy 15 months after exposure in subject that never regained consciousness



# Confidence Considerations to Support Level of Evidence

## Confidence Conclusions Primarily Based on:

- **Initial:** No studies available
- **Intermediate:** 1 case report
- **Extended:** 1 cross-sectional study









# Confidence Considerations to Support Level of Evidence

## Human – Morphological and Histological Effects

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

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

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



# Morphological and Histological Effects

Morphological and Histological Effects 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	
<i>Human</i>										
<b>Initial period</b>	No studies available.									<b>No rating</b>
<b>Intermediate period - Initial Low</b> (1 case report)	---	---	---	---	---	---	---	---	---	<b>Low</b>
<b>Extended period – Initial Moderate</b> (1 cross-sectional study)	---	---	---	---	---	---	---	---	---	<b>Moderate</b>
<b>Extended period – Initial Low</b> (1 case report)	---	---	---	---	---	---	---	---	---	<b>Low</b>

- **Moderate confidence** that acute sarin exposure is associated with morphological and histological changes in the brain years following acute exposure
- **Limitations:** Few studies available with small number of subjects



## 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): Inadequate 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): Inadequate level of evidence
- Extended time period (>1 year): Moderate level of evidence



---

Questions?