Learning, Memory, and Intelligence Effects

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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
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
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

#### Experimental Animal
- 4-features
  - Controlled exposure
  - Exposure prior to outcome
  - Individual outcome data
  - Comparison group used

#### Initial Confidence
- **High (++++)** 4 Features
- **Moderate (+++)** 3 Features
- **Low (++)** 2 Features
- **Very Low (+)** 1± Features

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

#### Factors Decreasing Confidence
- unexplained inconsistency
- risk of bias
- indirectness/applicability
- imprecision
- publication bias
Confidence Considerations to Support Level of Evidence

Animal – Learning, Memory, and Intelligence Effects

Factors that decreased confidence

- 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

- Imprecision
  - Wide confidence intervals and large standard deviations

- Unexplained Inconsistency

Factors that increased confidence

- Dose Response

**Initial and Intermediate**
- All

**Extended**
- Unexplained inconsistency
  - risk of bias
  - indirectness/applicability
  - imprecision
  - publication bias

**Initial and Intermediate**
- magnitude of effect
  - dose response
  - consistency (e.g., species)
  - residual confounding
  - other
### Learning, Memory, and Intelligence Evidence Profile for Sarin

<table>
<thead>
<tr>
<th>INITIAL CONFIDENCE for each body of evidence (# of studies)</th>
<th>Factors decreasing confidence</th>
<th>Factors increasing confidence</th>
<th>FINAL CONFIDENCE RATING</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Animal</strong></td>
<td>Risk of Bias</td>
<td>Unexplained Inconsistency</td>
<td>Indirectness</td>
</tr>
<tr>
<td>Initial period - Initial High (7 mammal studies)</td>
<td>↓</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Intermediate period – Initial High (7 mammal studies)</td>
<td>↓</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Extended period – Initial High (2 mammal studies)</td>
<td>↓</td>
<td>↓</td>
<td>---</td>
</tr>
</tbody>
</table>

- **Moderate Confidence** 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).
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

### Factors Decreasing Confidence
- unexplained inconsistency
- risk of bias
- indirectness/applicability
- imprecision
- publication bias

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

### Human Cross-sectional studies
- Controlled exposure
- Exposure prior to outcome
- Individual outcome data
- Comparison group used

### Initial Confidence
- **High (++++)**: 4 Features
- **Moderate (+++)**: 3 Features
- **Low (++)**: 2 Features
- **Very Low (+)**: 1≤ Features
Confidence Considerations to Support Level of Evidence

Human – Learning, Memory, and Intelligence Effects

• Factors that decreased confidence
  - Unexplained Inconsistency
    - No ability to evaluate consistency – single study
  - 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

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

Intermediate

Extended

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

- magnitude of effect
- dose response
- consistency (e.g., species)
- residual confounding
- other
Learning, Memory, and Intelligence Effects

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<tr>
<th>INITIAL CONFIDENCE for each body of evidence (# of studies)</th>
<th>Factors decreasing confidence “---” if no concern; “↓” if serious concern to downgrade confidence</th>
<th>Factors increasing confidence “---” if not present; “↑” if sufficient to upgrade confidence</th>
<th>FINAL CONFIDENCE RATING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of Bias</td>
<td>Unexplained Inconsistency</td>
<td>Indirectness</td>
<td>Large Magnitude</td>
</tr>
<tr>
<td>Initial period</td>
<td>No studies available</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate period - Initial Moderate (1 cross-sectional study)</td>
<td>---</td>
<td>↓</td>
<td>---</td>
</tr>
<tr>
<td>Intermediate period – Initial Low (2 case reports)</td>
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<td>---</td>
</tr>
<tr>
<td>Extended period – Initial Moderate (2 cross-sectional studies)</td>
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<td>Extended period – Initial Low (2 case series)</td>
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- **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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Level of Evidence Conclusions

- **Animal Studies**
  - Initial time period (>24 hours to 7 days): Moderate level of evidence
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  - 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
Questions?