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
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

**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

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 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
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).
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

### 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

3-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 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

Confidence Considerations to Support Level of Evidence

- Unexplained inconsistency
- Risk of bias
- Indirectness/applicability
- Imprecision
- Publication bias

Extended

Intermediate

Human – Learning, Memory, and Intelligence Effects

Effects

- 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 “---” 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>Imprecision</td>
</tr>
<tr>
<td>Human</td>
<td></td>
<td></td>
<td></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>
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</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>---</td>
</tr>
<tr>
<td>Extended period – Initial Low (2 case series)</td>
<td>↓</td>
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<td>---</td>
</tr>
</tbody>
</table>

- **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
Level of Evidence Conclusions

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Questions?