Changes in Cholinesterase Levels

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Changes in Cholinesterase Levels

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): High level of evidence
  – Intermediate time period (8 days to 1 year): Inadequate level of evidence
  – Extended time period (>1 year): Inadequate level of evidence
Changes in Cholinesterase (ChE) Levels

Animal Data

• Bodies of evidence
  – Initial time period: 11 studies
  – Intermediate time period: 8 studies
  – Extended time period: No studies identified

• Effects:
  – Initial: Lower ChE levels
    • Consistently lower ChE in blood/plasma in rats and monkeys, data on brain levels more heterogeneous
  – Intermediate: Lower ChE levels reported weeks to months
    • Decreased ChE activity blood in rats and monkeys in early weeks; fewer significant effects at later time periods of weeks to months
    • Decreased ChE activity in different brain regions; no effect found in some studies
    • Some evidence of compensatory upregulation of ChE brain activity weeks to months following acute exposure
  – Extended: No studies
**Animal – Changes in Cholinesterase**

- **Initial time period:** 11 studies
- **Intermediate time period:** 7 studies
- **Extended time period:** no studies

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<table>
<thead>
<tr>
<th>Factors Decreasing Confidence</th>
<th>Factors Increasing Confidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>unexplained inconsistency</td>
<td>magnitude of effect</td>
</tr>
<tr>
<td>risk of bias</td>
<td>dose response</td>
</tr>
<tr>
<td>indirectness/applicability</td>
<td>consistency (e.g., species)</td>
</tr>
<tr>
<td>imprecision</td>
<td>residual confounding</td>
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<tr>
<td>publication bias</td>
<td>other</td>
</tr>
</tbody>
</table>

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**Initial Confidence**

<table>
<thead>
<tr>
<th>Level</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>++++</td>
</tr>
<tr>
<td>Moderate</td>
<td>+++</td>
</tr>
<tr>
<td>Low</td>
<td>++</td>
</tr>
<tr>
<td>Very Low</td>
<td>+</td>
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</tbody>
</table>

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**Experimental Animal**

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

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**Confidence Considerations to Support Level of Evidence**

- **Initial confidence:**
  - Controlled exposure
  - Exposure prior to outcome
  - Individual outcome data
  - Comparison group used

---

**Initial time period:**

- 11 studies

**Intermediate time period:**

- 7 studies

**Extended time period:**

- No studies
Factors that could decrease confidence

- Risk of Bias
  - Probably high for 1 key question (randomization, exposure characterization, or outcome assessment) in lowest risk of bias studies (e.g., Pearce 1999; RamaRao 2011)
  - Most studies probably high risk of bias for details not reported (NR) on multiple questions
  - Downgrades of 1 or 2 levels considered

- No changes for other factors that could decrease confidence
Confidence Considerations to Support Level of Evidence

- Factors that decreased confidence
  - Risk of Bias
    - Probably high for 1 key question in low risk of bias studies
    - Most studies probably high risk of bias for details not reported (NR) on multiple questions

- Factors that increased confidence
  - Large Magnitude (*upgrade considered*)
    - ChE Suppression range 10-85%, heterogeneous data
  - Dose Response (*upgrade considered*"
    - Greater suppression with higher dose in some studies or across studies
  - Consistency (*upgrade considered*)
    - Suppression in rodents and primates, heterogeneous data

*Decision not to upgrade due to multiple risk of bias concerns
Changes in Cholinesterase Levels

<table>
<thead>
<tr>
<th>Cholinesterase Evidence Profile for Sarin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Factors decreasing confidence</strong></td>
</tr>
<tr>
<td>“---” if no concern; “↓” if serious concern to downgrade confidence</td>
</tr>
</tbody>
</table>

**INITIAL CONFIDENCE**

for each body of evidence

(# of studies)

<table>
<thead>
<tr>
<th>Risk of Bias</th>
<th>Unexplained Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Publication Bias</th>
<th>Large Magnitude</th>
<th>Dose Response</th>
<th>Residual Confounding</th>
<th>Consistency Species/Model</th>
<th>FINAL CONFIDENCE RATING</th>
</tr>
</thead>
</table>

**Animal**

<table>
<thead>
<tr>
<th>Period</th>
<th>Data Points</th>
<th>Risk of Bias</th>
<th>Unexplained Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Publication Bias</th>
<th>Large Magnitude</th>
<th>Dose Response</th>
<th>Residual Confounding</th>
<th>Consistency Species/Model</th>
<th>Confidence Rating</th>
</tr>
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<tbody>
<tr>
<td>Initial period - Initial High (11 mammal studies)</td>
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<tr>
<td>Intermediate period – Initial High (8 mammal studies)</td>
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<tr>
<td>Extended period No studies</td>
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- **Moderate Confidence** that acute sarin exposure is associated with suppression of ChE blood and brain levels in animals in the initial and intermediate time periods.
- Consistent evidence of suppression of ChE within days following acute sarin exposure, but the length of the suppression varied by study, and there was less evidence for suppression 1 week to 90 days.
- **Limitations:** risk-of-bias concerns, small sample sizes (n = 2–6 for most studies), and heterogeneity of the data (outcomes measured, when the outcomes were measured, the species or strain used, and method for administering sarin).
Changes in Cholinesterase Levels

Human Data

• Bodies of evidence
  – **Initial time period**: 2 non-randomized controlled trials, 2 case reports/series
  – **Intermediate time period**: 6 case reports/series
  – **Extended time period**: 1 cross-sectional study

• Effects:
  – **Initial**: Consistent evidence of lower ChE in blood/plasma 1–7 days following exposure
  – **Intermediate**: Consistent evidence of lower ChE in blood/plasma weeks to months following exposure
  – **Extended**: One cross-sectional study provided no evidence of changes in ChE >1 year following exposure
Confidence Considerations to Support Level of Evidence

Confidence Conclusions Primarily Based on:

- **Initial**: 2 controlled trial
- **Intermediate**: 6 case-reports
- **Extended**: 1 cross-sectional

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

- **Human Controlled Trial**
  - 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
Confidence Considerations to Support Level of Evidence

Confidence Conclusions Primarily Based on:

- **Initial**: 2 controlled trial
- **Intermediate**: 6 case-reports
- **Extended**: 1 cross-sectional

### Initial Confidence

- **High (++++)**: 4 Features
  - magnitude of effect
  - dose response
  - consistency (e.g., species)
  - residual confounding
  - other

- **Moderate (+++)**: 3 Features
  - Human Case Reports/Series
    - 2-features
    - Controlled exposure
    - Exposure prior to outcome
    - Individual outcome data
    - Comparison group used

- **Low (++)**: 2 Features
- **Very Low (+)**: 1≤ Features

### Factors Decreasing Confidence

- unexplained inconsistency
- risk of bias
- indirectness/applicability
- imprecision
- publication bias
Factors that could decrease confidence

Risk of Bias

- 2 controlled exposure studies (Baker 1996, Grob 1958) probably high for 1 key question
  - Randomization: not applicable in Baker, subjects served as own control; not reported for Grob
  - Exposure characterization: probably low for Baker; probably high for Grob due to 90% purity sarin; remaining 10% stated to potentially have anticholinesterase activity
  - Outcome assessment: definitely low or probably low for ChE detection methods. Blinding of outcome assessors not reported (NR). Overall rating NR based on lack of blinding.

Case reports and case series; probably high for 1 key question

- Confounding: no indication accounted for studies
- Outcome assessment: probably low for 3 of 7 studies; probably high for others based on blinding

No changes for other factors that could decrease confidence
Factors that decreased confidence

- Risk of Bias
  - Probably high for 1 key question in 2 controlled trials

Factors that increased confidence

- Large Magnitude
  - Consistent ChE Suppression range 48-66%
High confidence that acute sarin exposure suppresses ChE blood levels in humans over the initial period of 1–7 days following acute sarin exposure.

High confidence for suppressed ChE in the days following acute exposure is supported by the well-established response for immediate ChE inhibition in the first 24 hours following acute sarin exposure.

Limitations: risk-of-bias concerns, small sample sizes (n = 8–10 for the controlled trials), and uncertainties related to study design for the case reports/series.
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Level of Evidence Conclusions

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• **Human Studies**
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  – Extended time period (>1 year): Inadequate level of evidence
Questions?