Visual and Ocular Effects

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National Institute of Environmental Health Sciences
Level of Evidence Conclusions

• Animal 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): Inadequate level of evidence

• Human 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
Visual and Ocular Effects

Animal Data

- Bodies of evidence
  - **Initial time period**: 3 studies
  - **Intermediate time period**: 1 study
  - **Extended time period**: 1 study

- Effects:
  - **Initial**: No or inconsistent effects reported
    - No effects on pupil diameter in rats at 1–7 days in 2 studies
    - Increased pupil diameter in rats at 1–7 days in 1 study (Mioduszewski 2002)
      (pattern of effect does not correspond to human data and not clear if it is adverse or reflects recovery)
  - **Intermediate and Extended**: No effects observed
    - No effects on visual functional observational battery scores in 1 study (Kassa 2001)
      3–12 months after acute sarin exposure
### Confidence Considerations to Support Level of Evidence

#### Animal – Visual and Ocular Effects

- **Initial time period:** 3 experimental animal studies
- **Intermediate and Extended time periods:** 1 experimental animal study

#### 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

#### Table: 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>
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<tr>
<td>Low (++)</td>
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</table>

#### Experimental Animal - 4-features
- Controlled exposure
- Exposure prior to outcome
- Individual outcome data
- Comparison group used
Confidence Considerations to Support Level of Evidence

**Animal – Visual and Ocular Effects**

- **Factors that decreased confidence**
  - **Initial**
    - Unexplained Inconsistency
      - Inconsistent results (no effect and increase)
  - **Intermediate and Extended**
    - Unexplained Inconsistency
      - No ability to evaluate consistency – single study
    - Risk of Bias
      - Probably high for all 3 key questions (randomization, exposure characterization, and outcome assessment)

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

---

**Factors that decreased confidence**

- Unexplained Inconsistency
  - Inconsistent results (no effect and increase)

- Unexplained Inconsistency
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**Factors that decreased confidence**

- Unexplained Inconsistency
- Risk of Bias
- Indirectness/applicability
- Imprecision
- Publication bias

**Factors that increased confidence**

- Magnitude of effect
- Dose response
- Consistency (e.g., species)
- Residual confounding
- Other
No or inconsistent visual or ocular effects reported > 24 hours following acute sarin exposure

- Overall, **Inadequate to evaluate potential sarin-related effects** at all time periods based on the limited number of studies, risk-of-bias concerns, and no evidence of an effect that corresponds with the human data.

### Visual and Ocular Evidence Profile for Sarin

<table>
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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>
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<tr>
<td>Animal</td>
<td>Risk of Bias</td>
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<tr>
<td>Initial period - Initial High (3 mammal studies)</td>
<td>---</td>
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</tr>
<tr>
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<td>↓↓↓</td>
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- **Factors decreasing confidence**
  - Risk of Bias
  - Unexplained Inconsistency
  - Indirectness
  - Imprecision
  - Publication Bias

- **Factors increasing confidence**
  - Large Magnitude
  - Dose Response
  - Residual Confounding
  - Consistency Species/Model
Human Data

- Bodies of evidence
  - **Initial time period**: 5 case reports/series
  - **Intermediate time period**: 2 cross-sectional studies; 8 case reports/series
  - **Extended time period**: 1 prospective cohort study; 4 case reports/series

- Effects
  - **Initial**: Consistent evidence for pupil constriction (miosis) and evidence of other symptoms (e.g., blurred vision, ocular pain, difficulty focusing) 1–7 days following exposure
  - **Intermediate**: Consistent evidence for pupil constriction for weeks, suggests persistence following exposure; Then, pupil constriction not found at 1-2 months, suggests recovery
    - Slower visual evoked potentials (VEPs) reported at 6-8 months
    - Other symptoms reported in small percentages of subjects for months
  - **Extended**: Some evidence of symptoms in small percentage of study subjects 1–5 years following exposure
Confidence Considerations to Support Level of Evidence

Confidence Conclusions Primarily Based on:

- **Initial**: 5 case reports/series
- **Intermediate**: 2 cross-sectional studies
- **Extended**: 1 prospective cohort and 4 case reports/series

### Factors Decreasing Confidence

- unexplained inconsistency
- risk of bias
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- imprecision
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### Factors Increasing Confidence

- magnitude of effect
- dose response
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- residual confounding
- other

### Initial Confidence

- **High (++++)**: 4 Features
- **Moderate (+++)**: 3 Features
- **Low (++)**: 2 Features
- **Very Low (+)**: 1≤ Features

### Human Case Reports/Series

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

Confidence Conclusions Primarily Based on:

**Confidence Considerations to Support Level of Evidence**

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Confidence Considerations to Support Level of Evidence

Confidence Conclusions Primarily Based on:

- **Initial**: 5 case reports/series
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**Human Cross-sectional studies**
- 3-features
  - Controlled exposure
  - Exposure prior to outcome
  - Individual outcome data
  - Comparison group used

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**Factors Increasing Confidence**
- magnitude of effect
- dose response
- consistency (e.g., species)
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**Factors Decreasing Confidence**
- unexplained inconsistency
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Confidence Considerations to Support Level of Evidence

Human – Visual and Ocular Effects

• Factors that decreased confidence
  • Risk of Bias (case reports/series)
    – Probably high for 2 key questions in most studies (confounding and blinding of outcome assessors)
  • Risk of Bias (single prospective cohort)
    – Probably high or definitely high for 2 key questions and other serious risk-of-bias concerns

• Factors that increased confidence
  • Magnitude of Effect (upgrade considered*)
  • Consistency

*Decision to upgrade once based on magnitude of effect and consistency collectively, and supported by well-established response of immediate constriction of the pupils in the first 24 hours following acute sarin exposure

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- **Moderate confidence** that acute sarin exposure is associated with visual or ocular effects from days to months following exposure.
- **Limitations**: Risk-of-bias concerns, uncertainties related to study design for the case reports/series.
Level of Evidence Conclusions

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Questions?