Visual and Ocular Effects

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Visual and Ocular Effects

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
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
Animal – Visual and Ocular Effects

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

**Confidence Considerations to Support Level of Evidence**

**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 – Visual and Ocular Effects

- Factors that decreased confidence
  - Unexplained Inconsistency
    - Inconsistent results (no effect and increase)
  - 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
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.

<table>
<thead>
<tr>
<th>INITIAL CONFIDENCE</th>
<th>Factors decreasing confidence</th>
<th>Factors increasing confidence</th>
<th>FINAL CONFIDENCE RATING</th>
</tr>
</thead>
<tbody>
<tr>
<td>for each body of evidence (# of studies)</td>
<td>“---” if no concern; “↓” if serious concern to downgrade confidence</td>
<td>“---” if not present; “↑” if sufficient to upgrade confidence</td>
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<tr>
<td>Risk of Bias</td>
<td>Unexplained Inconsistency</td>
<td>Indirectness</td>
<td>Imprecision</td>
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<tr>
<td>Animal</td>
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<tr>
<td>Initial period - Initial High (3 mammal studies)</td>
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<tr>
<td>Intermediate period – Initial High (1 mammal study)</td>
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<tr>
<td>Extended period – Initial High (1 mammal study)</td>
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</tbody>
</table>
Visual and Ocular Effects

**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 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

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

**Human Case Reports/Series**
- 2-features
  - Controlled exposure
  - Exposure prior to outcome
  - Individual outcome data
  - Comparison group used
Confidence Considerations to Support Level of Evidence

Confidence Conclusions Primarily Based on:

- **Initial**: 5 case reports/series
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- magnitude of effect
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**Initial Confidence**

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

**Human Cross-sectional studies**

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

**Confidence Conclusions Primarily Based on:**

- moderate evidence (+++)
  - 3 Features
- low evidence (++)
  - 2 Features
- very low evidence (+)
  - 1≤ Features
- high evidence (++++)
  - 4 Features
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
### Visual and Ocular Evidence Profile for Sarin

#### INITIAL CONFIDENCE for each body of evidence (# of studies)

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk of Bias</th>
<th>Unexplained Consistency</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>
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</table>

- **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
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Questions?