Overall Hazard Conclusions

Andrew A. Rooney, PhD

Office of Health Assessment and Translation (OHAT)
National Institute of Environmental Health Sciences
Methods for Developing NTP Monographs

Evidence Integration: Developing Hazard Conclusions

(1) **Initial Hazard Conclusion**
Consider human and animal evidence together

(1) **Final Hazard Conclusion**
Consider impact of other relevant data such as relevant mechanistic data and biological plausibility of effect

Assess if there is:
- Strong support to increase hazard ID
- Strong opposition to decrease hazard ID
- Or not impact the hazard ID
Integrate Evidence to Develop Hazard Conclusions

- Hazard conclusions developed for 3 post-exposure time periods
  - Initial (>24 hours to 7 days):
  - Intermediate (8 days to 1 year):
  - Extended (>1 year):

- Conclusions with highest level of evidence for each time period used to reach the overall conclusions
Hazard Conclusions for Acute Sarin Exposure

Integrate Evidence to Develop Hazard Conclusions

- **Initial time period**
  - >24 hours to 7 days following sarin exposure

- **Changes in cholinesterase levels**
  - Animal: Moderate level of evidence
  - Human: High level of evidence
  - Initial hazard: Known to be a neurological hazard to humans conclusion
  - Final hazard conclusion* *Known to be a neurological hazard to humans* in the initial time period

>24 hours to 7 days after exposure based on suppression of cholinesterase

*after consideration of biological plausibility
Hazard Conclusions for Acute Sarin Exposure

Consideration of Other Relevant Data and Biological Plausibility

• Changes in cholinesterase
  – Well established that sarin binds to and inactivates ChE
  – Sarin-ChE complex undergoes irreversible dealkylation that permanently inhibits enzyme function
  – Build-up of the acetylcholine is associated with the cholinergic effects observed with higher exposures to sarin
  – Can take up to 3 months for the ChE to regenerate and therefore, Initial and Intermediate time periods

• Upgrade considered for potentially strong support from other relevant data for biological plausibility of effect
  – Already “Known to be hazard to humans”

Final Hazard Conclusion
Consider impact of other relevant data such as relevant mechanistic data and biological plausibility of effect

Assess if there is:
• Strong support to increase hazard
• Strong opposition to decrease hazard
• Or no impact on the hazard
Hazard Conclusions for Acute Sarin Exposure

Integrate Evidence to Develop Hazard Conclusions

• Intermediate time period
  – 8 days to 1 year following sarin exposure

• Suspected to be neurological hazard to humans based on multiple health effects
  – Suppression of cholinesterase
  – Visual and ocular effects
  – Learning and memory
  – Nervous system morphological and histological changes
Hazard Conclusions for Acute Sarin Exposure

Integrate Evidence to Develop Hazard Conclusions

• Extended time period
  – > 1 year following sarin exposure

• Suspected to be neurological hazard to humans based on multiple health effects
  – Learning and memory
  – Nervous system morphological and histological changes


**Monograph Development**
- The evaluation team

**Draft and DNTP Internal Review**
- John Bucher, NIEHS/DNTP
- Suril Mehta, NIEHS/DNTP
- Kyla Taylor, NIEHS/DNTP
- Mamta Behl, NIEHS/DNTP
- Brandy Beverly, NIEHS/DNTP
- Kembra Howdeshell, NIEHS/DNTP
- Vickie Walker, NIEHS/DNTP
- Windy Boyd, NIEHS/DNTP

**Technical Review**
- Jonathan Newmark, US Army retired

**Protocol Review**
- Roberta Scherer, Johns Hopkins
- Jonathan Newmark, US Army retired

**Management of the Peer Review**
- Mary Wolfe, NIEHS/DNTP
- Elizabeth Maull, NIEHS/DNTP
- Canden Byrd, ICF

---

### Evaluation Team

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrew A Rooney, PhD</td>
<td>NIEHS/DNTP, Project Lead</td>
</tr>
<tr>
<td>David Jett, PhD</td>
<td>NIH/NINDS, Project Lead</td>
</tr>
<tr>
<td>Pamela Lepp, PhD</td>
<td>UC Davis School of Veterinary Medicine</td>
</tr>
<tr>
<td>Alicia Livinski</td>
<td>NIH/OD/ORS</td>
</tr>
<tr>
<td>Constance McKee</td>
<td>I2 Grants Associates, LLC</td>
</tr>
<tr>
<td>Christina C. Niemeyer, PhD</td>
<td>I2 Grants Associates, LLC</td>
</tr>
<tr>
<td>Louise Assem, PhD</td>
<td>ICF</td>
</tr>
<tr>
<td>Robyn Blair, PhD</td>
<td>ICF</td>
</tr>
<tr>
<td>Natalie Blanton, MPH</td>
<td>ICF</td>
</tr>
<tr>
<td>Jeremy S. Frye, MLS</td>
<td>ICF</td>
</tr>
<tr>
<td>Susan Goldhaber, MPH</td>
<td>ICF</td>
</tr>
<tr>
<td>All Goldstone, MPH</td>
<td>ICF</td>
</tr>
<tr>
<td>Pamela Hartman, MEM</td>
<td>ICF</td>
</tr>
<tr>
<td>Kaendra Jones, MPH</td>
<td>ICF</td>
</tr>
<tr>
<td>Courtney Lembert</td>
<td>ICF</td>
</tr>
<tr>
<td>Camryn Lieb</td>
<td>ICF</td>
</tr>
<tr>
<td>Kristen Magnuson, MESM</td>
<td>ICF</td>
</tr>
<tr>
<td>Maureen Malloy</td>
<td>ICF</td>
</tr>
<tr>
<td>Devon Morgan</td>
<td>ICF</td>
</tr>
<tr>
<td>Pam Ross, MSPH</td>
<td>ICF</td>
</tr>
<tr>
<td>Johanna Rochester, PhD</td>
<td>ICF</td>
</tr>
<tr>
<td>Alessandra Schumacher</td>
<td>ICF</td>
</tr>
<tr>
<td>Robert Shin, MIHS</td>
<td>ICF</td>
</tr>
<tr>
<td>Kelly Shipkowski, PhD</td>
<td>ICF</td>
</tr>
<tr>
<td>Christopher Sibrizzi, MPH</td>
<td>ICF</td>
</tr>
<tr>
<td>Nicole Vetter, MLS</td>
<td>ICF</td>
</tr>
<tr>
<td>Ashley R. Williams, MSEE</td>
<td>ICF</td>
</tr>
</tbody>
</table>

---

**Acknowledgments**

- Evaluation Team
Questions?