Overall Hazard Conclusions

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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
Hazard Conclusions for Acute Sarin Exposure

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
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  – Suril Mehta, NIEHS/DNTP
  – Kyla Taylor, NIEHS/DNTP
  – Mamta Behl, NIEHS/DNTP
  – Brandy Beverly, NIEHS/DNTP
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  – Vickie Walker, NIEHS/DNTP
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• Technical Review
  – Jonathan Newmark, US Army retired

• Protocol Review
  – Roberta Scherer, Johns Hopkins
  – Jonathan Newmark, US Army retired

• Management of the Peer Review
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  – Elizabeth Maull, NIEHS/DNTP
  – Canden Byrd, ICF

Acknowledgments

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Questions?