

Overall Hazard Conclusions

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Methods for Developing NTP Monographs

Evidence Integration: Developing Hazard Conclusions

(1) Initial Hazard Conclusion

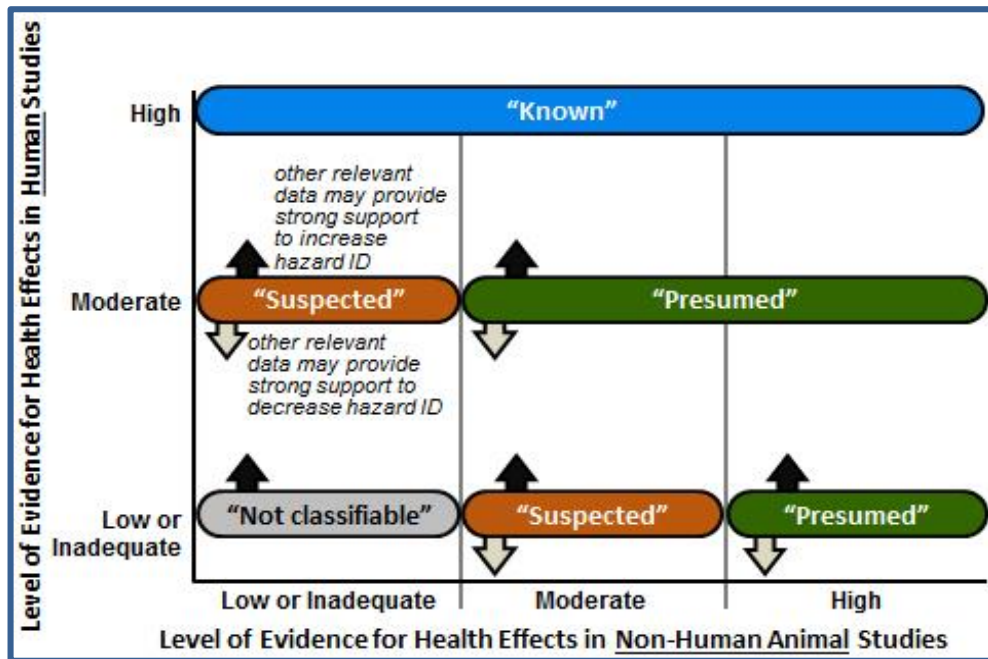
Consider human and animal evidence together

(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

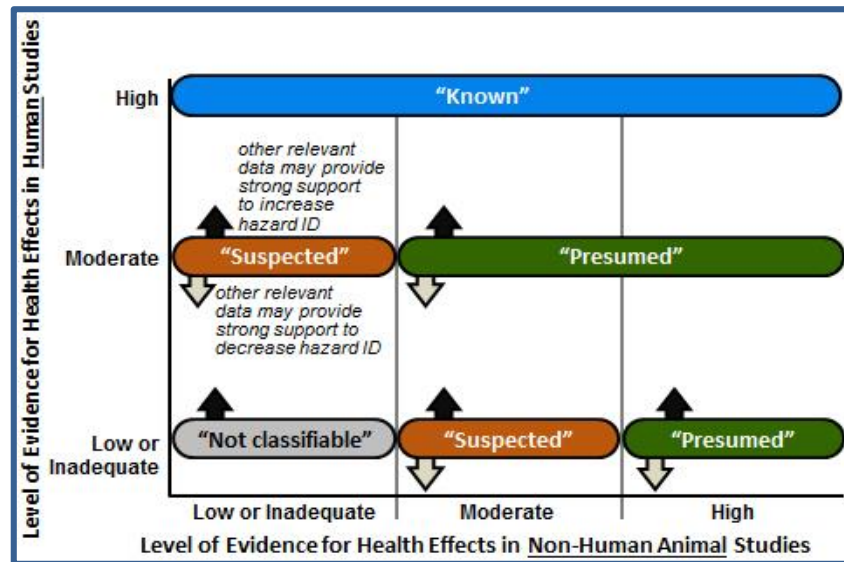




Hazard Conclusions for Acute Sarin Exposure

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

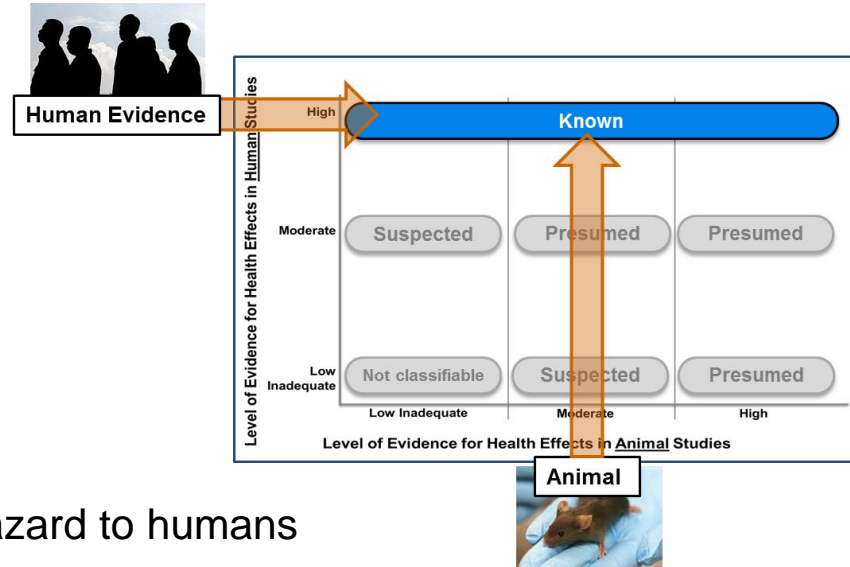
Integrate Evidence to Develop Hazard Conclusions

- **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

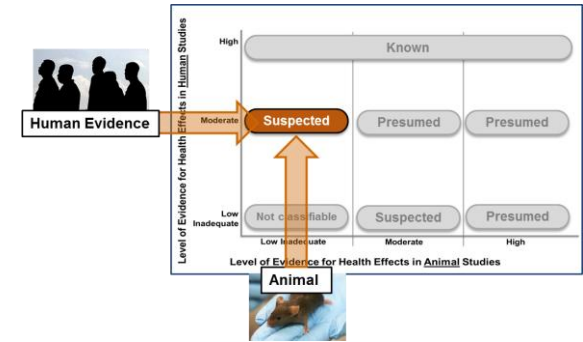


Hazard Conclusions for Acute Sarin Exposure

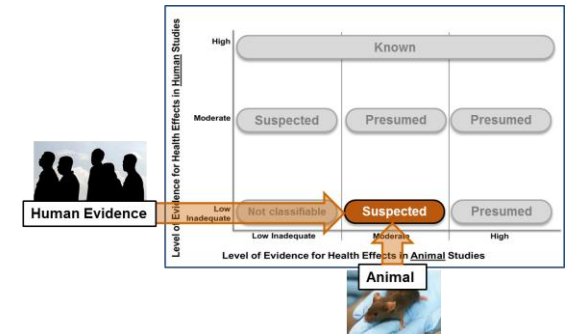
Integrate Evidence to Develop Hazard Conclusions

- **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

Moderate Human x Low / Inadequate Animal



Low / Inadequate Human x Moderate Animal



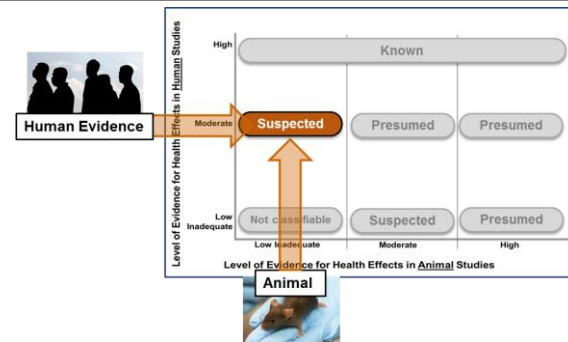


Hazard Conclusions for Acute Sarin Exposure

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

Moderate Human x Low / Inadequate Animal





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Questions?