

# Overall Hazard Conclusions

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# Methods for Developing NTP Monographs

## Evidence Integration: Developing Hazard Conclusions

### (1) Initial Hazard Conclusion

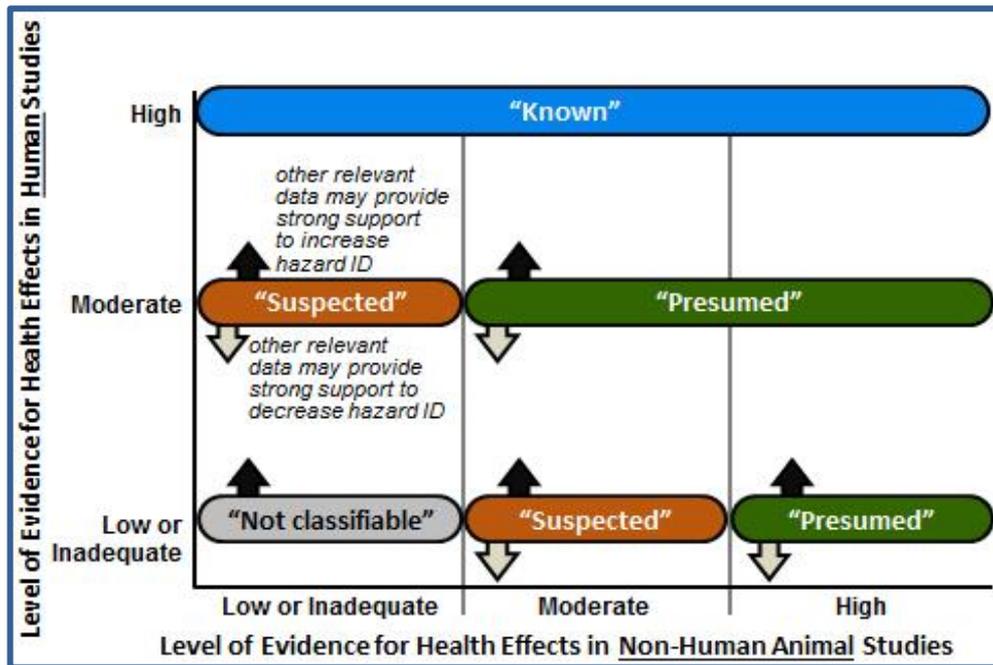
Consider human and animal evidence together

### (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

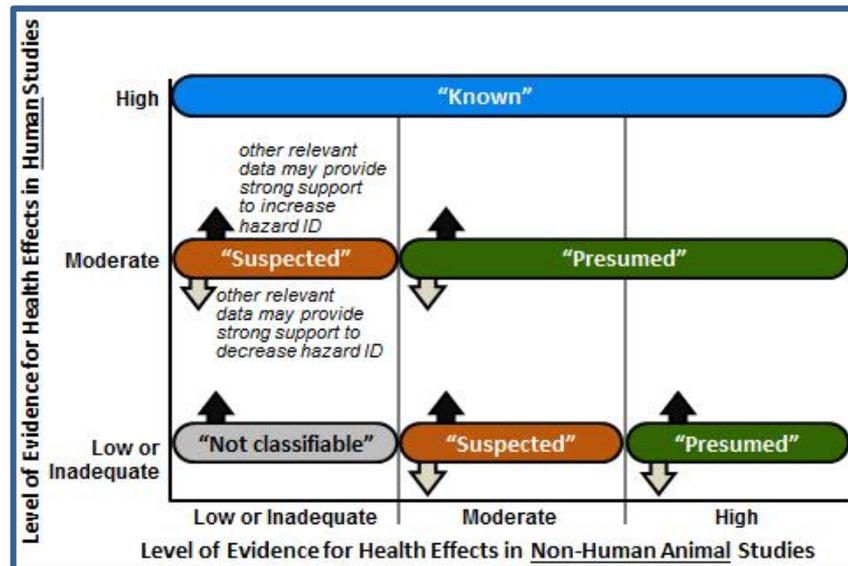




# Hazard Conclusions for Acute Sarin Exposure

## 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

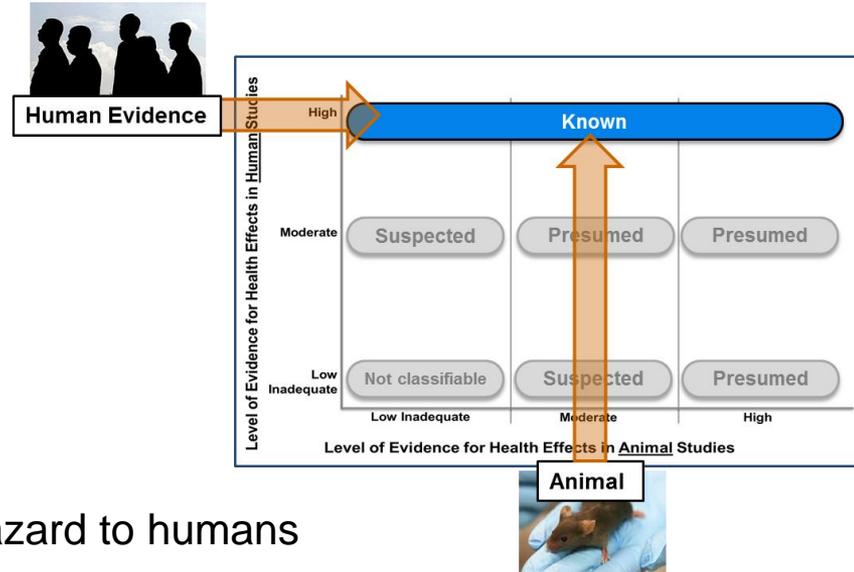
## Integrate Evidence to Develop Hazard Conclusions

- **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

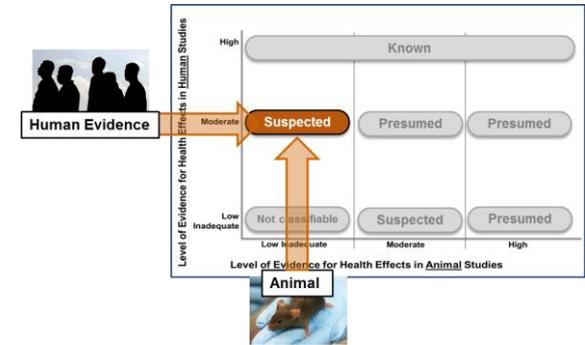


# Hazard Conclusions for Acute Sarin Exposure

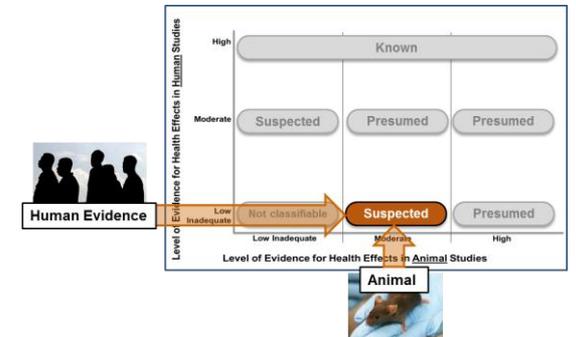
## Integrate Evidence to Develop Hazard Conclusions

- **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



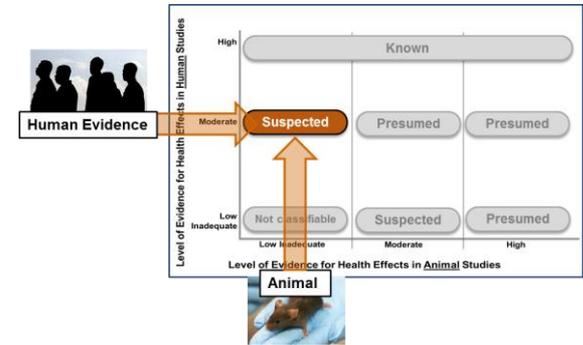


# Hazard Conclusions for Acute Sarin Exposure

## 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?