NTP
National Toxicology Program

NTP Monograph on the

Systematic Review of Long-term Neurological Effects Following Acute Exposure to Sarin

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National Institute of Environmental Health Sciences

NTP Board of Scientific Counselors Meeting
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Sarin

$C_4H_{10}FO_2P$

- Synthetic compound, related to organophosphate insecticides
- One of the “G-series” less persistent nerve agents discovered and synthesized in Germany in 1930s and 1940s
- Use as a chemical weapon due to extreme potency as nerve agent
  - Attacks the nervous system by blocking action of the enzyme acetylcholinesterase to prevent the break down of acetylcholine
  - Excess acetylcholine in nerve synapses leads to overstimulation (cholinergic crisis) of nerves and muscles, which can affect all organ systems

Health Effects of Sarin Exposure

$C_4H_{10}FO_2P$

- Acute effects of sarin exposure are well known
  - Most symptoms are from inhibition of acetylcholinesterase and the cholinergic syndrome of overstimulation of nerves and muscles
  - Range of symptoms from drooling or excessive sweating, to paralysis, convulsions, respiratory failure, and death
- Long-term neurological effects of exposure to sarin are not well characterized in humans
- National Academies of Sciences review (NAS 2004)
  - Sufficient evidence for **ACUTE effects**
  - Limited evidence for **LONG-TERM effects**

Countermeasures Against Chemical Threats Program

- The CounterACT program, a trans-NIH initiative, promotes the development of medical countermeasures to prevent and treat conditions caused by potential and existing chemical threats
- CounterACT requested that NTP conduct a systematic review of the evidence for long-term neurological health effects of sarin to
  - Characterize the evidence for long-term neurological effects following acute exposure to sarin, and
  - Inform the potential need to develop therapeutics to treat long-term neurological effects

Office of Health Assessment and Translation (OHAT)

- OHAT develops literature-based evaluations to assess the evidence that environmental substances cause health effects
- Evaluations are conducted following the OHAT Approach for Systematic Review and Evidence Integration
- When the evidence is sufficient to support conclusions, the resulting NTP Monograph describes the methods, results, and NTP hazard conclusions

https://ntp.niehs.nih.gov/go/ohat

Systematic Review and Evidence Integration

Systematic Review

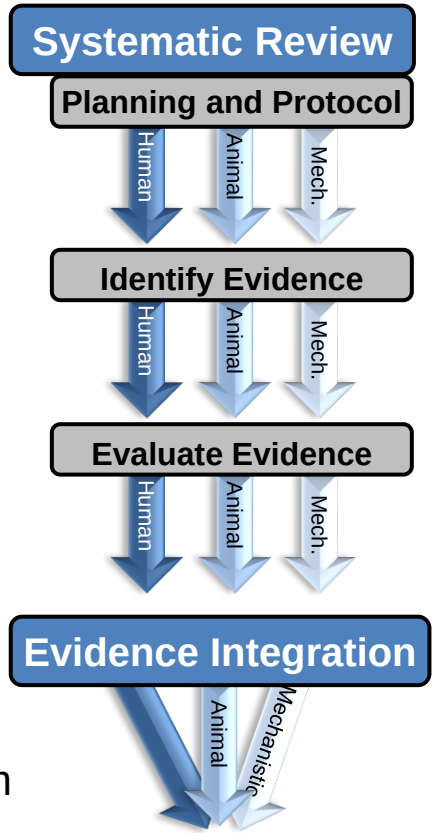
A predefined, multistep process to identify, select, critically assess, and synthesize data from published studies to answer a specific question

Systematic Review Process

- Develop specific research question and protocol
- Perform comprehensive literature search
- Select relevant studies and extract data
- Assess individual study quality
- Data analysis

Evidence Integration

A process for developing hazard conclusions by integrating evidence from human and experimental animal studies with consideration of the degree of support from mechanistic data



Systematic Review of Evidence for Long-term Neurological Effects

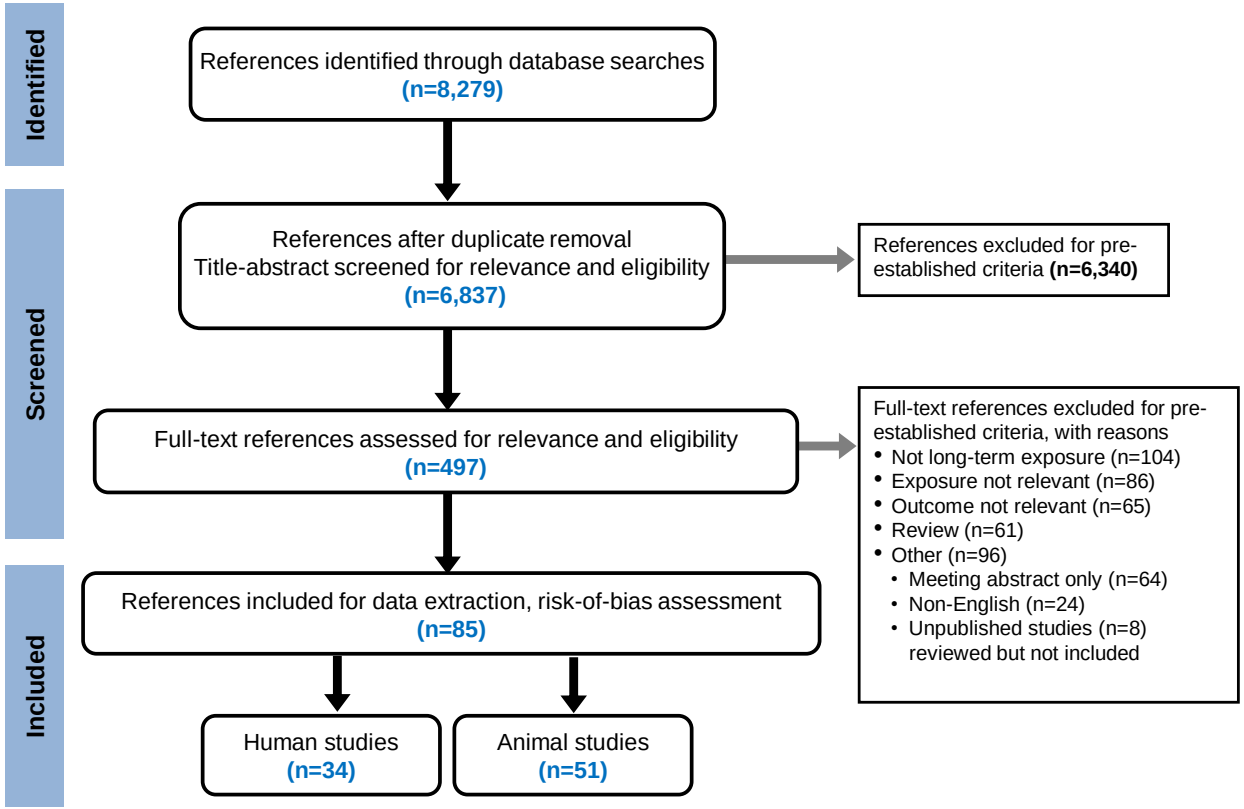
- **Objective**
  To evaluate the evidence for long-term neurological effects in humans and animals following acute exposure to sarin

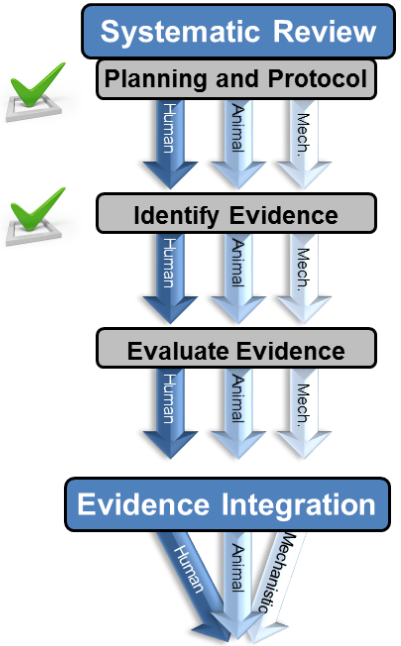
- **Long-term effects**
  For nerve agents, defined as any effect >24 hours after exposure

- **3 post-exposure time periods**
  Evidence of effects characterized within separate time periods
  - **“Initial”**: >24 hours to 7 days after exposure
  - **“Intermediate”**: 8 days to 1 year after exposure
  - **“Extended”**: >1 year after exposure

Sarin Systematic Review

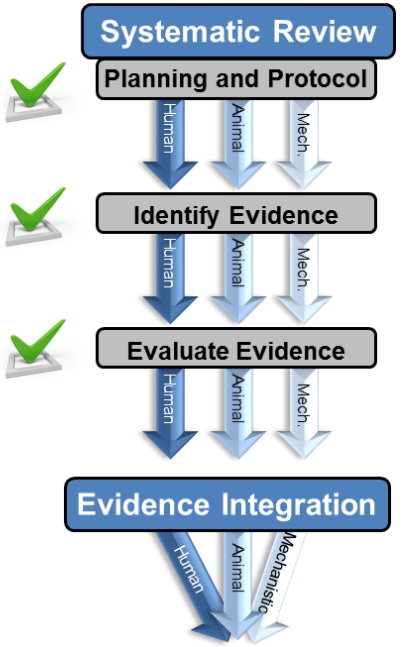
Literature Search and Screening

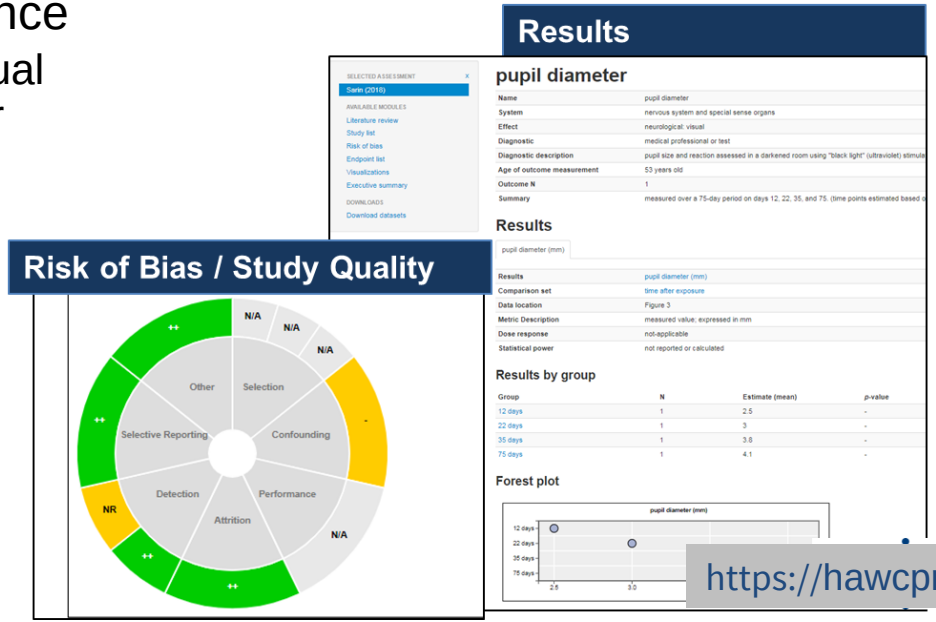




Extract Data and Evaluate Individual Studies

- Identifying Evidence
  - Extract data into web-based project pages
- Evaluating Evidence
  - Assess individual study quality or internal validity



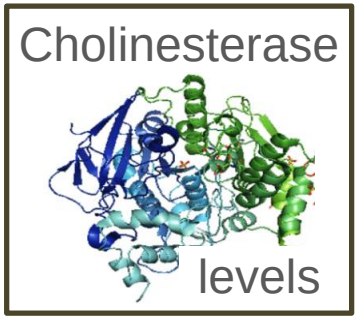


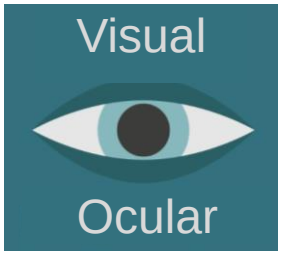
https://hawcproject.org/assessment/302/

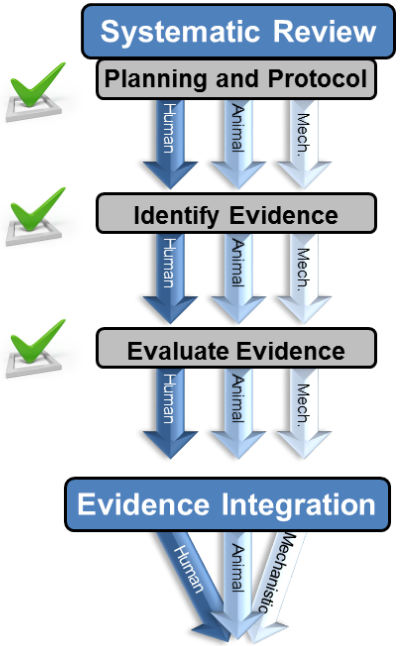
Consideration of Sarin Health Effects Evidence

- Integrating Evidence
  - Results were grouped according to same or similar outcomes to develop bodies of evidence

➡ 4 main health effect categories were identified

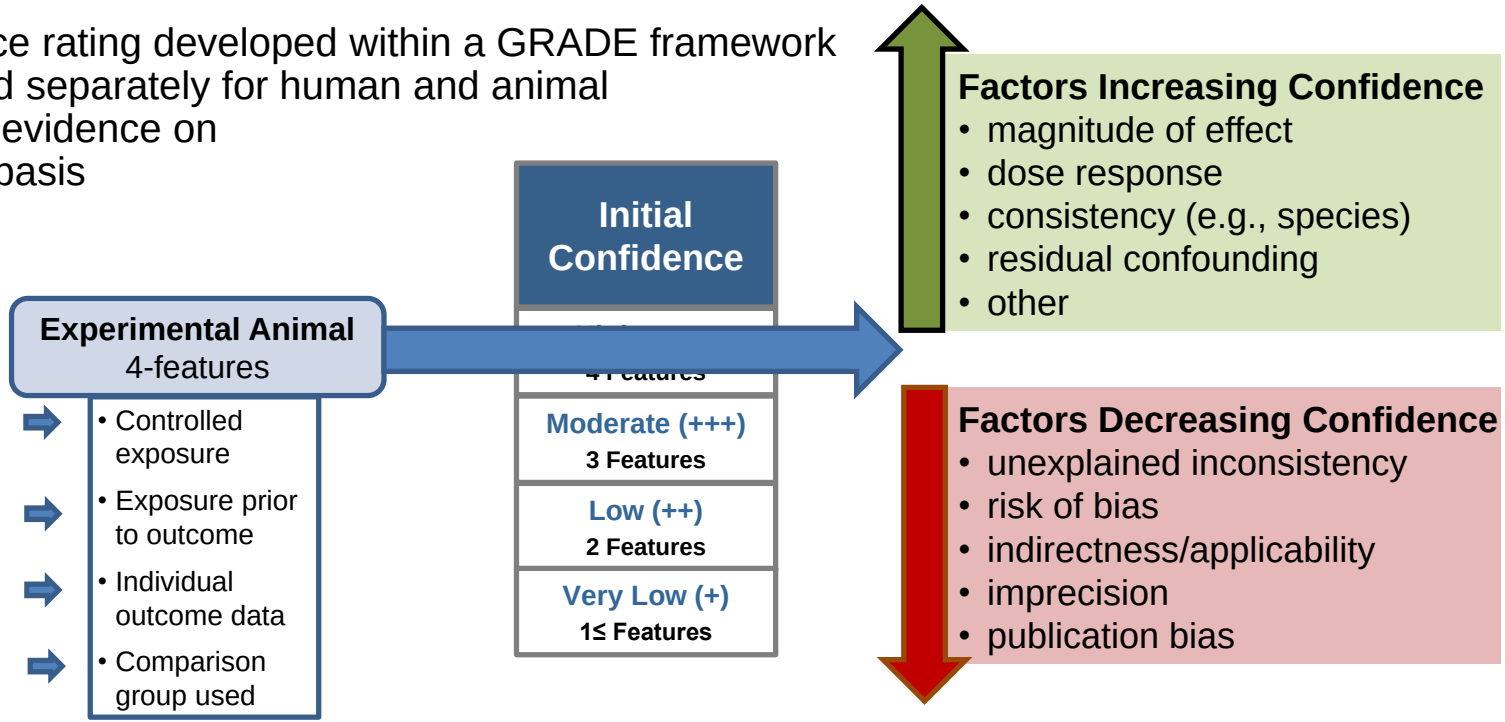






Evidence Integration: Rating Confidence in the Body of Evidence

- Rating is a measure of how confident you are that findings from a group of studies reflect the true relationship between exposure to a substance and effect
- Confidence rating developed within a GRADE framework
  Performed separately for human and animal bodies of evidence on outcome basis



Initial confidence set based on 4-features

Grading of Recommendations, Assessment, Development and Evaluations (GRADE)

Methods for Developing NTP Monographs

Integrate Evidence to Develop Hazard Conclusions

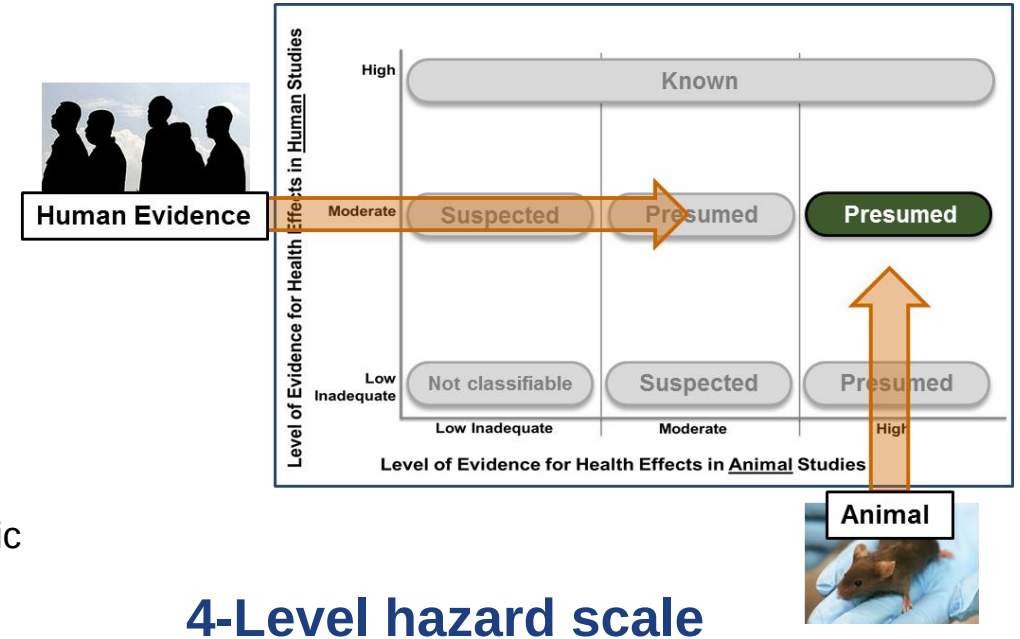
For each time period:
Conclusions with highest level of evidence were used to reach the overall conclusions

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

(2) Final Hazard Conclusion
Consider impact of any relevant mechanistic data and biological plausibility of effect

Assess if there is:

- Strong support to increase hazard ID
- Strong opposition to decrease hazard ID



4-Level hazard scale
known, *presumed*, *suspected*, and *not classifiable*

Peer Review of Draft NTP Monograph

– Pam Factor-Litvak, PhD	Professor of Epidemiology, Columbia University Medical Center, New York, NY
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Pam Factor-Litvak, PhD
Chair

Peer Review Meeting at NIEHS Research Triangle Park, NC and via WebEx on Feb 4, 2019

Conclusion for Each Time Period

Peer Review of NTP's Draft Conclusions

- **Initial time period:** Effects 1 to 7 days after exposure
  - *Known to be a long-term neurological hazard to humans*
  - Based on suppression of cholinesterase which results in nervous system disruption due to acetylcholine buildup

The panel agreed with the draft NTP conclusion

Conclusion for Each Time Period

Peer Review of NTP's Draft Conclusions

- **Intermediate time period:** 8 days to 1 year after exposure
  - *Suspected to be a long-term neurological hazard to humans*
  - Based on multiple effects including suppression of cholinesterase, visual and ocular effects, effects on learning and memory, and morphological and histological changes in nervous system tissue
  - *Expert panel had lower confidence in the body of evidence for learning and memory and suggested not using it to support the hazard conclusion*

The panel agreed with the draft NTP conclusion

Conclusion for Each Time Period

Peer Review of NTP's Draft Conclusions

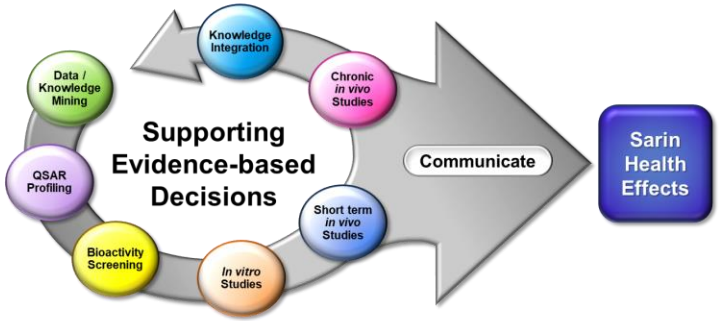
- **Extended time period**: >1 year after exposure
  - *Suspected to be a long-term neurological hazard to humans*
  - Based on multiple effects including effects on learning and memory effects and morphological and histological changes in nervous system tissue

The panel agreed with the draft NTP conclusion

Looping Back to NIH CounterACT in the Pipeline

The translation of the NTP Sarin Monograph into tangible impact is in process with NIH CounterACT

National Institutes of Health
Counter ACT
Countermeasures Against Chemical Threats



- Support ongoing research by HHS and DoD on the long-term effects of sarin and related compounds.
- Identify research gaps in our knowledge of the effects of sarin and potentially for similar nerve agent chemical threats.
- Identify specific health outcomes that would require medical intervention.
- Provide human and animal supportive evidence for the justification of FDA approvals of drug candidates that reduce long-term effects of sarin and related chemical threats.

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  - The evaluation team
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  - Kembra Howdeshell, NIEHS/DNTP
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- **Management of the Peer Review**
  - Mary Wolfe, NIEHS/DNTP
  - Elizabeth Maull, NIEHS/DNTP
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Thank you

Questions?