NTP
National Toxicology Program

Introduction to the

Draft NTP Monograph on Systematic Review of Long-term Neurological Effects Following Acute Exposure to Sarin

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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
- Used 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:**
    a dose-dependent cholinergic syndrome is evident seconds to hours subsequent to sarin exposure that resolves in days to months
  - Limited evidence for **LONG-TERM effects:**
    at sarin doses that cause cholinergic signs, suggestive evidence for a variety of subsequent long-term neurological 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
- Nomination noted that long-term neurological effects following acute exposure to sarin are not well characterized
- CounterACT requested that NTP conduct a systematic review of the evidence for long-term neurological health effects of sarin
- The systematic review will 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
  - Hazard conclusions are reached by integrating “levels of evidence” from human and non-human animal studies with consideration of biological plausibility and the degree of support from mechanistic data

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

Draft NTP Monograph on Sarin

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

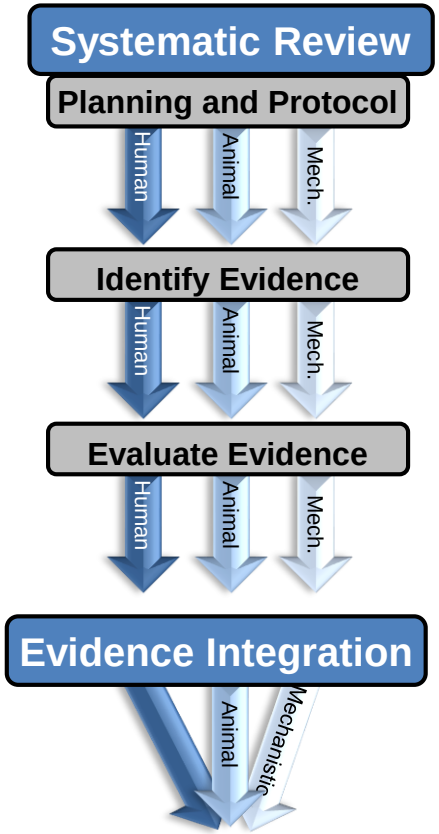
- **Long-term effects**
  For nerve agents, defined as any effect >24 hours after exposure

- **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

Methods for Developing NTP Monographs

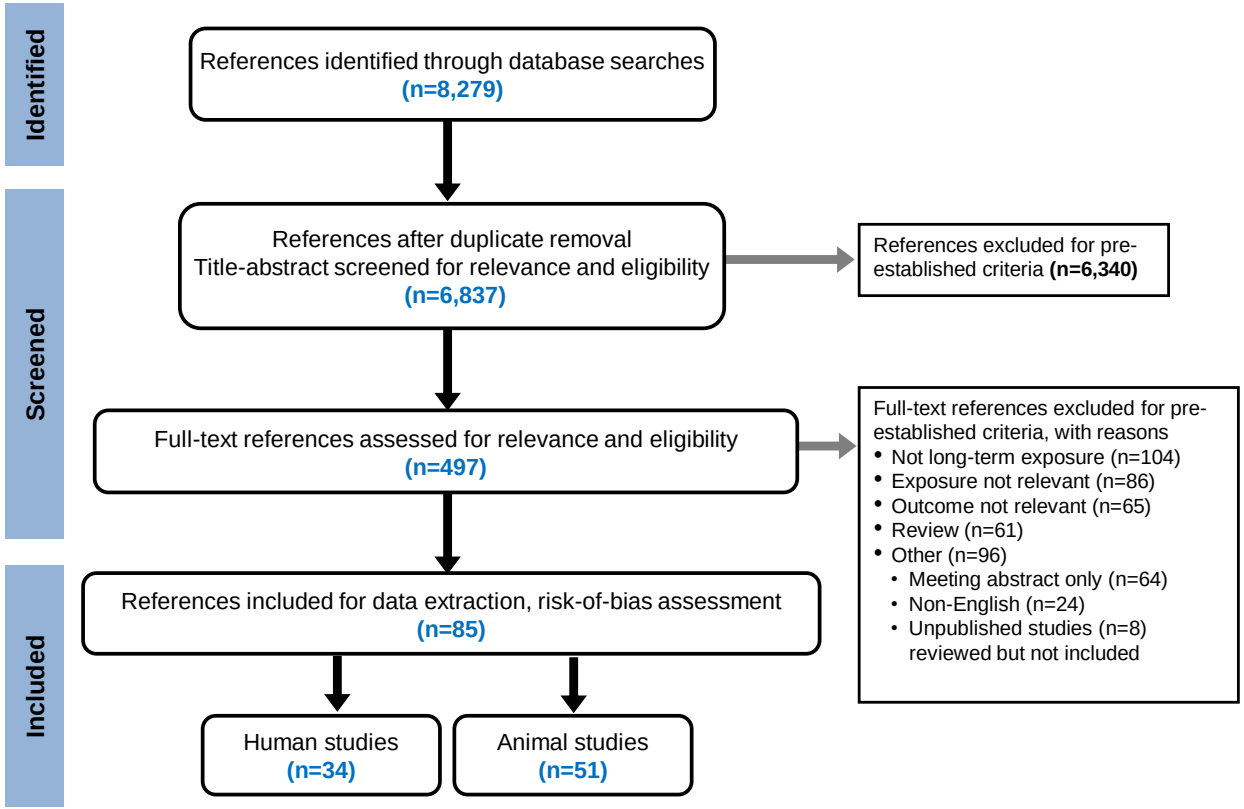
Stepwise Methods

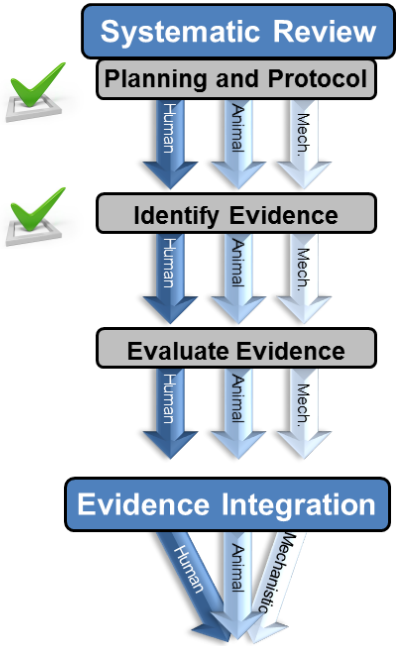
- **Problem Formulation and Protocol Development**
  - Refine research question and develop systematic review protocol
  - Peer review and posting revised protocol
- **Identifying Evidence**
  - Perform comprehensive literature search
  - Select relevant studies
  - Extract data into web-based project pages in Health Assessment Workspace Collaborative (HAWC)
- **Evaluating Evidence**
  - Assess individual study quality/risk of bias – also in HAWC
- **Integrating Evidence**
  - Identify bodies of evidence - studies grouped by outcome (animal, human)
  - Develop confidence ratings for bodies of evidence
  - Translate confidence rating into levels of evidence
  - Develop hazard identification conclusions



Methods for Developing NTP Monographs

Consideration of Sarin Health Effects Evidence





Methods for Developing NTP Monographs

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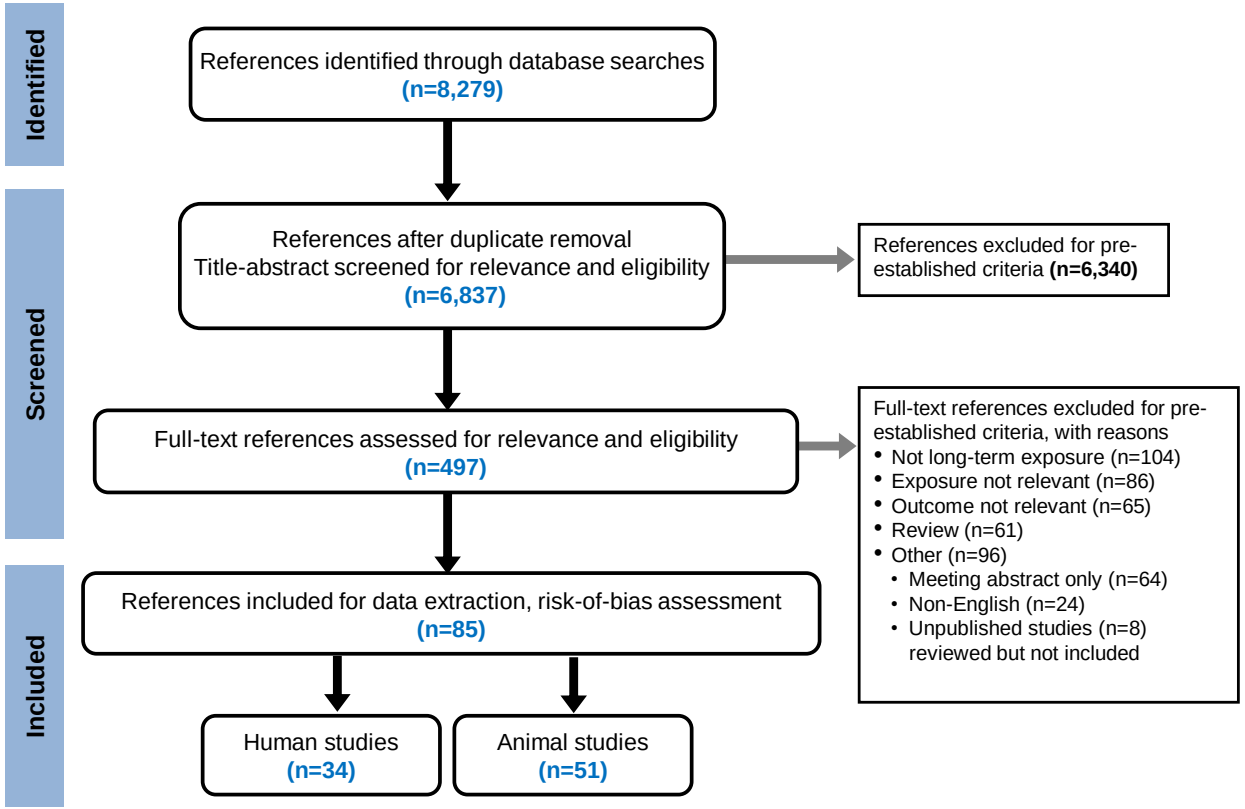
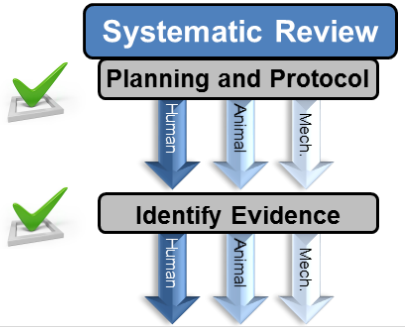


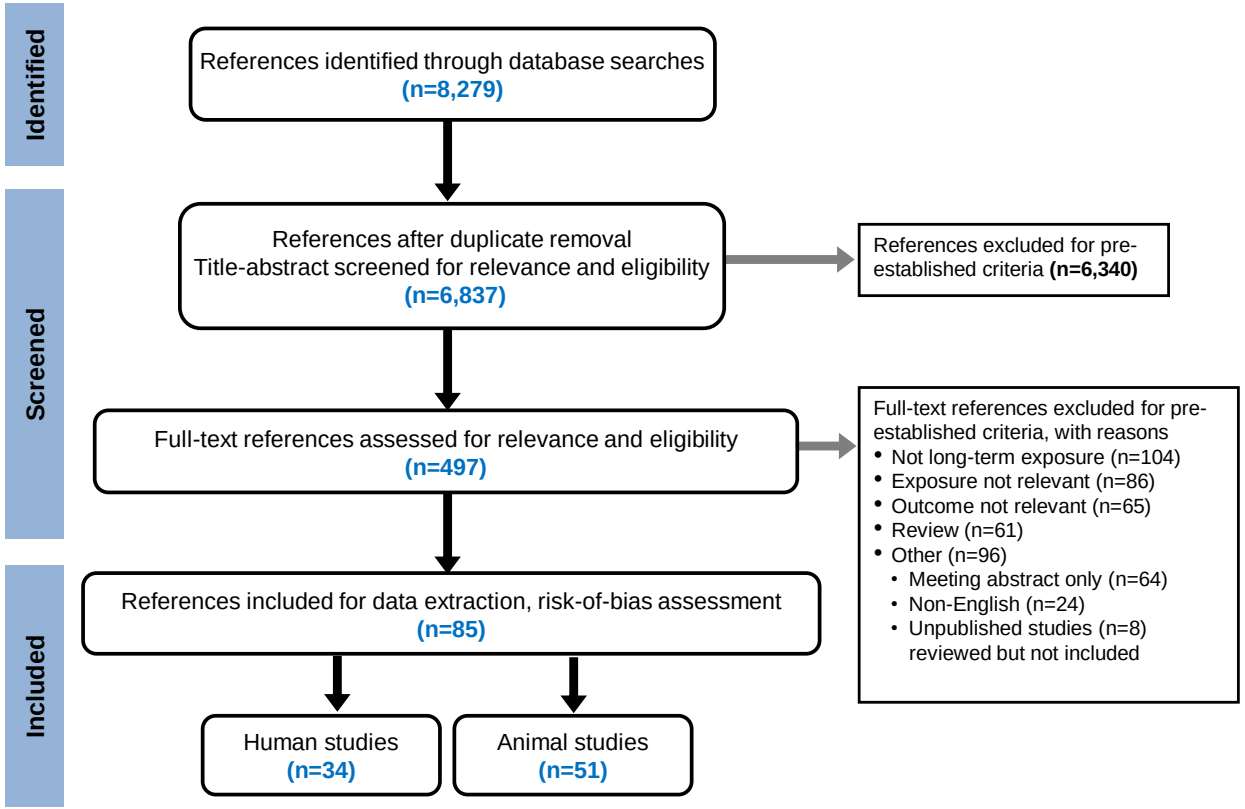


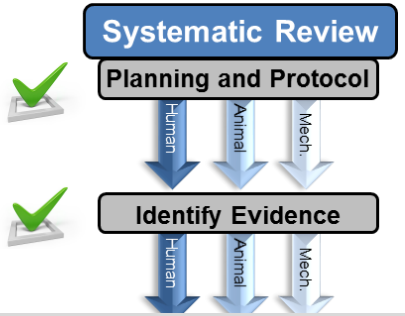
Non-English Language Publications

- 24 identified at title-abstract level
- All excluded based on review at that level (e.g., title and English language abstract)
- Determined made that the studies would be unlikely to impact conclusions (e.g., same population/data as other study)

Methods for Developing NTP Monographs

Consideration of Sarin Health Effects Evidence



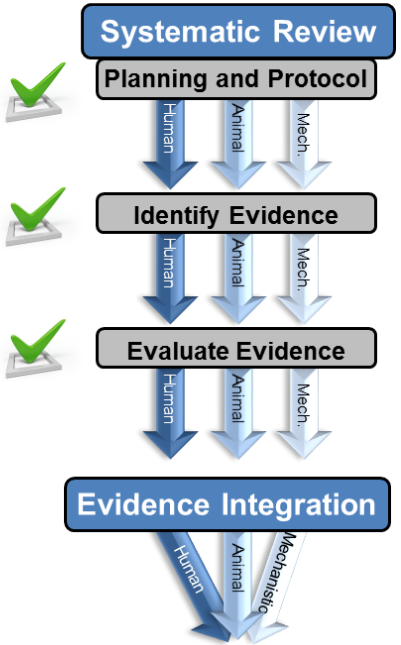


Unpublished studies

- For transparency, only publicly available data considered
- 8 studies/reports identified that had not been peer previewed
- Determined made that the data from these studies would not impact conclusions (e.g., subsequently published, only added to already heterogeneous endpoints)

Consideration of Sarin Health Effects Evidence

- Identifying Evidence
- Evaluating Evidence
- Integrating Evidence



➡ Results are grouped by same or similar outcomes to develop bodies of evidence

➡ 4 main health effect categories were identified

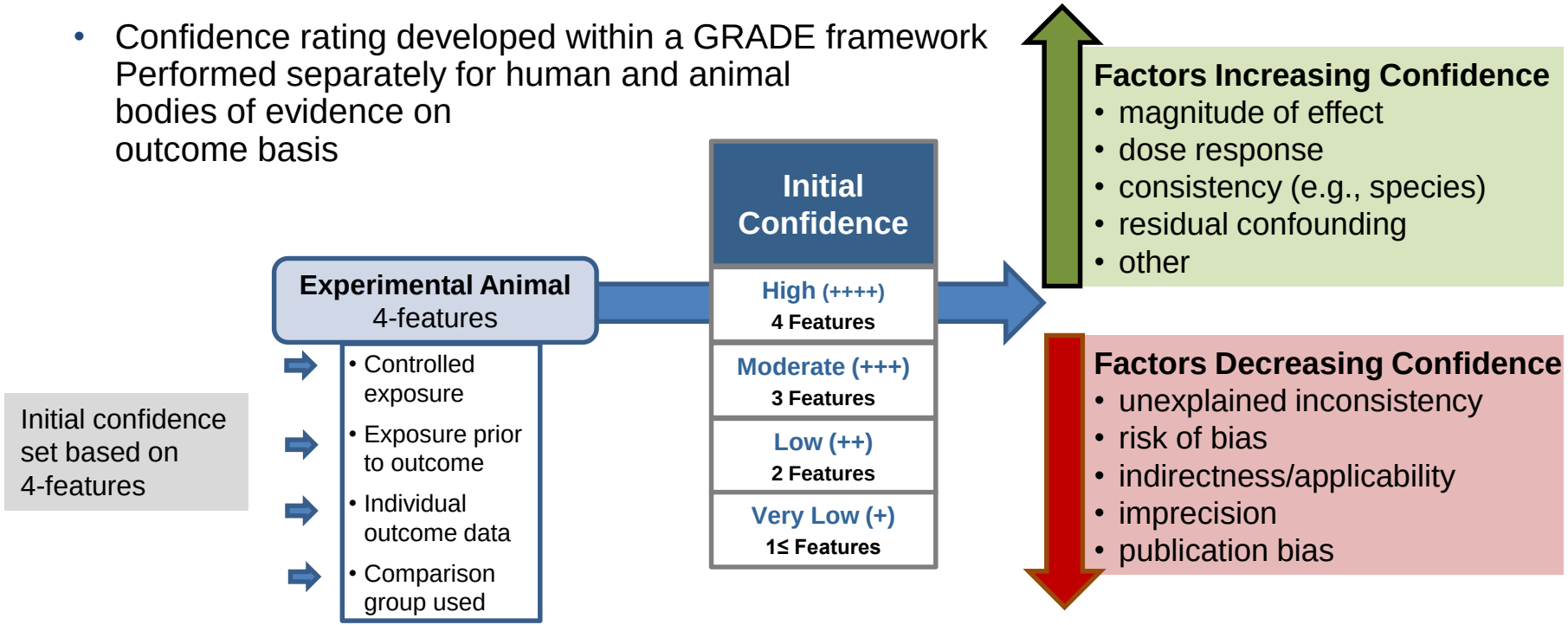
- Changes in cholinesterase levels
- Visual and ocular effects
- Learning, memory and intelligence
- Nervous system morphological and histological changes

➡ Other outcomes were considered (data in Appendix 4)

Methods for Developing NTP Monographs

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

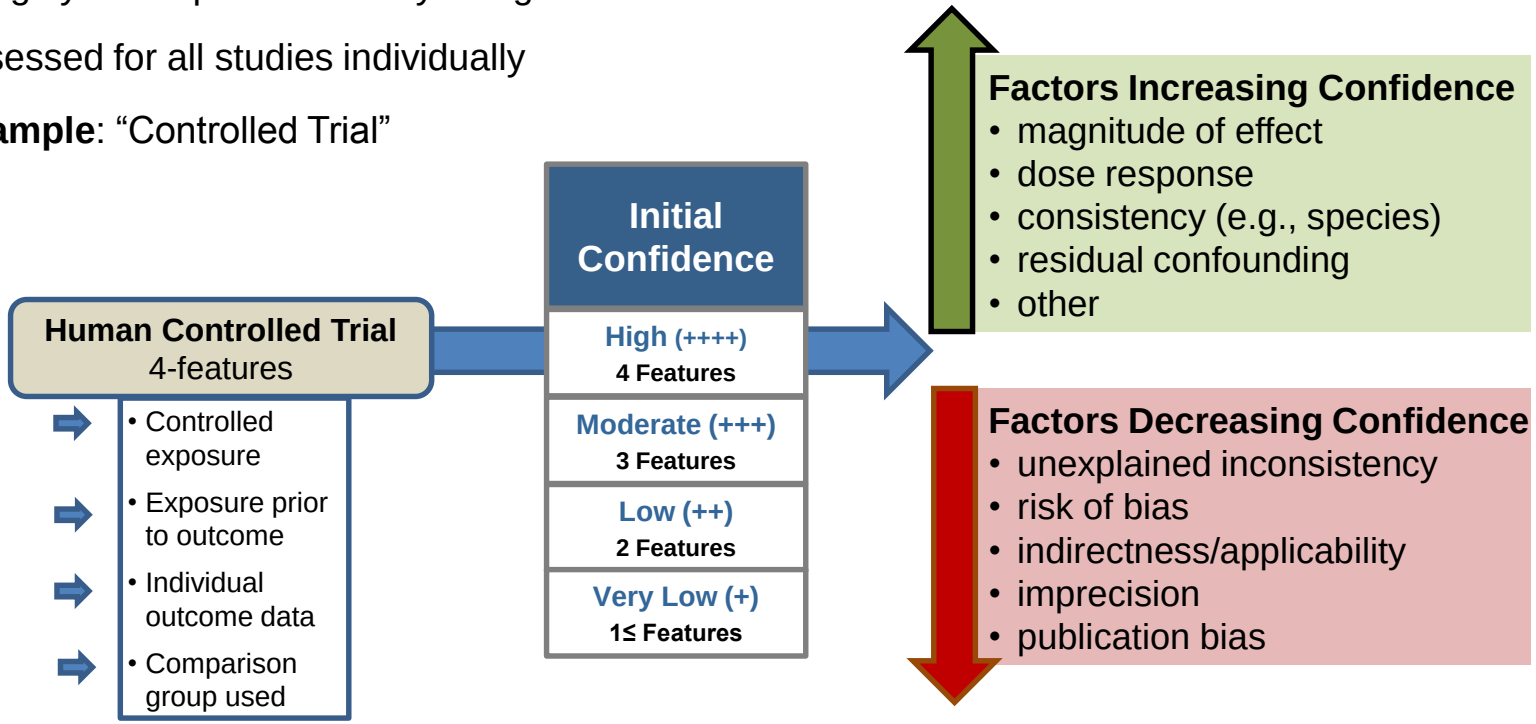


Grading of Recommendations, Assessment, Development and Evaluations (GRADE)

Methods for Developing NTP Monographs

Evidence Integration: Rating Confidence in the Body of Evidence

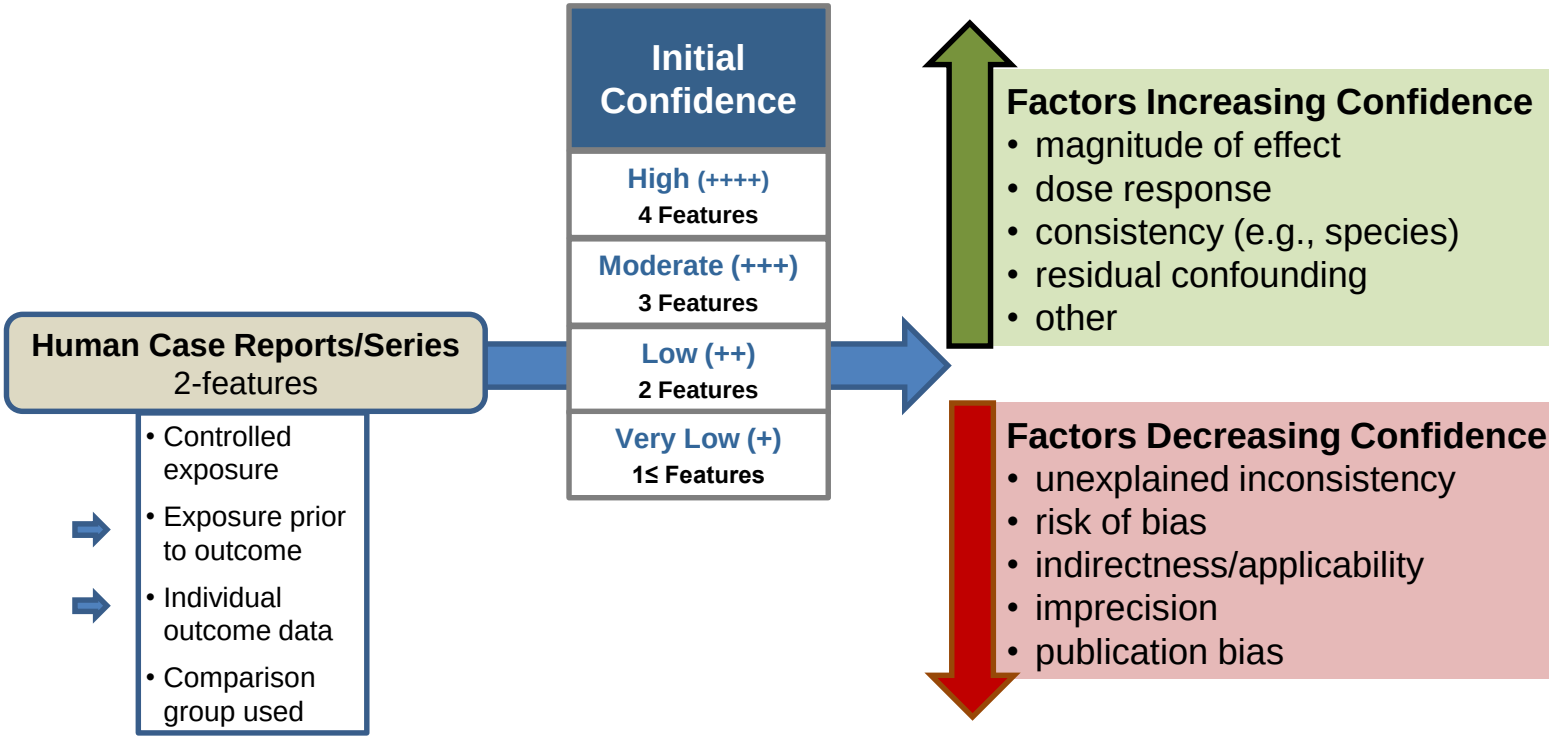
- Initial confidence set based on 4 features
  - Roughly corresponds to study designs
  - Assessed for all studies individually
  - **Example**: "Controlled Trial"



Methods for Developing NTP Monographs

Evidence Integration: Rating Confidence in the Body of Evidence

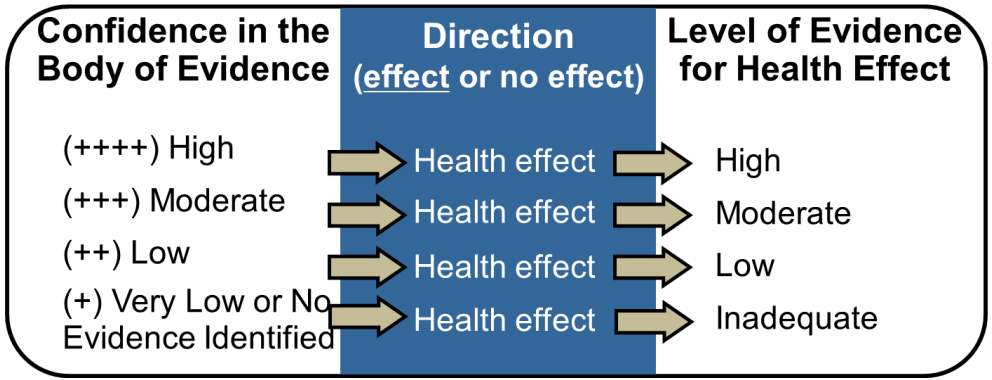
- Initial confidence set based on 4 features
  - **Example**: “case report” on a subject or “case series” tracking subjects with known exposure



Methods for Developing NTP Monographs

Evidence Integration: Translating Confidence Ratings Into Level of Evidence

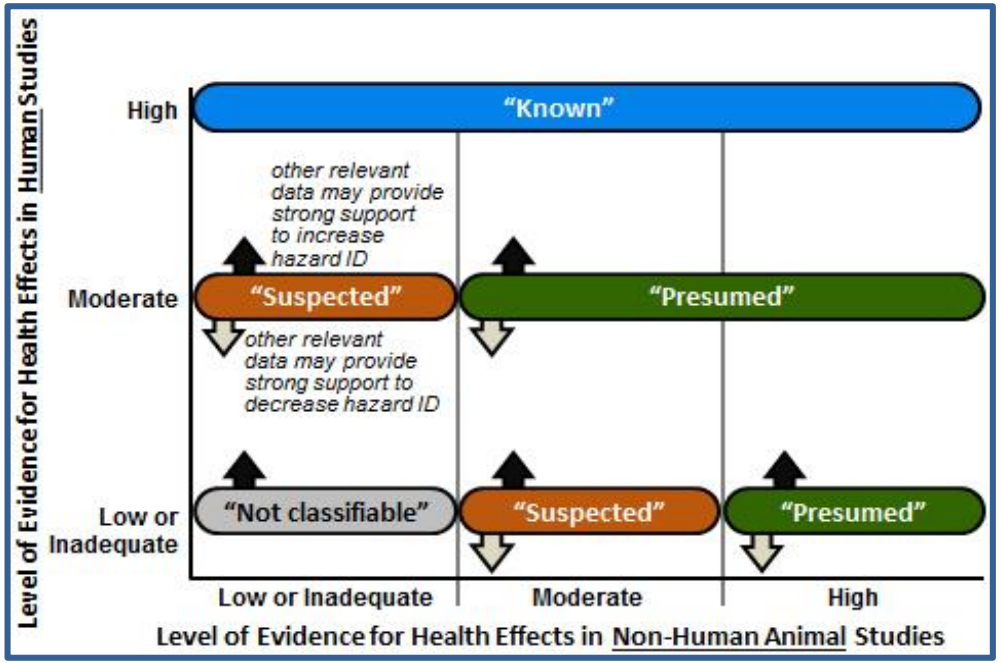
- Level of Evidence Considers:
  - Confidence rating in body of evidence from previous step
  - The direction of the outcome (health effect or no effect)
  - If there is evidence of health effect
    - High to high, moderate to moderate, low to low
    - Very low or no evidence to inadequate



Level of Evidence Conclusions

- **High Level of Evidence**
  - There is high confidence in the body of evidence for an association between acute exposure to sarin and the health outcome.
- **Moderate Level of Evidence**
  - There is moderate confidence in the body of evidence for an association between acute exposure to sarin and the health outcome.
- **Low Level of Evidence**
  - There is low confidence in the body of evidence for an association between acute exposure to sarin and the health outcome.
- **Inadequate Level of Evidence**
  - There is insufficient evidence available to assess if acute exposure to sarin is associated with the health outcome, or no data are available.
- **Evidence of No Health Effect**
  - There is high confidence in the body of evidence that acute exposure to sarin is not associated with the health outcome.

Evidence Integration: Developing Hazard Conclusions



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

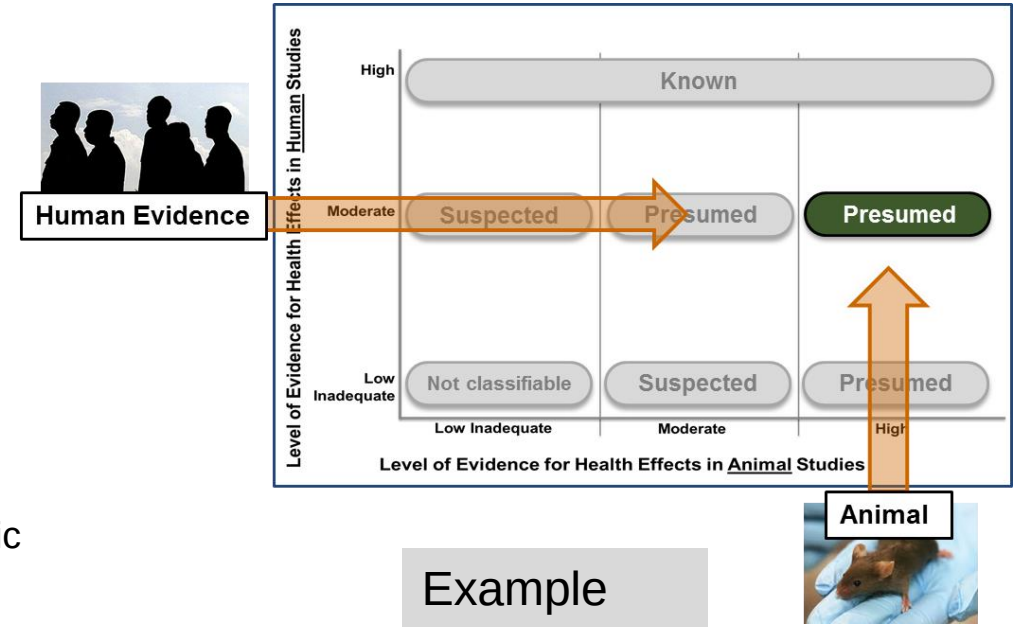
(2) Final Hazard Conclusion
Consider impact of any relevant mechanistic data and biological plausibility of effect

Assess if there is:

- Strong support to increase hazard ID
- Strong opposition to decrease hazard ID
- Or not impact the hazard ID

Integrate Evidence to Develop Hazard Conclusions

Hazard conclusions developed for 3 post-exposure time periods (initial, intermediate, extended) for the main health effect categories



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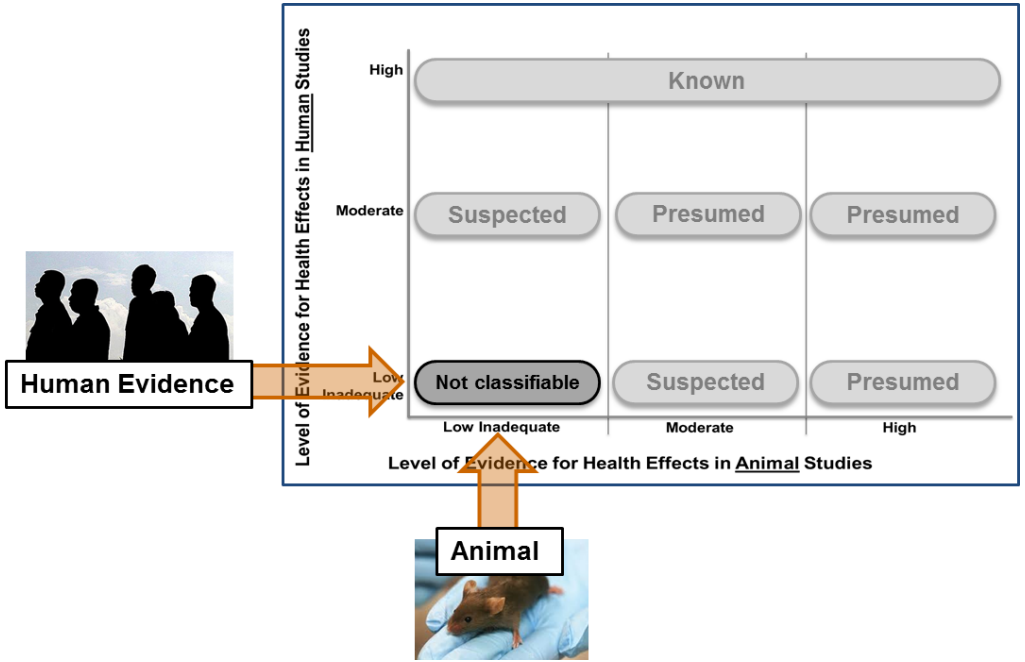
Example to illustrate the method

Integrate Evidence to Develop Hazard Conclusions

Note: outcomes with level of evidence ratings that would support conclusion of "Not classifiable" included in Appendix 4



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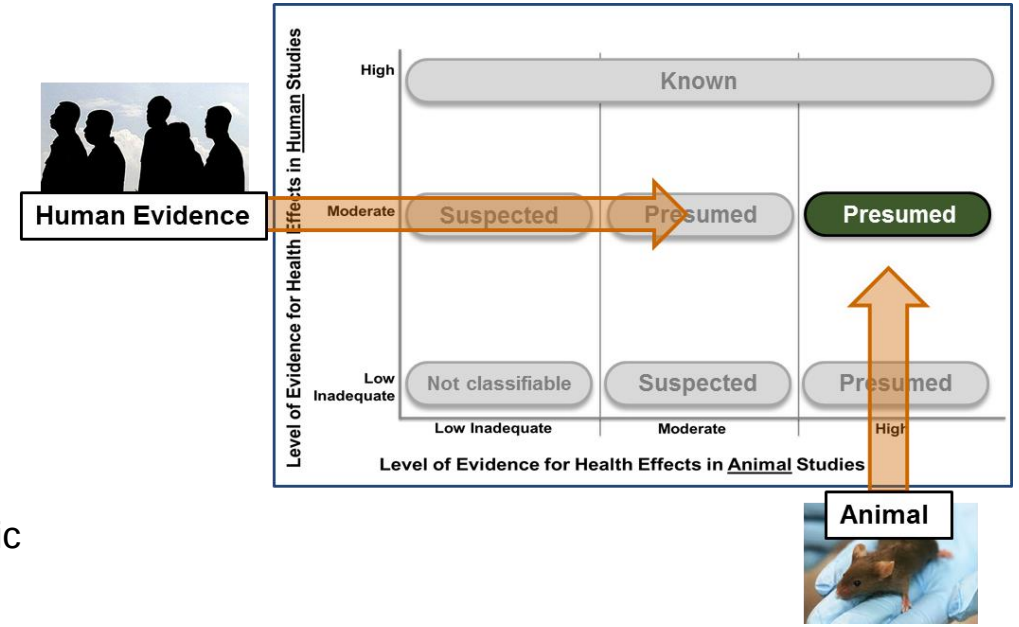
Integrate Evidence to Develop Hazard Conclusions

Conclusions with highest level of evidence for each time period are used to reach the overall conclusions



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Questions?