

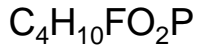
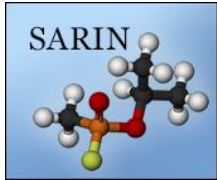
Introduction to the

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

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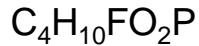
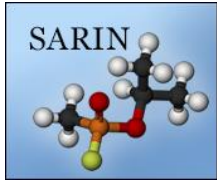




- Synthetic compound, related to organophosphate insecticides
- One of the “G-series” less persistent nerve agents discovered and synthesized in Germany in 1930s and 1940s
- Used as a chemical weapon due to extreme potency as nerve agent
  - Attacks the nervous system by blocking action of the enzyme 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



- 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



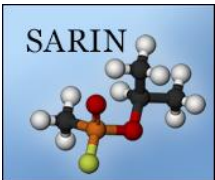
## Office of Health Assessment and Translation (OHAT)

- 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





## 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

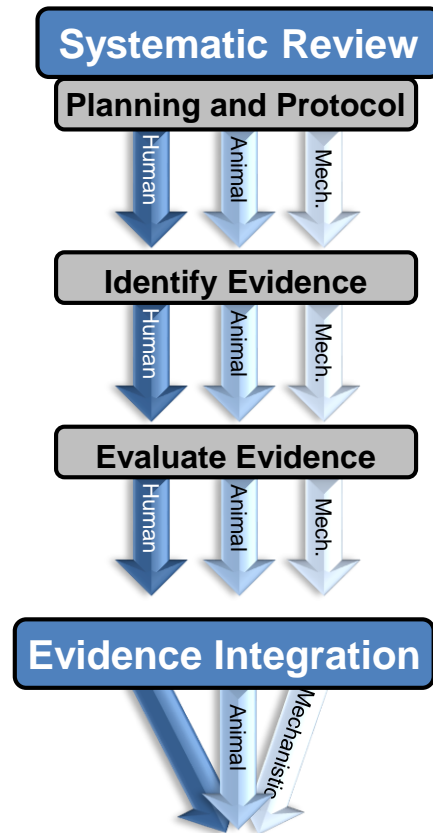
- “**Initial**”: >24 hours to 7 days after exposure
- “**Intermediate**”: 8 days to 1 year after exposure
- “**Extended**”: >1 year after exposure



# Methods for Developing NTP Monographs

## Stepwise Methods

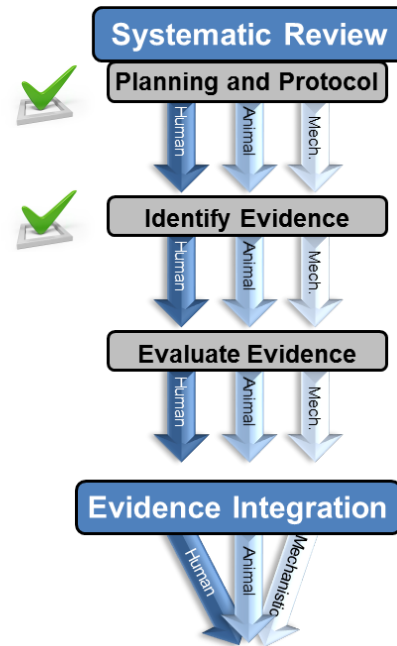
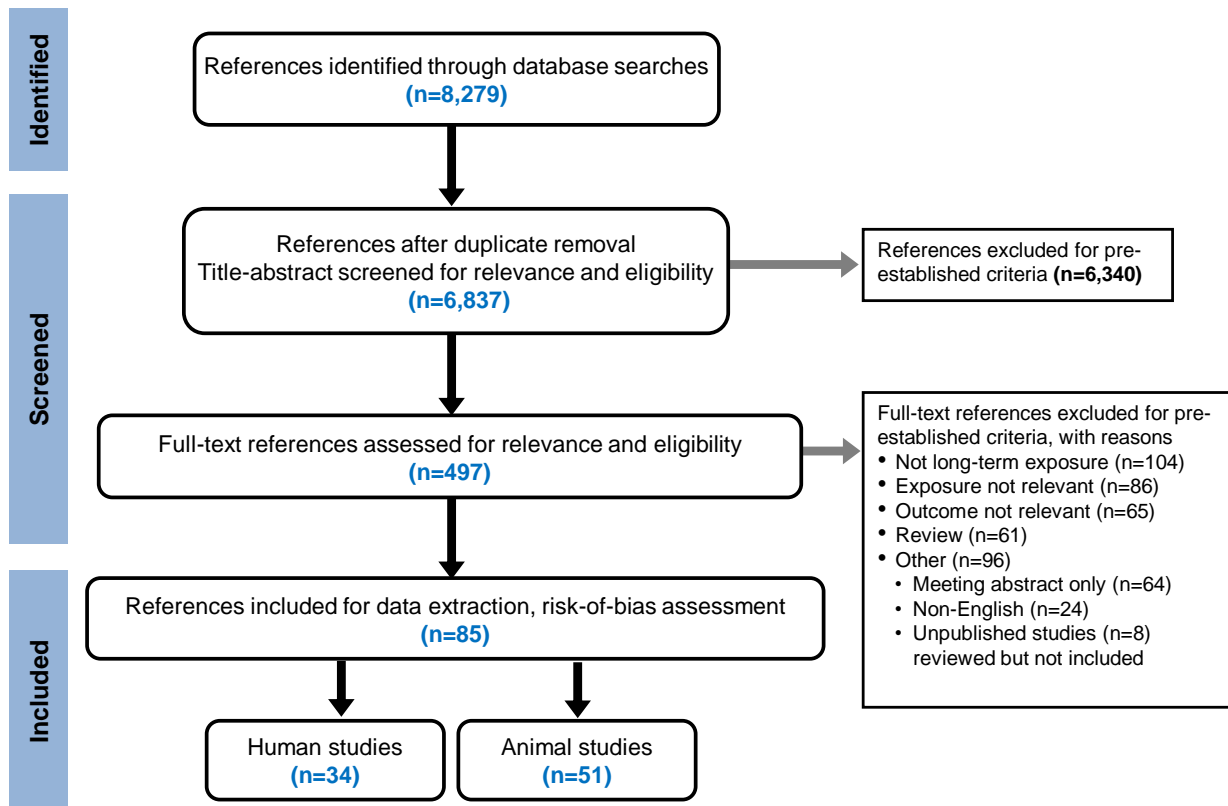
- **Problem Formulation and Protocol Development**
  - Refine research question and develop systematic review protocol
  - Peer review and posting revised protocol
- **Identifying Evidence**
  - Perform comprehensive literature search
  - Select relevant studies
  - Extract data into web-based project 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

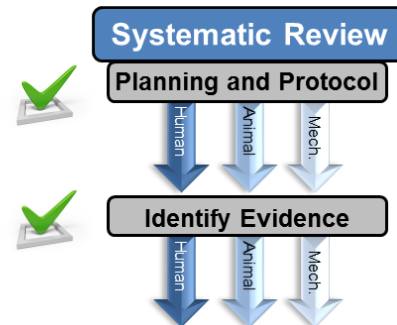
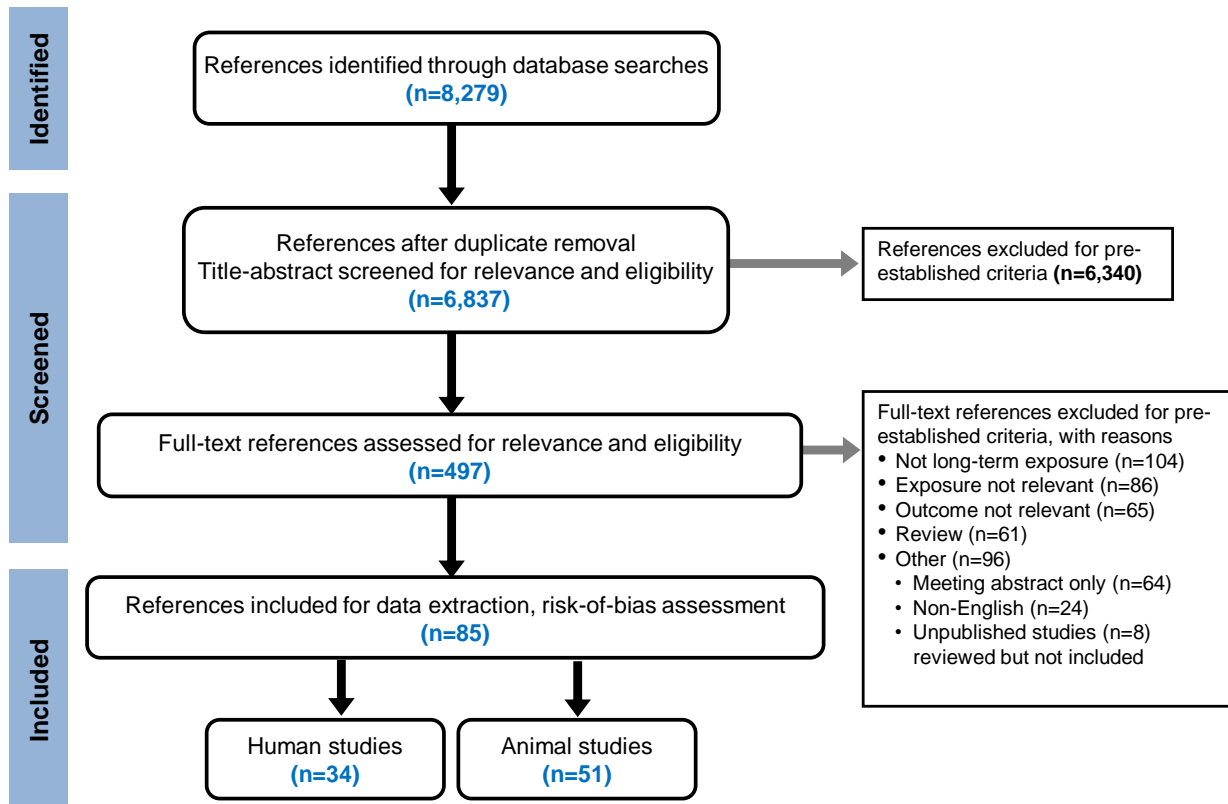






# Methods for Developing NTP Monographs

## Consideration of Sarin Health Effects Evidence



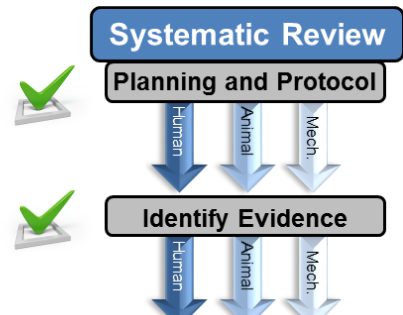
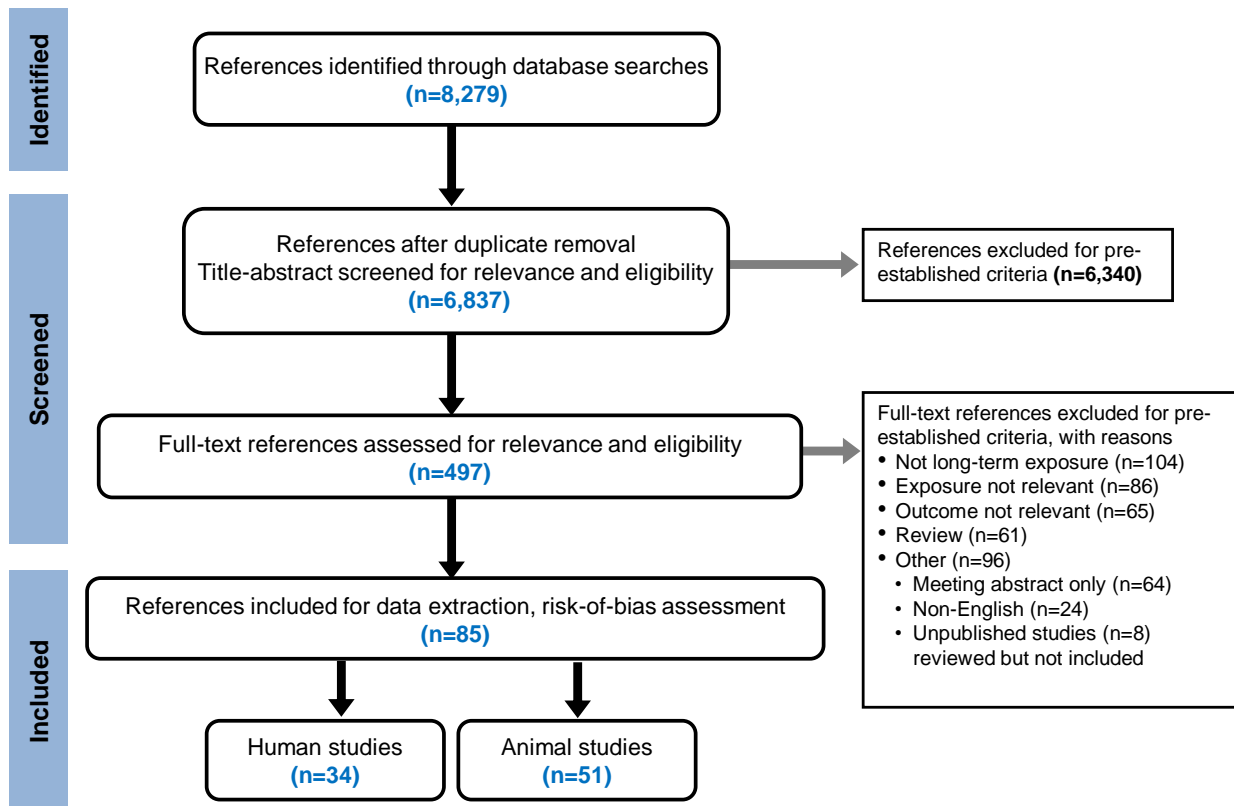
### Non-English Language Publications

- 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

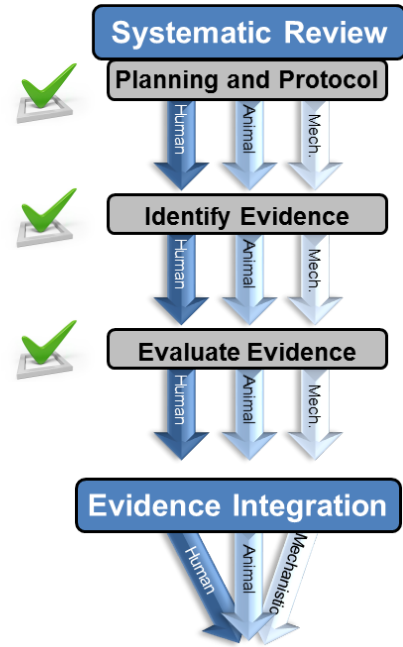
- For transparency, only publicly available data considered
- 8 studies/reports identified that had not been peer reviewed
- Determined made that the data from these studies would not impact conclusions (e.g., subsequently published, only added to already heterogeneous endpoints)



# Methods for Developing NTP Monographs

## 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)

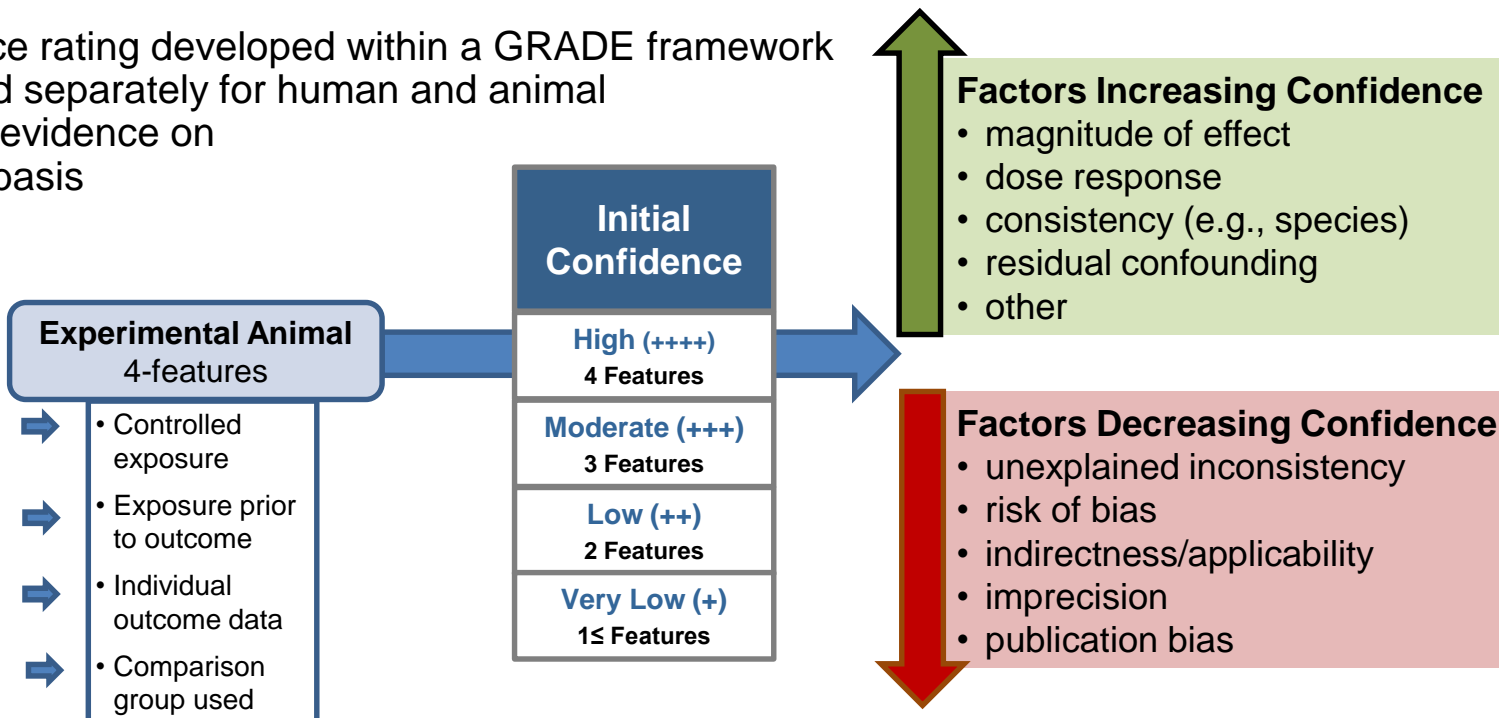




# Methods for Developing NTP Monographs

## 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

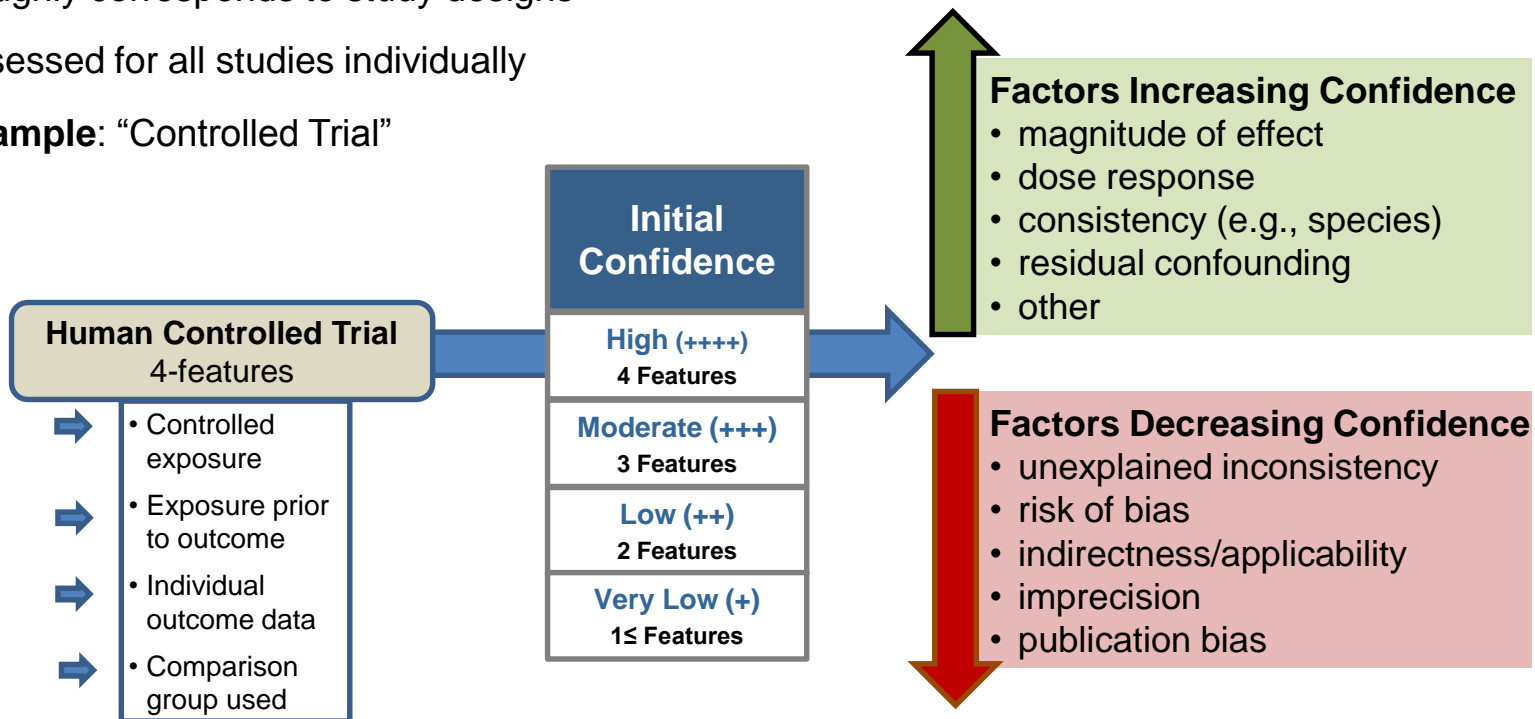




# Methods for Developing NTP Monographs

## 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”

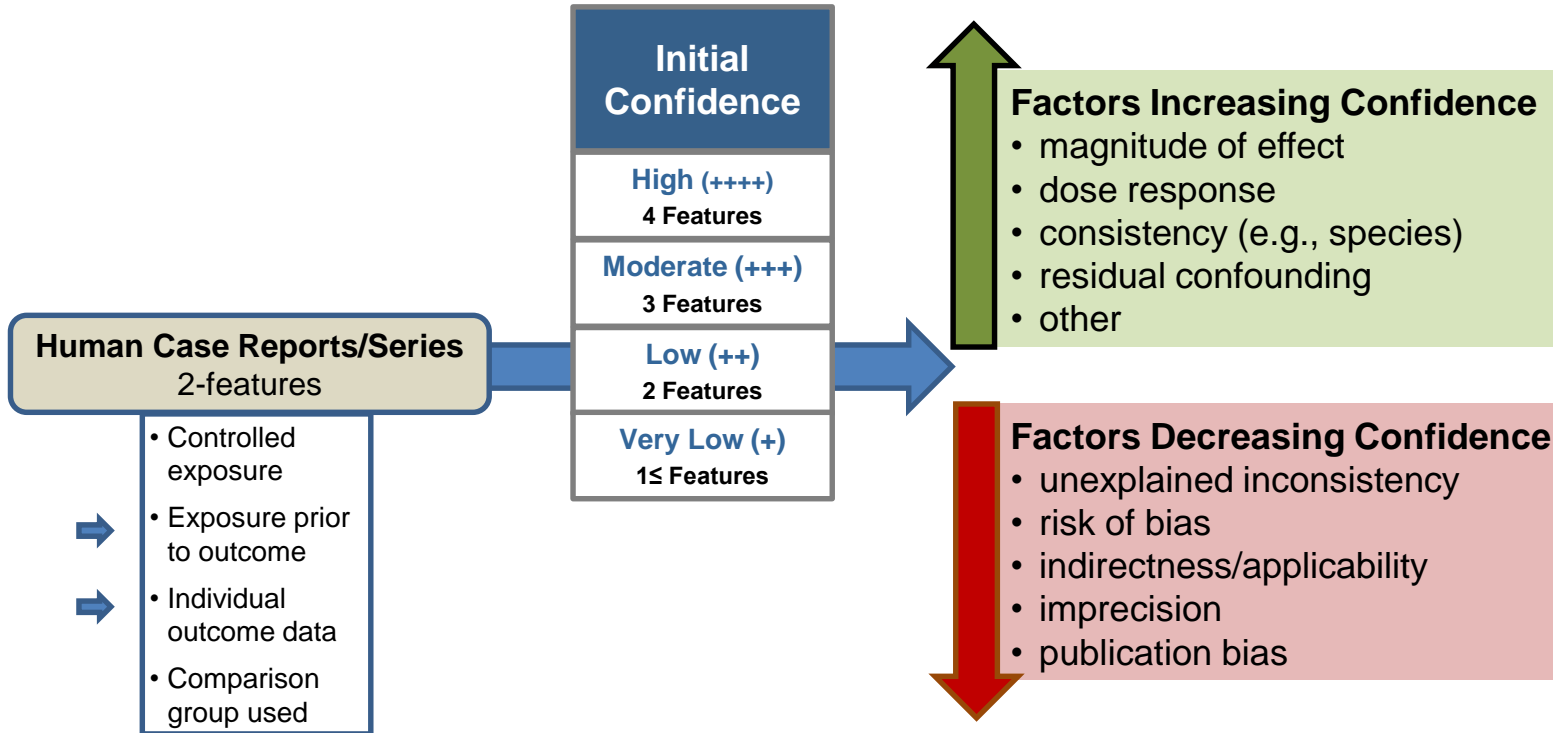




# Methods for Developing NTP Monographs

## 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

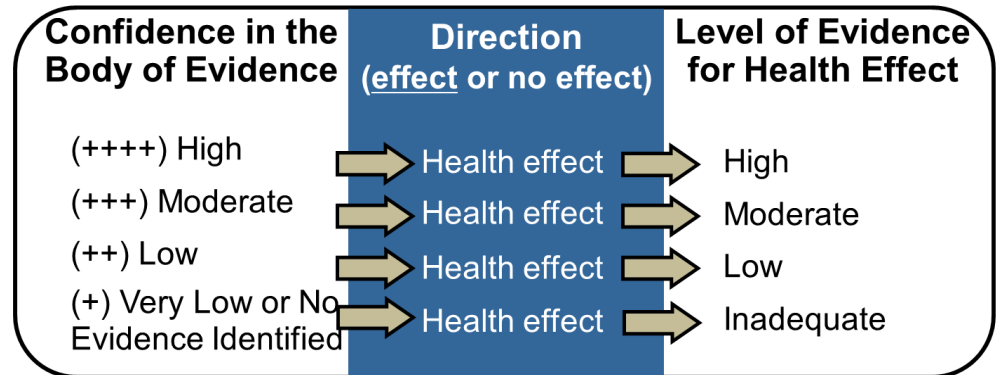




# Methods for Developing NTP Monographs

## 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.





# Methods for Developing NTP Monographs

## Evidence Integration: Developing Hazard Conclusions

### (1) Initial Hazard Conclusion

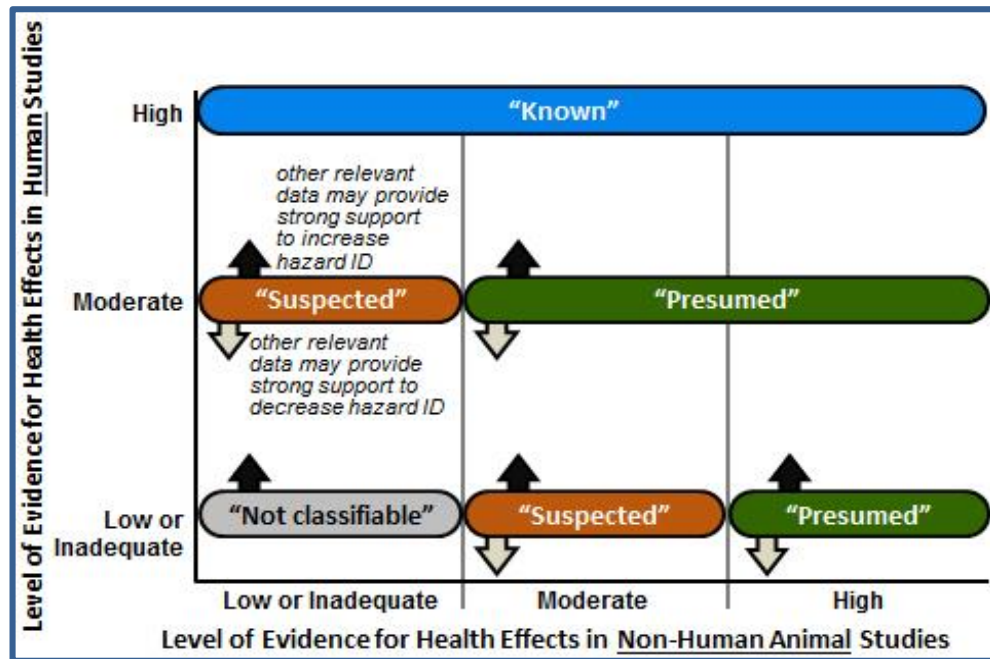
Consider human and animal evidence together

### (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





# Methods for Developing NTP Monographs

## Integrate Evidence to Develop Hazard Conclusions

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

### (1) Initial Hazard Conclusion

Consider human and animal evidence together

### (2) Final Hazard Conclusion

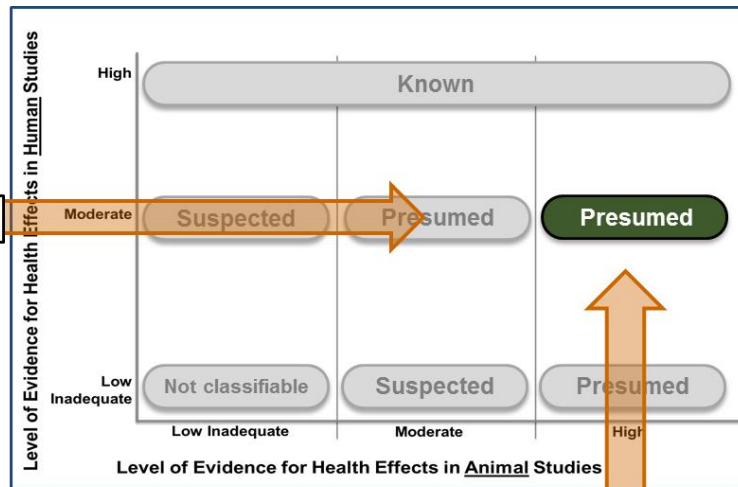
Consider impact of any relevant mechanistic data and biological plausibility of effect

Assess if there is:

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



Human Evidence



Animal

Example  
to illustrate  
the method



# Methods for Developing NTP Monographs

## Integrate Evidence to Develop Hazard Conclusions

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

### (1) Initial Hazard Conclusion

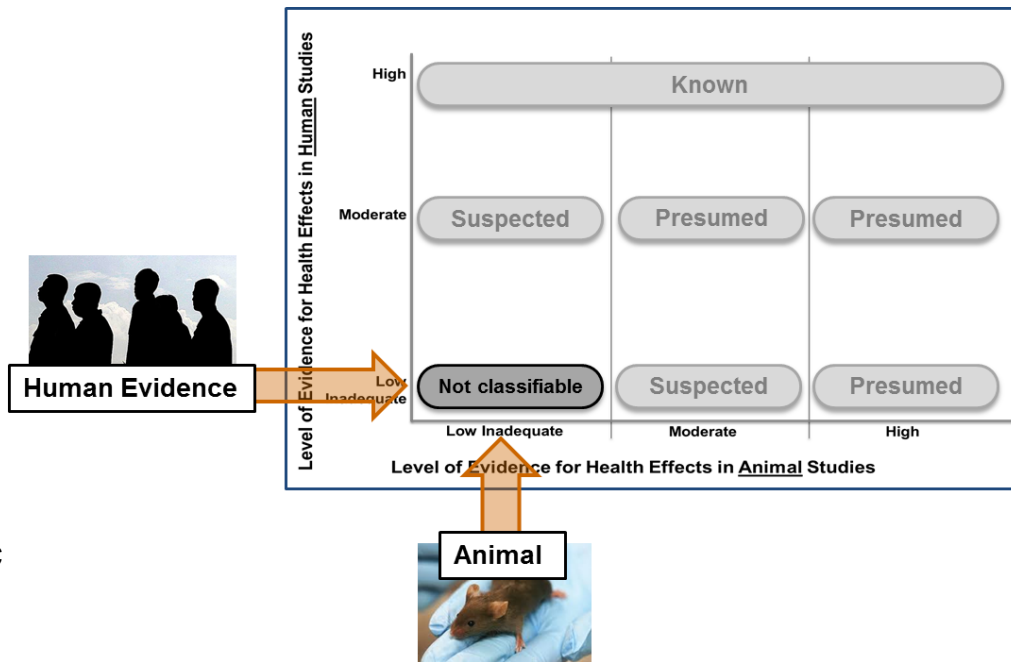
Consider human and animal evidence together

### (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





# Methods for Developing NTP Monographs

## Integrate Evidence to Develop Hazard Conclusions

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

### (1) Initial Hazard Conclusion

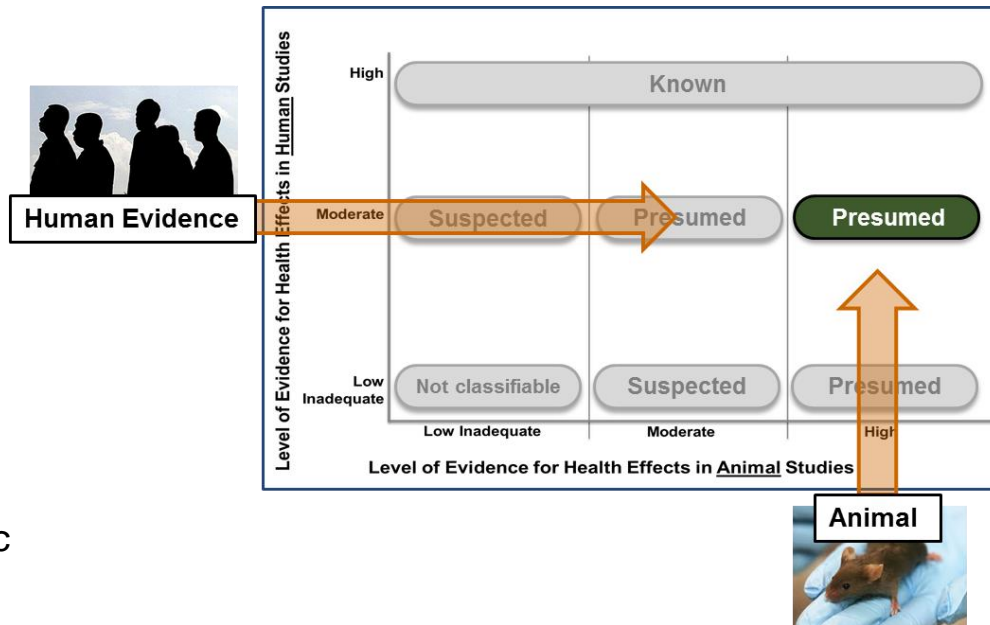
Consider human and animal evidence together

### (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
- Or not impact the hazard ID





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Questions?