

Changes in Cholinesterase Levels

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Level of Evidence Conclusions

- **Animal Studies**

- Initial time period (>24 hours to 7 days): Moderate level of evidence
- Intermediate time period (8 days to 1 year): Moderate level of evidence
- Extended time period (>1 year): Inadequate level of evidence

- **Human Studies**

- Initial time period (>24 hours to 7 days): High level of evidence
- Intermediate time period (8 days to 1 year): Inadequate level of evidence
- Extended time period (>1 year): Inadequate level of evidence



Changes in Cholinesterase (ChE) Levels

Animal Data

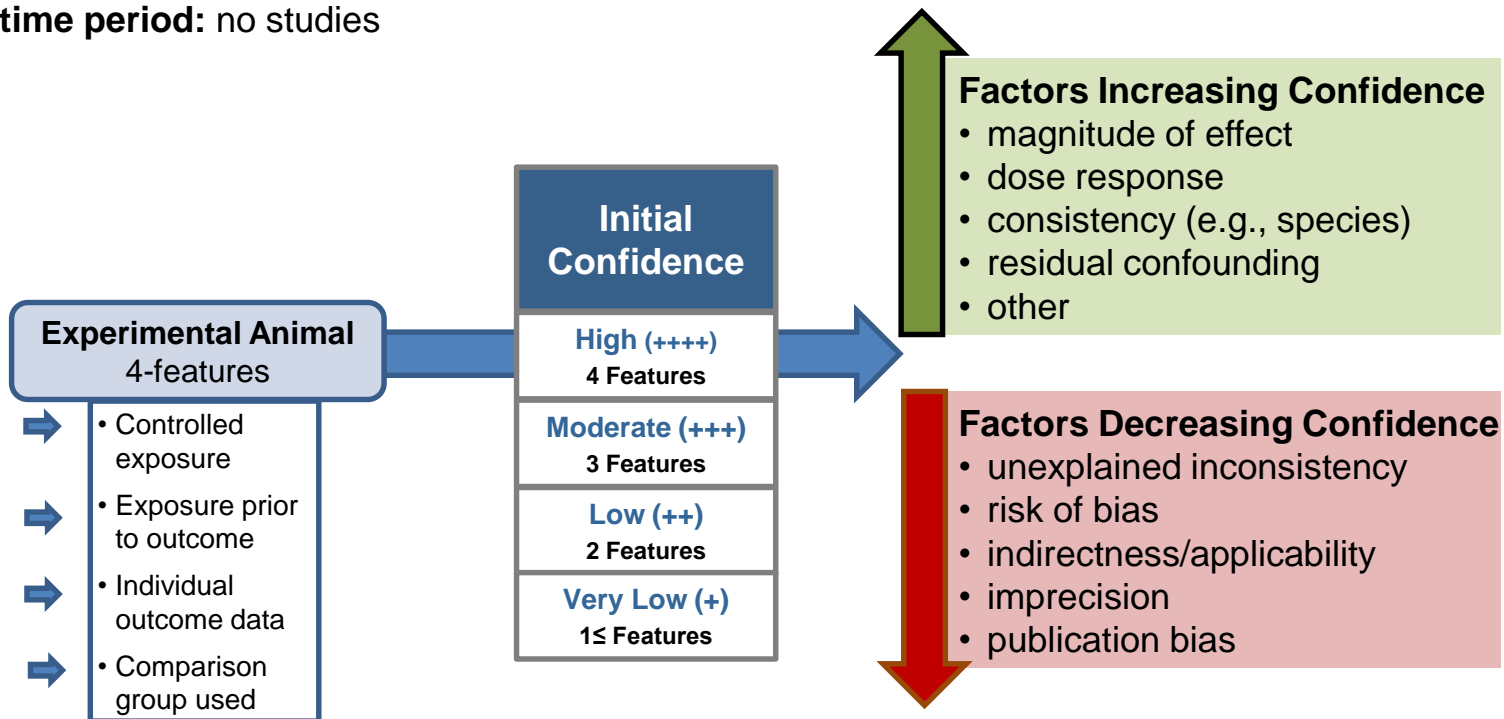
- Bodies of evidence
 - **Initial time period:** 11 studies
 - **Intermediate time period:** 8 studies
 - **Extended time period:** No studies identified
- Effects:
 - **Initial:** Lower ChE levels
 - Consistently lower ChE in blood/plasma in rats and monkeys, data on brain levels more heterogeneous
 - **Intermediate:** Lower ChE levels reported weeks to months
 - Decreased ChE activity blood in rats and monkeys in early weeks; fewer significant effects at later time periods of weeks to months
 - Decreased ChE activity in different brain regions; no effect found in some studies
 - Some evidence of compensatory upregulation of ChE brain activity weeks to months following acute exposure
 - **Extended:** No studies



Confidence Considerations to Support Level of Evidence

Animal – Changes in Cholinesterase

- **Initial time period:** 11 studies
- **Intermediate time period:** 7 studies
- **Extended time period:** no studies






Confidence Considerations to Support Level of Evidence

- Factors that could decrease confidence

- Risk of Bias

- Probably high for 1 key question (randomization, exposure characterization, or outcome assessment) in lowest risk of bias studies (e.g., Pearce 1999; RamaRao 2011)
- Most studies probably high risk of bias for details not reported (NR) on multiple questions
- Downgrades of 1 or 2 levels considered

- No changes for other factors that could decrease confidence

- 
- unexplained inconsistency
 - risk of bias
 - indirectness/applicability
 - imprecision
 - publication bias

Initial
and
Intermediate




Confidence Considerations to Support Level of Evidence

- Factors that decreased confidence

- Risk of Bias 

- Probably high for 1 key question in low risk of bias studies
- Most studies probably high risk of bias for details not reported (NR) on multiple questions

- 
- unexplained inconsistency
 - risk of bias
 - indirectness/applicability
 - imprecision
 - publication bias

- Factors that increased confidence

- Large Magnitude (*upgrade considered**)


- ChE Suppression range 10-85%, heterogenous data

- Dose Response (*upgrade considered**)

- Greater suppression with higher dose in some studies or across studies

- Consistency (*upgrade considered**)

- Suppression in rodents and primates, heterogeneous data

- 
- magnitude of effect
 - dose response
 - consistency (e.g., species)
 - residual confounding
 - other

*Decision not to upgrade due to multiple risk of bias concerns



Changes in Cholinesterase Levels

Cholinesterase Evidence Profile for Sarin										
INITIAL CONFIDENCE for each body of evidence (# of studies)	Factors decreasing confidence “---” if no concern; “↓” if serious concern to downgrade confidence					Factors increasing confidence “---” if not present; “↑” if sufficient to upgrade confidence				FINAL CONFIDENCE RATING
	Risk of Bias	Unexplained Inconsistency	Indirectness	Imprecision	Publication Bias	Large Magnitude	Dose Response	Residual Confounding	Consistency Species/Model	
<i>Animal</i>										
Initial period - Initial High (11 mammal studies)	↓	---	---	---	---	---	---	---	---	Moderate
Intermediate period – Initial High (8 mammal studies)	↓	---	---	---	---	---	---	---	---	Moderate
Extended period No studies	---	---	---	---	---	---	---	---	---	No rating

- **Moderate Confidence** that acute sarin exposure is associated with suppression of ChE blood and brain levels in animals in the initial and intermediate time periods
- Consistent evidence of suppression of ChE within days following acute sarin exposure, but the length of the suppression varied by study, and there was less evidence for suppression 1 week to 90 days
- **Limitations:** risk-of-bias concerns, small sample sizes (n = 2–6 for most studies), and heterogeneity of the data (outcomes measured, when the outcomes were measured, the species or strain used, and method for administering sarin)



Human Data

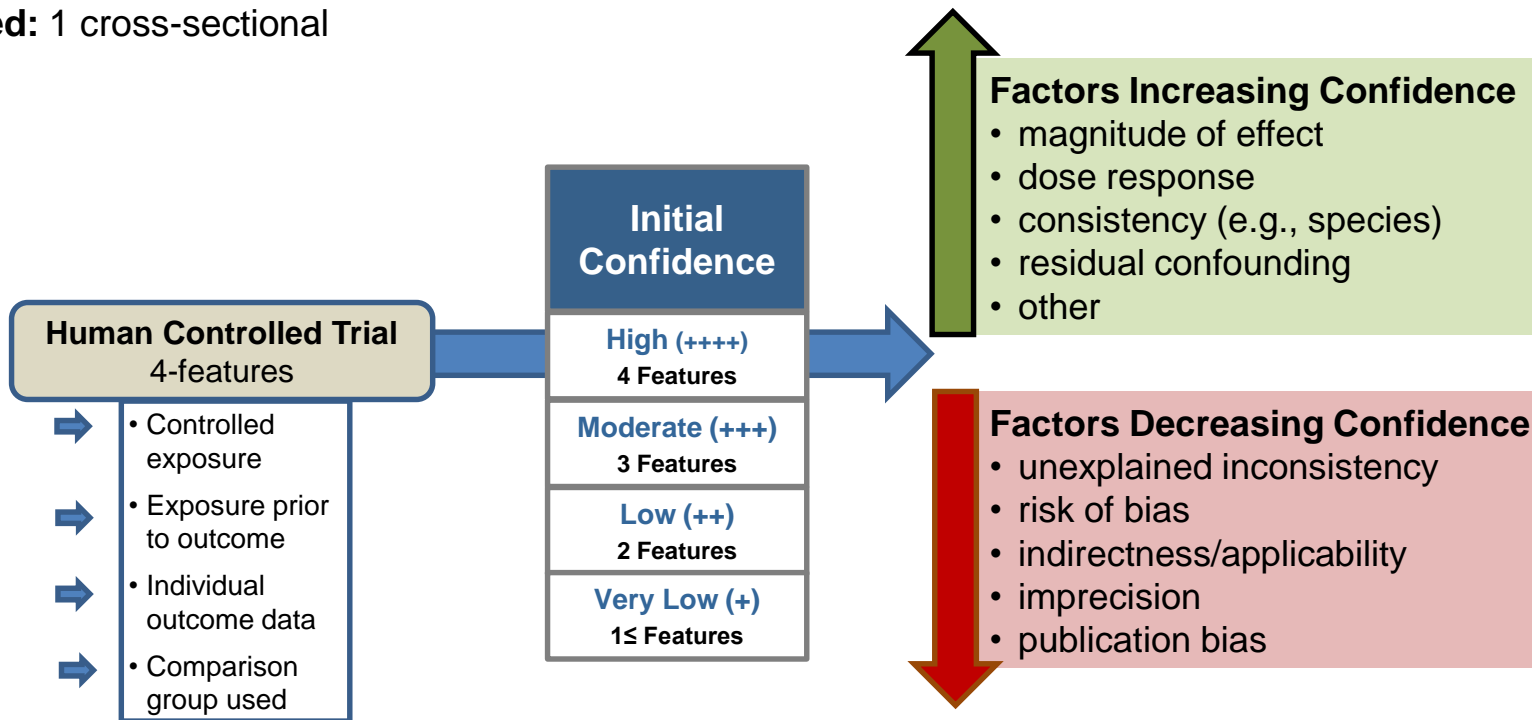
- Bodies of evidence
 - **Initial time period:** 2 non-randomized controlled trials, 2 case reports/series
 - **Intermediate time period:** 6 case reports/series
 - **Extended time period:** 1 cross-sectional study
- Effects:
 - **Initial:** Consistent evidence of lower ChE in blood/plasma 1–7 days following exposure
 - **Intermediate:** Consistent evidence of lower ChE in blood/plasma weeks to months following exposure
 - **Extended:** One cross-sectional study provided no evidence of changes in ChE >1 year following exposure



Confidence Considerations to Support Level of Evidence

Confidence Conclusions Primarily Based on:

- **Initial:** 2 controlled trial
- **Intermediate:** 6 case-reports
- **Extended:** 1 cross-sectional

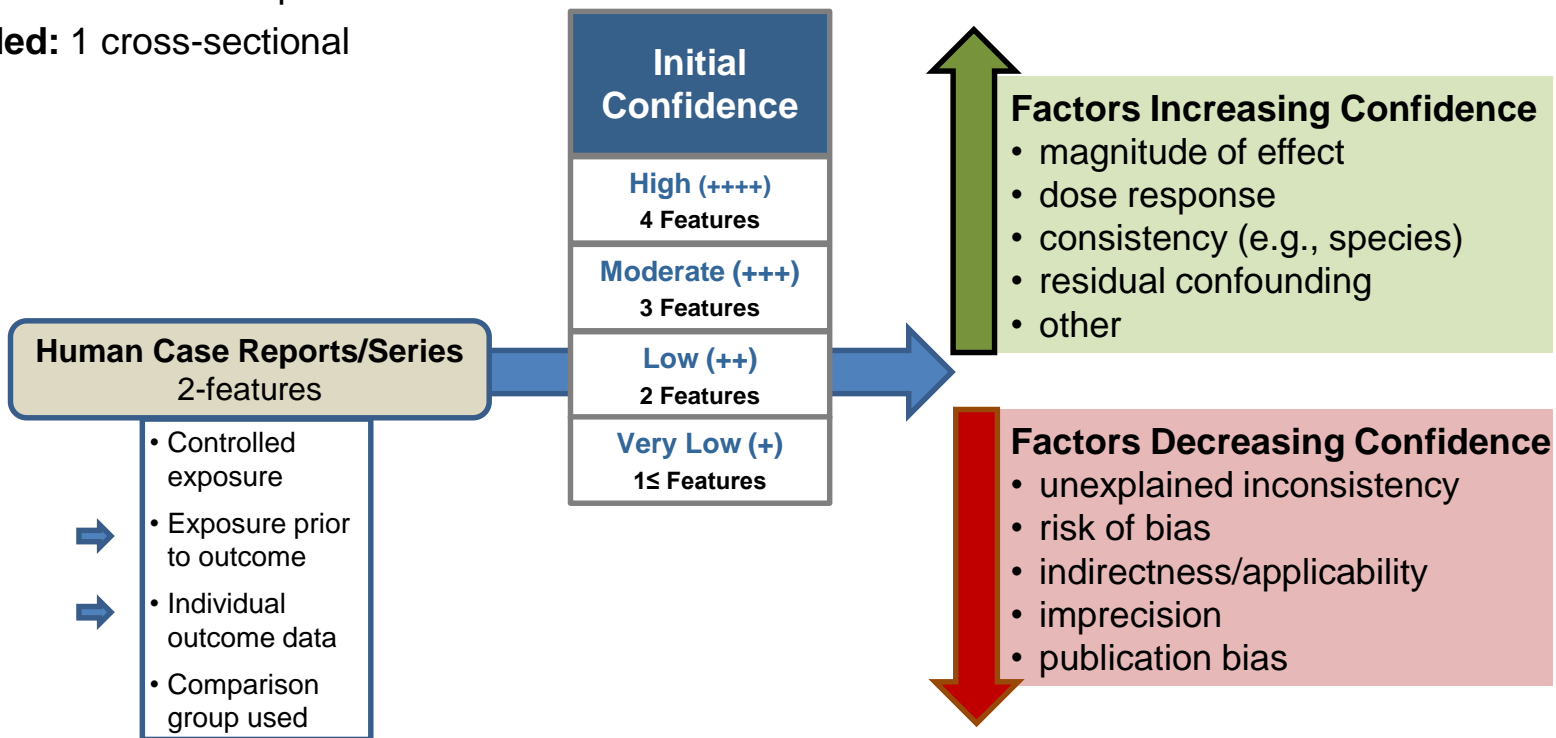




Confidence Considerations to Support Level of Evidence

Confidence Conclusions Primarily Based on:

- **Initial:** 2 controlled trial
- **Intermediate:** 6 case-reports
- **Extended:** 1 cross-sectional





Confidence Considerations to Support Level of Evidence


- Factors that could decrease confidence

- Risk of Bias

Initial

2 controlled exposure studies (Baker 1996, Grob 1958)
probably high for 1 key question

- **Randomization:** not applicable in Baker, subjects served as own control; not reported for Grob
- **Exposure characterization:** probably low for Baker; probably high for Grob due to 90% purity sarin; remaining 10% stated to potentially have anticholinesterase activity
- **Outcome assessment:** definitely low or probably low for ChE detection methods. Blinding of outcome assessors not reported (NR). Overall rating NR based on lack of blinding.

- 
- unexplained inconsistency
 - risk of bias
 - indirectness/applicability
 - imprecision
 - publication bias

Initial
and
Intermediate

Case reports and case series; probably high for 1 key question

- **Confounding:** no indication accounted for studies
- **Outcome assessment:** probably low for 3 of 7 studies; probably high for others based on blinding

- No changes for other factors that could decrease confidence




Confidence Considerations to Support Level of Evidence

- Factors that decreased confidence

All

- Risk of Bias ↓

- Probably high for 1 key question in 2 controlled trials


- 
- unexplained inconsistency
 - risk of bias
 - indirectness/applicability
 - imprecision
 - publication bias

- Factors that increased confidence

Initial

- Large Magnitude ↑

- Consistent ChE Suppression range 48-66%

- 
- magnitude of effect
 - dose response
 - consistency (e.g., species)
 - residual confounding
 - other



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<i>Human</i>										
Initial period - Initial High (2 non-randomized controlled trials)	↓	---	---	---	---	↑	---	---	---	High
Intermediate period – Initial Low (6 case reports/series)	↓	---	---	---	---	---	---	---	---	Very Low
Extended period – Initial Moderate (1 cross-sectional study)	↓	---	---	---	---	---	---	---	---	Low

- **High confidence** that acute sarin exposure suppresses ChE blood levels in humans over the initial period of 1–7 days following acute sarin exposure
- High confidence for suppressed ChE in the days following acute exposure is supported by the well-established response for immediate ChE inhibition in the first 24 hours following acute sarin exposure
- **Limitations:** risk-of-bias concerns, small sample sizes (n = 8–10 for the controlled trials), and uncertainties related to study design for the case reports/series



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Questions?