Actions from Peer Review of the Draft NTP Monograph on the Systematic Review of Long-Term Neurological Effects Following Acute Exposure to the Organophosphorus Nerve Agent Sarin

February 4, 2019

The National Toxicology Program (NTP) convened a Peer Review Panel (“the Panel”) via webcast on February 4, 2019, to peer review the Draft NTP Monograph on the Systematic Review of Long-Term Neurological Effects Following Acute Exposure to the Organophosphorus Nerve Agent Sarin. Meeting information, including the draft monograph, is currently archived under NTP’s “Past Events.”¹ A meeting report will be prepared and posted to the NTP website when completed.

The Panel peer reviewed the draft monograph and provided its opinion on NTP’s preliminary level of evidence conclusions and hazard identification conclusions on long-term neurological effects following acute sarin exposure. NTP will consider the Panel’s peer-review comments in finalizing the monograph. When completed, the monograph will be published on the NTP website.³

Preliminary Level of Evidence Conclusions

Cholinesterase Levels: Animal Studies

- The Panel voted to accept (5 yes, 2 no, 0 abstentions) the level of evidence conclusion as written: the scientific evidence from experimental animal studies for a decrease in cholinesterase levels during the initial time period (>24 hours to 7 days) after acute sarin exposure supports a moderate level of evidence.
- The Panel voted to accept unanimously (7 yes, 0 no, 0 abstentions) the level of evidence conclusion as written: the scientific evidence from experimental animal studies for a decrease in cholinesterase levels during the intermediate time period (8 days to 1 year) after acute sarin exposure supports a moderate level of evidence.
- The Panel voted to accept unanimously (7 yes, 0 no, 0 abstentions) the level of evidence conclusion as written: the lack of scientific evidence from experimental animal studies for changes in cholinesterase levels during the extended time period (>1 year) after acute sarin exposure supports an inadequate level of evidence.

Cholinesterase Levels: Human Studies

- The Panel voted to accept unanimously (7 yes, 0 no, 0 abstentions) the level of evidence conclusion as written: the scientific evidence from human studies for a decrease in cholinesterase levels during the initial time period (>24 hours to 7 days) after acute sarin exposure supports a high level of evidence.
- The Panel recommended unanimously (7 yes, 0 no, 0 abstentions) the level of evidence conclusion with the following marked changes: the scientific evidence from human studies for changes in cholinesterase levels during the intermediate time period (8 days to 1 year) after acute sarin exposure supports a moderate low level of evidence.
- The Panel voted to accept unanimously (7 yes, 0 no, 0 abstentions) the level of evidence conclusion as written: the lack of scientific evidence from human studies for changes in

¹ https://ntp.niehs.nih.gov/go/meeting
³ https://ntp.niehs.nih.gov/go/sarin
cholinesterase levels during the extended time period (>1 year) after acute sarin exposure supports an *inadequate level of evidence*.

**Visual and Ocular Effects: Animal Studies**

- The Panel voted to accept (5 yes, 2 no, 0 abstentions) the level of evidence conclusion as written: the lack of scientific evidence from experimental animal studies for visual and ocular effects during the initial time period (>24 hours to 7 days) after acute sarin exposure supports an *inadequate level of evidence*.
- The Panel voted to accept unanimously (7 yes, 0 no, 0 abstentions) the level of evidence conclusion as written: the lack of scientific evidence from experimental animal studies for visual and ocular effects during the intermediate time period (8 days to 1 year) after acute sarin exposure supports an *inadequate level of evidence*.
- The Panel voted to accept unanimously (7 yes, 0 no, 0 abstentions) the level of evidence conclusion as written: the lack of scientific evidence from experimental animal studies for visual and ocular effects during the extended time period (>1 year) after acute sarin exposure supports an *inadequate level of evidence*.

**Visual and Ocular Effects: Human Studies**

- The Panel voted to accept unanimously (7 yes, 0 no, 0 abstentions) the level of evidence conclusion as written: the scientific evidence from human studies for visual and ocular effects during the initial time period (>24 hours to 7 days) after acute sarin exposure supports a *moderate level of evidence*.
- The Panel voted to accept unanimously (7 yes, 0 no, 0 abstentions) the level of evidence conclusion as written: the scientific evidence from human studies for visual and ocular effects during the intermediate time period (8 days to 1 year) after acute sarin exposure supports a *moderate level of evidence*.
- The Panel recommended unanimously (7 yes, 0 no, 0 abstentions) the level of evidence conclusion with the following marked changes: the scientific evidence from human studies for visual and ocular effects during the extended time period (>1 year) after acute sarin exposure supports an *inadequate low level of evidence*.

**Learning, Memory, and Intelligence: Animal Studies**

- The Panel recommended unanimously (7 yes, 0 no, 0 abstentions) the level of evidence conclusion with the following marked change: the scientific evidence from experimental animal studies for effects on learning, memory, and intelligence during the initial time period (>24 hours to 7 days) after acute sarin exposure supports a *moderate low level of evidence*.
- The Panel recommended unanimously (7 yes, 0 no, 0 abstentions) the level of evidence conclusion with the following marked change: the scientific evidence from experimental animal studies for effects on learning, memory, and intelligence during the intermediate time period (8 days to 1 year) after acute sarin exposure supports a *moderate low level of evidence*.
- The Panel voted to accept unanimously (7 yes, 0 no, 0 abstentions) the level of evidence conclusion as written: the scientific evidence from experimental animal studies for effects on learning, memory, and intelligence during the extended time period (>1 year) after acute sarin exposure supports a *low level of evidence*.

**Learning, Memory, and Intelligence: Human Studies**

- The Panel voted to accept unanimously (7 yes, 0 no, 0 abstentions) the level of evidence conclusion as written: the lack of scientific evidence from human studies for effects on learning,
memory, and intelligence during the initial time period (>24 hours to 7 days) after acute sarin exposure supports an *inadequate level of evidence*.

- The Panel voted to accept unanimously (7 yes, 0 no, 0 abstentions) the level of evidence conclusion as written: the scientific evidence from human studies for effects on learning, memory, and intelligence during the intermediate time period (8 days to 1 year) after acute sarin exposure supports a *low level of evidence*.

- The Panel voted to accept unanimously (7 yes, 0 no, 0 abstentions) the level of evidence conclusion as written: the scientific evidence from human studies for effects on learning, memory, and intelligence during the extended time period (>1 year) after acute sarin exposure supports a *moderate level of evidence*.

**Nervous System Morphological and Histological Changes: Animal Studies**

- The Panel voted to accept (5 yes, 2 no, 0 abstentions) the level of evidence conclusion as written: the scientific evidence from experimental animal studies for nervous system morphological and histological changes during the initial time period (>24 hours to 7 days) after acute sarin exposure supports a *moderate level of evidence*.

- The Panel voted to accept (5 yes, 2 no, 0 abstentions) the level of evidence conclusion as written: the scientific evidence from experimental animal studies for nervous system morphological and histological changes during the intermediate time period (8 days to 1 year) after acute sarin exposure supports a *moderate level of evidence*.

- The Panel voted to accept unanimously (7 yes, 0 no, 0 abstentions) the level of evidence conclusion as written: the lack of scientific evidence from experimental animal studies for nervous system morphological and histological changes during the extended time period (>1 year) after acute sarin exposure supports an *inadequate level of evidence*.

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**Other Outcomes That Did not Reach Hazard Conclusions**

- The Panel concurred with the statement that the evidence from both the human and animal studies of sleep disruption, anxiety and fear, avoidance and depression, activity/strength, other neurological symptoms, electroencephalogram, and other sensory effects after acute sarin exposure supports *inadequate or low levels of evidence* due to fewer studies, inconsistency in findings, heterogeneity of data, and study limitations.
Preliminary Hazard Identification Conclusions

- The Panel voted to accept unanimously (7 yes, 0 no, 0 abstentions) the hazard identification conclusion as written: for the initial time period (>24 hours to 7 days) following acute sarin exposure, sarin is known to be a neurological hazard to humans based on suppression of cholinesterase which indicates nervous system disruption via acetylcholine build up.

- The Panel voted to accept (6 yes, 1 no, 0 abstentions) the hazard identification conclusion with the following marked change: for the intermediate time period (8 days to 1 year) following acute sarin exposure, sarin is suspected to be a 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 tissues.

- The Panel voted to accept (6 yes, 1 no, 0 abstentions) the hazard identification conclusion as written: for the extended time period (>1 year) following acute sarin exposure, sarin is suspected to be a neurological hazard to humans based on multiple effects including effects on learning and memory, and morphological and histological changes in nervous system tissues.