

Report on Peer Review of Draft NTP Monograph on Sarin

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Background Materials

- NTP's website on the evaluation of potential long-term neurological effects of sarin: <https://ntp.niehs.nih.gov/go/sarin>
- Peer review of the draft NTP Monograph was conducted by an *ad hoc* expert panel in a public meeting held February 4, 2019: <https://ntp.niehs.nih.gov/events/past/index.html?type=&&date=2019-02-04> for meeting materials and peer review report

Overview

Sarin is a highly toxic organophosphorus nerve agent that was developed for chemical warfare during World War II and continues to be used in conflicts despite prohibition by international treaties. While the immediate effects of sarin exposure are well known, the evidence for neurological effects in the period from days to years after acute exposure to sarin were not well characterized. The National Institutes of Health (NIH) Countermeasures Against Chemical Threats (CounterACT) program asked NTP to evaluate the publicly available literature on potential long-term neurological effects associated with acute sarin exposure to inform the research focus on treatment options for prolonged effects of sarin.

NTP conducted a systematic review to evaluate the evidence for long-term neurological effects in humans and animals following acute exposure to sarin. A protocol was developed and utilized for this evaluation following the Office of Health Assessment and Translation (OHAT) approach for systematic review and evidence integration. To address the nomination, any effect observed 24 hours after exposure was considered *long-term*. Hazard conclusions were considered for three time periods after exposure: initial (>24 hours–7 days), intermediate (8–364 days), and extended (greater than or equal to 1 year) periods.

The literature search and screening process identified 34 human studies and 51 animal studies (from 6,837 potentially relevant references) that met the objective and inclusion criteria. Four main health-effect categories of neurological response were identified as having sufficient data to reach hazard conclusions: (1) cholinesterase levels; (2) visual and ocular effects; (3) learning, memory, and intelligence; and (4) morphology and histopathology in nervous system tissues. Hazard conclusions were considered for these four main health-effect categories at all three time-periods after exposure. The conclusions with the highest level of evidence for each time period were used to reach the overall conclusions.

NTP concludes that acute sarin exposure is:

- *known to be a neurological hazard to humans* in the initial time period of >24hours–7 days after exposure based on suppression of cholinesterase;
- *suspected to be a neurological hazard to humans* in the intermediate time period of 8 days–1 year after exposure based on multiple effects, including suppression of cholinesterase, visual and ocular effects, and morphological and histological changes in nervous system tissues; and
- *suspected to be a neurological hazard to humans* in the extended time period of greater than or equal to 1 year after exposure based on multiple effects, including effects on learning and memory and morphological and histopathological changes in nervous system tissues.

The panel agreed with the draft conclusions for all three time periods and provided valuable comments that were considered during finalization of the NTP Monograph. For example, NTP expanded the discussion of key data gaps based on feedback received from the panel as well as NIH CounterACT. Considering the context in which humans are typically exposed to sarin (i.e., during wartime situations and terrorist attacks), there is a need for immediate treatment as well as gathering data that could help inform future responses. Because exposures are rare, and unpredictable events, there could be value to developing a rapid research response capability so that emergency response would include the latest treatment knowledge for the victims and collect vital human clinical data soon after chemical exposures. NTP is in the process of formatting the document for posting.