A Streamlined, Scientifically Rigorous Approach to Categorize Health Hazards

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Based on 2018 NASEM Report:
Review of Report and Approach to Evaluating Long-Term Health Effects in Army Test Subjects

Statement of Task

- Evaluate "The Army's Report" - literature review and analysis of 100+ chemical and biological agents, drugs, medications, and substances
  - Were potential long-term health effects appropriately identified?
  - Was the weight-of-evidence approach to characterize associations between agents and their potential effects adequate?
- Evaluate Army's "Memorandum" - approach to evaluate agent- and outcome-specific associations
- Prepare two reports
  - Interim report released in February 2018 (NASEM 2018a)
  - Final report (NASEM 2018b)

Sponsor: US Army

Committee

Ivan Rusyn (Chair), Texas A&M University
Erin Bell, University at Albany
Gerry Boss, University of California at San Diego
James Cleaver, University of California at San Francisco
Pamela Lein, University of California at Davis
Catherine McCarty, University of Minnesota
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Kenneth Still, Portland State University
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Staff: Susan Martel, Tamara Dawson

Background and Context

Army Testing

- 1942-1975 testing on human subjects.
- >100 test agents, including chemical warfare agents, biological agents, medications, vaccine, and other substances.

Potential Long-Term Health Effects

- Periodic evaluations of the scientific literature.
- Army required to notify subjects about new information about potential health effects and to provide medical care for disease or conditions proximately caused by exposures during the tests.

Background and Context (cont.)

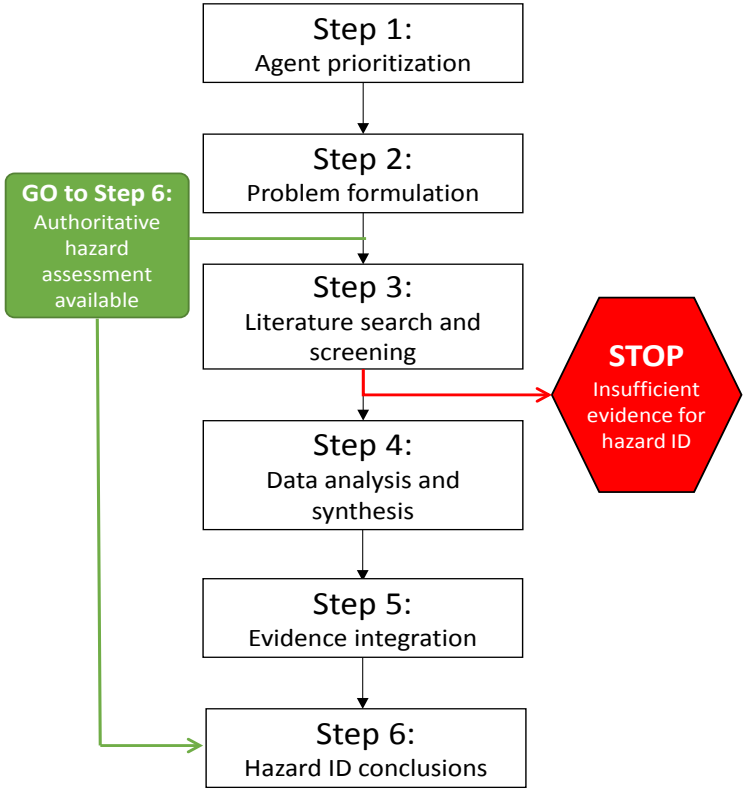
Potential Long-Term Health Effects

- **2016 court injunction** required an update to 2006 notification.
- Strategy needed to update literature reviews and to make determinations about general causation.
- Results will inform adjudication of applications for medical care.
- Army has **120 days from receipt of application to make a determination**.

Committee's Proposed Strategy

Recommendation:

- The Army should develop a ***streamlined, scientifically rigorous approach*** to categorize health hazards.
- The committee proposed a six step process.



Proposed Strategy

Step 1:
Agent prioritization

STEP 1: AGENT PRIORITIZATION

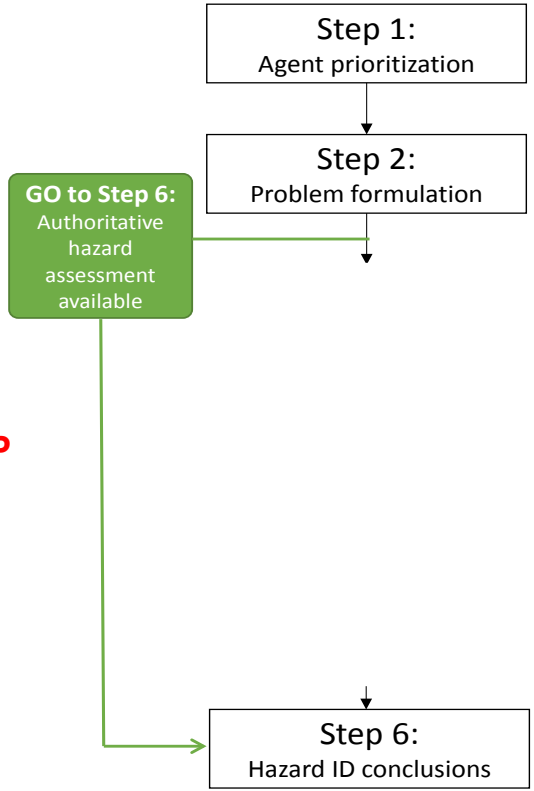
Prioritize the list of relevant factors on the basis of:

- Applications from veterans
- The number of subjects likely exposed to each test agent
- The Report findings (i.e., some form of prior literature review)
- Established hazard classifications

Proposed Strategy

STEP 2: PROBLEM FORMULATION

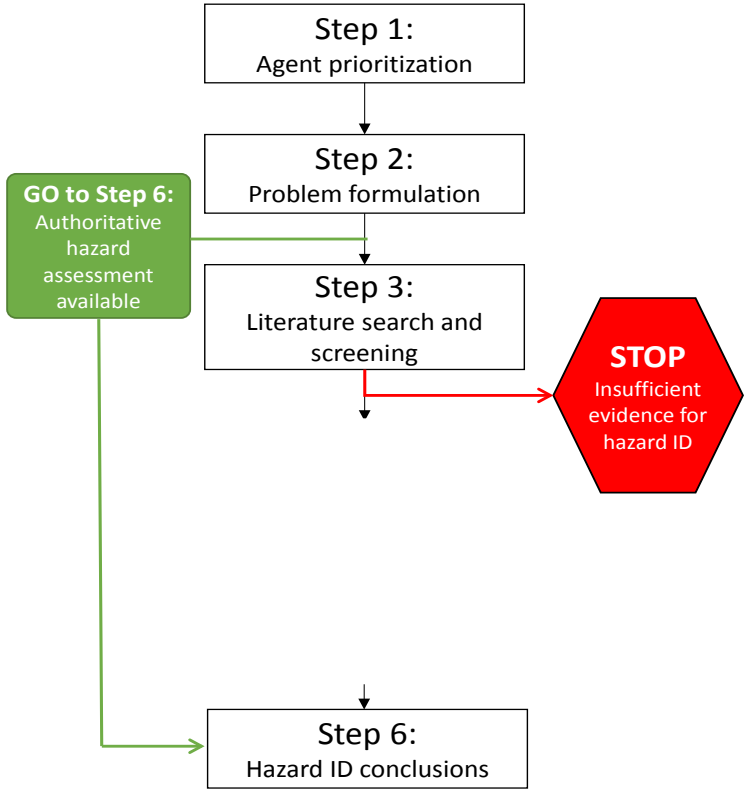
- Define scope for evidence evaluation (e.g., exposure routes, durations, types of data)
- Formulate a question
- Determine whether hazard or risk assessments are available from ***authoritative sources:***
  - ***Cancer effects: e.g., ACGIH, EPA, IARC, IOM, NASEM, NTP***
  - ***Non-cancer effects: e.g., ACGIH, ATSDR, EPA, IOM, NASEM, NTP***
- If deemed relevant and appropriate, adopt hazard identification conclusion (go to Step 6)
- If not available or appropriate, develop a review protocol for answering the question (go to Step 3)



Proposed Strategy

STEP 3: LITERATURE SEARCH AND SCREENING

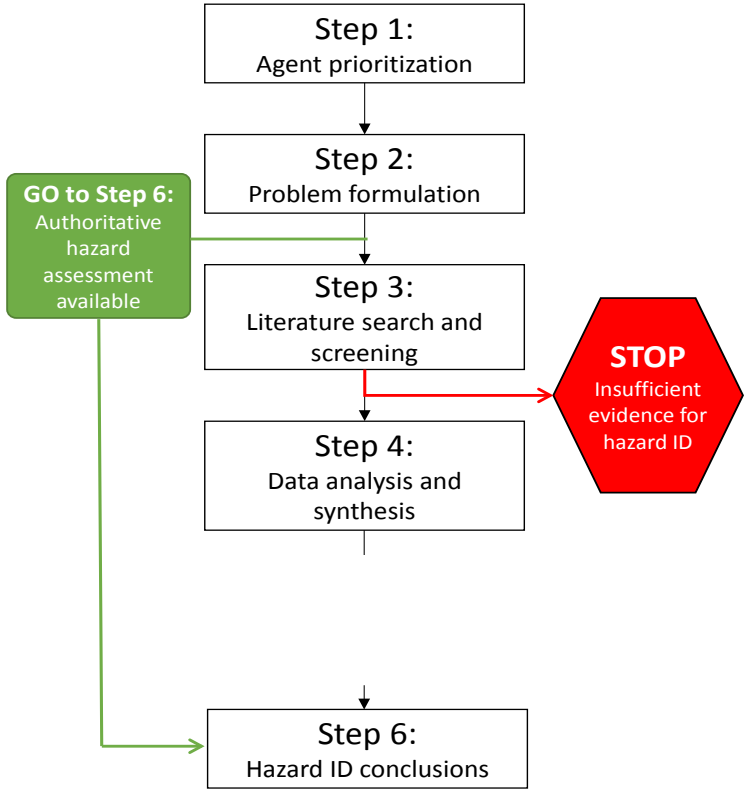
- Develop a review protocol:
  - Define search strategy (e.g., databases, search terms, dates)
  - Define inclusion and exclusion criteria to determine relevance
  - Provide guidelines for determining study quality
- ***Follow systematic review principles to the extent possible***
- Document literature search results



Proposed Strategy

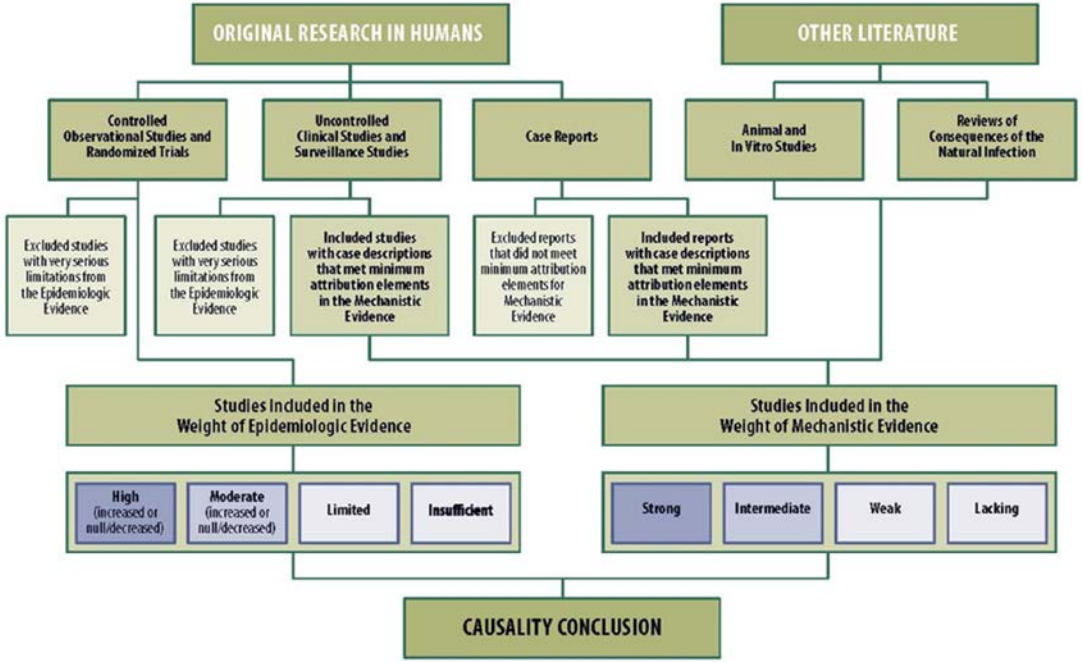
STEP 4: DATA ANALYSIS AND SYNTHESIS

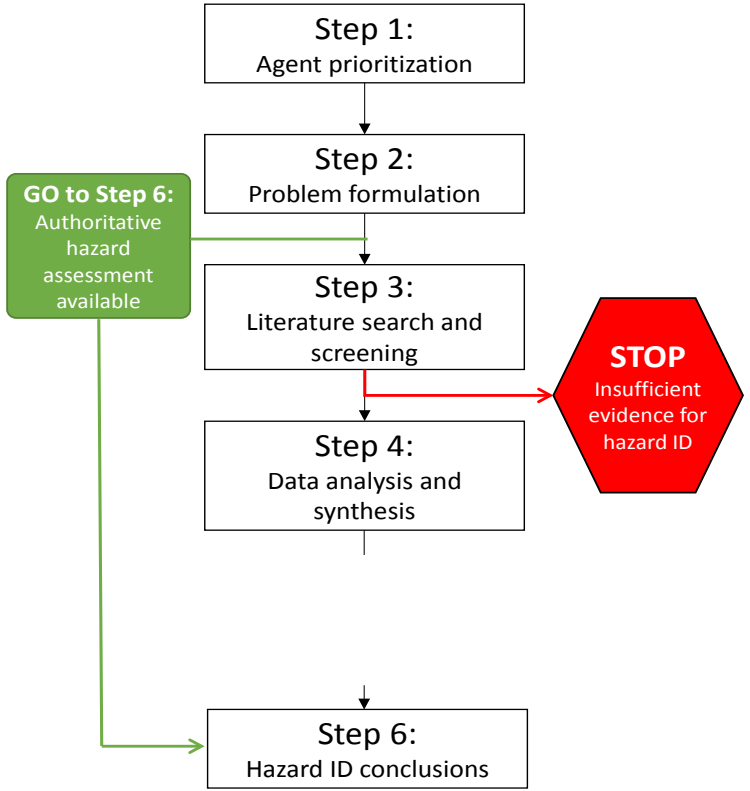
- Evaluate individual study quality
- Synthesize each line of evidence by considering such factors as the consistency across study designs, species, and populations; dose response; and magnitude of the effect.



Proposed Strategy

STEP 4: DATA ANALYSIS AND SYNTHESIS



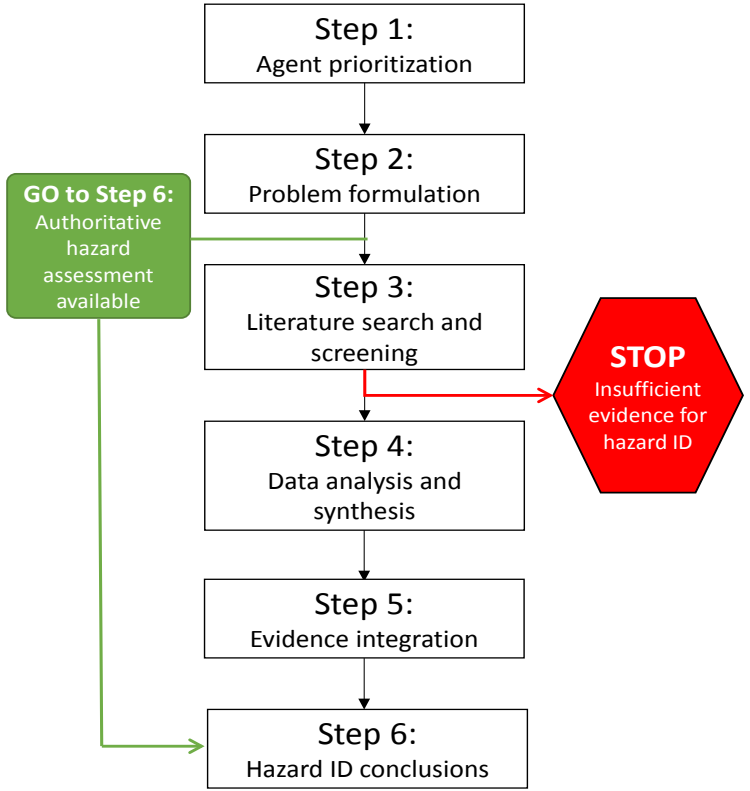


Process of reviewing epidemiological and mechanistic evidence in the IOM Vaccine Approach (IOM, 2012)

Proposed Strategy

STEP 5: EVIDENCE INTEGRATION

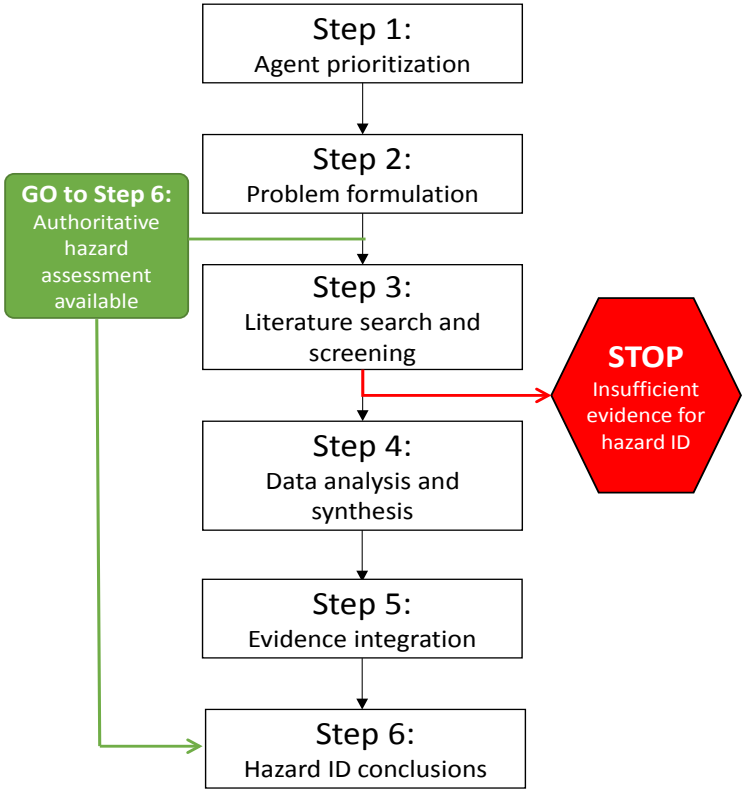
- Is the most critical step in the strategy because it involves determining **a causality conclusion** on the basis of the **strength of association** between an agent and an adverse health effect
- The different lines of evidence that were analyzed separately in Steps 3 and 4 are integrated using **expert judgement**
- The **transparency** and **documentation** of this step is critical for the credibility and confidence in the conclusions drawn from the available evidence



Proposed Strategy

STEP 5: EVIDENCE INTEGRATION

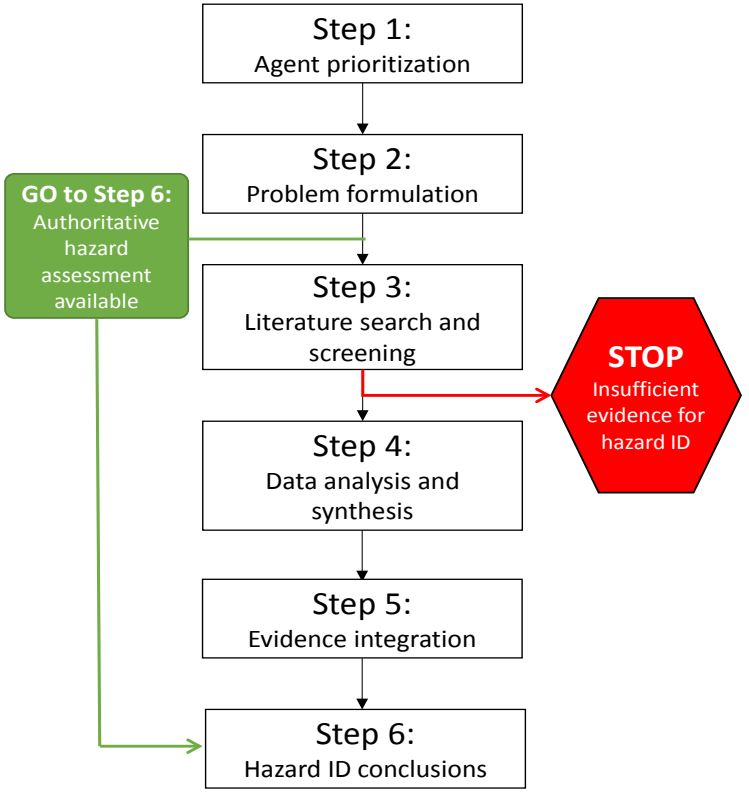
- Specify the weight-of-evidence approach that will be used to make determinations about associations (e.g., existing approach, adaptation of an approach, or alternative approach):
  - Institute of Medicine (IOM, 2000, 2012; NASEM, 2016) to draw causality conclusions rely primarily on epidemiological evidence
  - NTP (NTP, 2015) approach includes explicit consideration of animal data and epidemiological data, as well as mechanistic data
  - IARC approach (IARC 2019) includes all lines of evidence



Proposed Strategy

STEP 6: DRAWING HAZARD IDENTIFICATION CONCLUSIONS

- May depend on the method for evidence integration and the choice of "hazard classes"
- Must include a concluding statement that specifies:
  - the test agent,
  - exposure scenario(s),
  - health effect(s), and
  - strength of association



Conclusions

- The committee recommends that the [Agency] develop a ***streamlined***, ***scientifically rigorous*** approach to categorize health hazards and, given the number of agents to be reviewed, a strategy to prioritize the evaluations

- The proposed strategy was based on best practices in hazard identification and systematic review, which the [Agency] can tailor to its needs

- It is likely that animal and mechanistic data will be important in hazard evaluations for many test agents and substances; therefore, different integrative weight-of-evidence frameworks may be considered

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