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IRIS Assessment Plan for Chloroform

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AUTHORS | CONTRIBUTORS

Assessment Team

Ted Berner (Assessment Manager)	U.S. EPA/ORD/NCEA
Amina Wilkins	
Jenny Li	
Amanda Persad	
Audrey Galizia	

Executive Direction

Tina Bahadori	NCEA Center Director
Mary Ross	NCEA Deputy Center Director
Kris Thayer	IRIS Division Director
Vincent Cogliano	IRIS Division Director (2010-2017)
Emma Lavoie	Assistant Center Director for Scientific Support
Samantha Jones	NCEA Associate Director for Health (acting)

Contributors and Production Team

Hillary Hollinger	HERO Librarian
Ryan Jones	HERO Director
Vicki Soto	Project Management Team
Dahnish Shams	
Maureen Johnson	

1. INTRODUCTION

The Integrated Risk Information System (IRIS) Program is undertaking a reassessment of the health effects of chloroform via inhalation. IRIS assessments provide high quality, publicly available information on the toxicity of chemicals to which the public might be exposed. These assessments are not regulations, but provide a critical part of the scientific foundation for decisions made in EPA program and regional offices to protect public health.

Before beginning an assessment, the IRIS Program consults with EPA program and regional offices to define the scope of the assessment, including the nature of the hazard characterization needed, identification of the most important exposure pathways, and level of detail needed to inform program and regional office decisions. Based on the scope defined by EPA, the IRIS Program undertakes problem formulation activities to frame the scientific questions that will be the focus of the assessment, which is conducted using systematic review methodology.

This document presents the draft assessment plan for chloroform, including a summary of the IRIS Program's scoping and initial problem formulation conclusions, objectives and specific aims of the assessment; draft PECO (Populations, Exposures, Comparators, and Outcomes) framework that outlines the evidence considered most pertinent to the assessment; and identification of key areas of scientific complexity. Brief background information on uses and potential for human exposure is provided for context.

2. SCOPING AND INITIAL PROBLEM FORMULATION

2.1. BACKGROUND

Chloroform (trichloromethane) is a colorless, volatile liquid with a distinct odor. Chloroform is nonflammable. It is slightly soluble in water and is readily miscible with most organic solvents. Because chloroform is relatively volatile, it tends to escape from contaminated environmental media (e.g., water or soil) into air and may also be released in vapor form from some types of industrial or chemical operations. Therefore, humans may be exposed to chloroform not only by ingestion of chloroform in drinking water, food, or soil, but also by dermal contact with contaminated media (especially water) and by inhalation of vapor (especially in indoor air).

An assessment of chloroform is available on the IRIS website and consists of (1) an inhalation assessment, (2) an oral assessment, and (3) a mode of action (MOA) analysis for cancer (https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=25). The inhalation assessment (posted in 1987) derived an inhalation unit risk (IUR) for chloroform of 2.3×10^{-5} per $\mu g/m^3$. This IUR was based on an oral gavage study in mice that employed a route-to-route extrapolation without the use of a physiologically based pharmacokinetic (PBPK) model.[1] That assessment did not include the derivation of a reference concentration (RfC) for chloroform. The oral assessment (posted in 2001) yielded a reference dose (RfD) of 1×10^{-2} mg/kg-day. Also posted in 2001, the MOA analysis concluded that chloroform is likely carcinogenic to humans by all routes of exposure only under high-exposure conditions that lead to cytotoxicity and regenerative hyperplasia in susceptible tissues. Based on this MOA analysis, the RfD was determined to be protective with respect to cancer because, at the RfD, cytotoxicity—a key event in the MOA for cancer—was not observed. The inhalation assessment posted in 1987 was never updated to address the route-to-route extrapolation approach or the more recent MOA analysis.

As a result, the methodology used to derive the IUR posted in 1987 has two shortcomings: (1) it utilized a route-to-route extrapolation approach that did not employ a PBPK model, and (2) it incorporated a linear extrapolation approach for dose-response that implicitly assumes a risk of cancer at all nonzero exposures to chloroform (i.e., no threshold). The MOA analysis added in 2001, however, concluded that for cancer, chloroform exhibits a "threshold" by all routes of exposure, and thus a chloroform dose that does not elicit cytotoxicity presents no cancer risk. Therefore, the assumption underlying the IUR dose-response approach (linear extrapolation with no threshold) is inconsistent with the MOA analysis.

[1]Conducting a route-to-route extrapolation without the use of a PBPK model is no longer advocated because of the potential inaccuracy of this methodology, especially when converting doses from the oral to the inhalation route of exposure.

2.2. SCOPING SUMMARY

The chloroform inhalation assessment will be updated by deriving an RfC based on available inhalation data from human or animal studies and evaluating this RfC in light of the MOA analysis posted in 2001. During scoping, the IRIS Program met with EPA program and regional offices that had interest in an updated IRIS assessment for chloroform to discuss specific assessment needs. Table 1 provides a summary of input from this outreach. EPA's Office of Land and Emergency Management (OLEM), EPA's Office of Air and Radiation (OAR), and Region 4 expressed a specific need for an inhalation reference value for chloroform. Derivation of an RfC will address these program and regional office needs. In addition, the MOA analysis posted in 2001 will be used to determine whether this newly derived RfC is protective with respect to cancer. Finally, the derivation of the RfD and the analysis that determined the RfD was protective with respect to cancer will not be reevaluated as part of this update to the chloroform assessment because EPA program and regional offices did not express a specific need for an updated oral reference value for chloroform.

Table 1. EPA program or regional office interest in an updated chloroform assessment

Program or regional office[1]	Inhalation	Statutes/Regulations	Description of Authority/Regulation	Anticipated Uses/Interest
OLEM	✓	Comprehensive Environmental Response, Compensation and Liability Act (CERCLA) – Section 102	Authorizes EPA to promulgate regulations designating chemicals as hazardous substances which, when released into the environment, may present substantial danger to public health or welfare or the environment.	Up-to-date toxicity values (i.e., an RfC) are needed to set risk-based screening levels, derive baseline risks, establish clean-up levels, and evaluate clean-up progress at contaminated sites, many of which experience chloroform vapor intrusion.
Region 4	✓			Chloroform is present as a volatile contaminant at many industrial sites. Up-to-date toxicity values (i.e., an RfC) are needed to conduct regional risk assessment-related activities at these contaminated sites.
OAR	✓	Clean Air Act (CAA) – Section 112	Section 112 (b) defines the original list of 189 hazardous air pollutants (HAP). Under Section 112(c) of the CAA, EPA must identify and list source categories that emit HAP and then set emission standards for those listed source categories under CAA Section 112(d). CAA Section 112(b)(3)(A) specifies that any person may petition the Administrator to modify the list of HAP by adding or deleting a substance. Section 112(d) states that the EPA must establish NESHAPs for each category or subcategory of major sources and area sources of HAPs [listed pursuant to Section 112(c)]. The standards must require the maximum degree of emission reduction that the EPA determines to be achievable by each particular source category. Different criteria for maximum achievable control technology (MACT) apply for new and existing sources. Less stringent standards, known as generally available control technology (GACT) standards, are allowed at the Administrator's discretion for area sources.	Chloroform is classified as a hazardous air pollutant (HAP) under the Clean Air Act (CAA). OAR is mandated under CAA to periodically conduct risk and technology reviews (RTRs) for HAPs in which up-to-date toxicity values are needed to evaluate residual risk.
[1]OLEM (Office of Land and Emergency Management); OAR (Office of Air and Radiation); Region 4 serves Alabama, Florida, Georgia, Kentucky, Mississippi, North Carolina, South Carolina, Tennessee and 6 tribes.				

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2.3. PROBLEM FORMULATION

This assessment will consider all adverse effects elicited by inhalation exposure to chloroform for which data are available. The IRIS Program anticipates there will be fewer than 30 PECO-relevant studies, and the following health effects are likely to warrant inclusion in this assessment: nasal cavity effects, nervous system effects, liver and kidney effects, immune system effects, and reproductive/developmental effects.

3. OVERALL OBJECTIVE, SPECIFIC AIMS AND DRAFT POPULATIONS, EXPOSURES, COMPARATORS, AND OUTCOMES (PECO) FRAMEWORK

The overall objective of this assessment is to identify adverse health effects and characterize exposure-response relationships for these effects of chloroform to support development of toxicity values. More specifically, the objective of this assessment is to derive an RfC for chloroform without the need for route-to-route extrapolation by using inhalation dose-response data from human or animal studies. In addition, the MOA analysis for cancer for chloroform posted on the IRIS website in 2001 will be used to determine whether this newly derived RfC is protective with respect to cancer. If so, the current IUR for chloroform will be removed from the IRIS website. If not, the available inhalation data will be evaluated to determine whether they can be used to derive a revised IUR for chloroform that would then replace the existing IUR. This assessment will use systematic review methods to evaluate the epidemiological and toxicological literature for chloroform, including consideration of relevant mechanistic evidence. The evaluations conducted in this assessment will be consistent with relevant EPA guidance.[2] The systematic review protocol will be disseminated after review of the draft assessment plan and will reflect changes made to the specific aims and PECO framework in response to public input.

3.1. SPECIFIC AIMS

- Identify epidemiological (i.e., human) and toxicological (i.e., experimental animal) literature reporting effects of exposure to chloroform via inhalation as outlined in the PECO framework.

- Use an iterative approach to determine which mechanistic studies are most important to summarize, based on factors such as robustness of the evidence in humans and animals, likelihood to impact evidence synthesis conclusions for human health, and directness or relevance of the model systems for understanding potential human health hazards. For chloroform, evaluating individual mechanistic studies for cancer-related outcomes is not anticipated to be critical because of the existing MOA analysis. So, for mechanistic information, this assessment will rely on other published authoritative sources, such as public health agency reports and expert review articles.

[2]EPA guidance documents: http://www.epa.gov/iris/basic-information-about-integrated-risk-information-system#guidance/

- Conduct study evaluations (risk of bias and sensitivity) for individual epidemiological and toxicological studies. Studies with critical deficiencies will be considered uninformative and not considered further.

- Extract data on relevant health outcomes from epidemiological and toxicological studies included based on study evaluation.

- Synthesize the evidence across studies, assessing similar health outcomes using a narrative approach or meta-analysis (if appropriate).

- For each health outcome, express confidence in conclusions from across studies (or subsets of studies) within human and animal evidence streams, evaluating each evidence stream (human and animal) separately.

- For each health outcome, integrate results across evidence streams (human and animal) to conclude whether a substance is hazardous to humans. Identify and discuss issues concerning potentially susceptible populations and life stages. Biological support provided from mechanistic studies and non-mammalian model systems will be considered based on the iterative prioritization approach outlined in the PECO framework.

- Derive an RfC, as supported by the available data.

- Subsequent to RfC derivation, evaluate the protectiveness of the RfC against cancer based on the 2001 MOA analysis. If the RfC is protective against cancer, the IUR posted in 1987 would be removed from the IRIS website. If not, the available inhalation data will be evaluated to see if they are amenable to deriving a revised IUR for chloroform that would then replace the existing IUR.

- Characterize uncertainties and identify key data gaps and research needs such as limitations of the evidence base, limitations of the systematic review, and consideration of dose-relevance and pharmacokinetic differences when extrapolating findings from higher-dose animal studies to lower levels of human exposure.

3.2. DRAFT PECO FRAMEWORK

A PECO (Populations, Exposures, Comparators, and Outcomes) framework is used as an aid to focus the research question(s), search terms, and inclusion/exclusion criteria in a systematic review. The draft PECO framework for chloroform (Table 2) was based on (1) nomination of the chemical for assessment, (2) discussions with scientists in EPA program and regional offices to determine the scope of the assessment that will best meet Agency needs, and (3) preliminary review of the health effects literature for chloroform (primarily reviews and authoritative health assessment documents) to identify the major health hazards associated with exposure to chloroform via inhalation and key areas of scientific complexity.

Table 2. Draft PECO framework for the chloroform assessment

PECO element	Evidence
Populations	**Human:** Any population and life stage (e.g., children, general population, occupational, or high exposure from an environmental source). The following study designs will be considered most informative: controlled exposure, cohort, case-control, cross-sectional, and ecological. Note: Case reports and case series will be tracked during study screening, but are not the primary focus of this assessment. They may be retrieved for full-text review and subsequent evidence synthesis if no or few informative study designs are available. Case reports also can be used as supportive information to establish biologic plausibility for some target organs and health outcomes.
	Animal: Nonhuman mammalian animal species (whole organism) of any life stage (including preconception, in utero, lactation, peripubertal, and adult stages).
	Nonmammalian model systems/in vitro/in silico: Nonmammalian model systems (e.g., fish, amphibians, birds, *Caenorhabditis elegans*); human or animal cells, tissues, or biochemical reactions (e.g., ligand binding assays) with in vitro exposure regimens; bioinformatics pathways of disease analysis; or high throughput screening data. These studies are tagged during title and abstract screening and an iterative approach is used to prioritize their inclusion for full-text retrieval and evidence synthesis based on likelihood to impact evidence synthesis conclusions for human health[a]
Exposures	**Human:** Exposure to chloroform (CASRN 67-66-3), including occupational exposures, via inhalation. Exposures quantified by either actual exposure measurements or occupational exposure history are preferred.
	Animal: Any exposure to chloroform via inhalation. Studies employing chronic exposures or short-term developmental-only exposures will be considered the most informative. Studies involving exposures to mixtures will be included only if they include an arm with exposure to chloroform alone.
	Nonmammalian model systems/in vitro/in silico: Exposure via growth or assay medium.
Comparators	**Human:** A comparison or reference population exposed to lower levels (or no exposure/exposure below detection limits) of chloroform, or exposed to chloroform for shorter periods of time.
	Animal: A concurrent control group exposed to vehicle-only treatment.
	In vitro: Mammalian cells, bacterial strains for mutagenicity assays or cell-free assay components (targets) exposed to an appropriate control.
Outcomes	All health outcomes (both cancer and noncancer). In general, endpoints related to clinical diagnostic criteria, disease outcomes, histopathological examination, or other apical/phenotypic outcomes will be prioritized for evidence synthesis over outcomes such as biochemical measures. As discussed above, based on preliminary screening work, EPA anticipates that a systematic review for health effect categories other than those identified (i.e., nasal cavity effects, nervous system effects, liver and kidney effects, immunotoxic effects, and reproductive/developmental effects) will not be undertaken unless a significant amount of new evidence is found upon review of references during the comprehensive literature search.

[a]**Note:** An iterative approach is used to prioritize evidence from nonmammalian model systems (e.g., fish, amphibians, birds, *C. elegans*), in vitro, in silico, and other types of mechanistic studies based on likelihood to impact evidence synthesis conclusions for human health. Evidence from these studies will be tagged preliminarily during title/abstract screening as "Other Informative Studies" or "Supplemental Information" according to hazard categories or types of mechanistic outcomes/pathways. These studies are prioritized for full-text retrieval and evidence synthesis to focus on those studies most important to summarize, based on factors such as robustness of the evidence in humans and animals, directness or relevance of the model systems, and concentrations tested. For example, if robust epidemiological or nonhuman mammalian evidence is available, the need to conduct a thorough assessment of individual nonmammalian and mechanistic studies could be diminished unless controversial issues need to be resolved, e.g., issues related to applicability of animal evidence to humans or shape of the dose-response relationship at low exposure levels.

3.3. ASSESSMENT APPROACH

The chloroform inhalation assessment will be updated by deriving an RfC based on available inhalation data in human or animal studies and evaluating this RfC in light of the MOA analysis posted on the IRIS website in 2001. The newly derived RfC will inform whether the current IUR will be updated or removed.

3.4. KEY SCIENCE ISSUES

No specific key science issues have been identified outside of those described in the background and scoping summary.