Use of Human Studies for Derivation of an Acute Inhalation Reference Concentration (RfC) for Formaldehyde

Deborah Burgin, PhD, DABT

Antimicrobials Division, OPP

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Human Studies Rule Requirements

Michelle Arling, JD

Human Studies Rule Overview

- Human Studies (HS) rule outlines the requirements for consultations with the HSRB
  - Intentional exposure studies initiated after April 2006
  - All proposals for intentional exposure studies initiated after April 2006
  - Intentional exposure studies conducted prior to April 2006 with the intent to identify or measure a toxic effect
- The HS rule applies to “research involving intentional exposure of human subjects” but does not cover “observational research”

Intentional Exposure vs. Observational Studies

Intentional Exposure Studies

- Defined in HS rule
- Limited to adults and non-pregnant, non-nursing women
- Evaluated from scientific and ethical perspectives
- Under HS rule, consultation HSRB required prior to EPA's reliance on the research

Observational Studies

- No definition – not "intentional exposure"
- No HS rule restrictions on participants age, pregnancy status
- Evaluated from scientific and ethical perspectives
- No requirements under the HS rule for consultation with HSRB

OCSPP Weight of Evidence Assessment - Formaldehyde Acute Inhalation Exposure

Deborah Burgin, PhD, DABT

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Outline

- Risk Assessment Definitions
- Overview of Weight of Evidence
- Summarize Data
  - Kulle and Hanrahan
  - Andersen and Mueller
  - Lang and Liu
- OPP and OPPT exposure scenarios
  - Peak, 8-hour, and 24-hour Points of Departures
  - Duration adjustments and Haber's Law
- Proposed Points of Departures

Risk Assessment Definitions

- Control – background response with dosing
- Endpoint – the toxic effect upon which the risk assessment is based
- LOAEL – Lowest Observed Adverse Effect Level – The lowest dose from a study at which adverse toxic effects are observed
- NOAEL – No Observed Adverse Effect Level -The dose below the LOAEL at which no adverse toxic effects are observed
- Point of Departure – any dose level used to quantify the risk

Weight of Evidence Under TSCA

- TSCA requires that, to the extent that EPA makes a decision based on science under TSCA sections 4, 5, or 6, EPA must use scientific standards and base those decisions on the best available science and on the weight of the scientific evidence. 15 U.S.C. 2625(h) and (i).

Weight of Evidence for OCSPP Assessments

- WoE analysis may include the following considerations:
  - Quality of data and the extent to which effects can be replicated within a laboratory and across different laboratories
    - Strengths and limitations of the evidence
    - Effects induced and the potency, magnitude, and severity of effects
    - Consistency, pattern, range, and interrelationships of effects observed across studies, species, strains, and sexes
  - Conditions under which effects occur (e.g., dose, route, duration, life-stage)

Background

- IRIS recently completed their draft Toxicological Review of Formaldehyde - Inhalation
  - Characterized chronic noncancer and cancer risks from inhalation exposure to HCHO.
  - Shorter inhalation durations (acute, short-term) exposures are not the focus of the IRIS formaldehyde assessment.
- Due to FIFRA registered use patterns and TSCA conditions of use, OCSPP needs to develop acute (24 hrs or less) and short-term inhalation PODs.

Background

- Multitude of human studies relevant to acute and short-term exposures to formaldehyde in the published literature.
  - IRIS identified several observational and controlled human exposure studies for their chronic RfC.
  - Several endpoints considered: sensory irritation, pulmonary function, immune-mediated conditions, respiratory tract pathology.
- OCSPP selected sensory irritation due to rapid onset and rapid resolution when exposure ceases; appropriate for acute inhalation POD derivation.
  - Appropriate for selection due to anticipated exposures from OCSPP's registered uses and conditions of use.

OCSPP Acute Exposure Durations

- Peak Exposure: short-term, immediate exposure level (not to be exceeded during a 15-minute period).
- 8-Hour Exposure: representative of a typical workday. These exposure scenarios will be assessed for worker exposures to HCHO.
- 24-Hour Exposure: This exposure duration is used to assess exposures to HCHO for the general population and residential scenarios.

Study Selection

- OCSPP evaluated the studies IRIS identified as appropriate for derivation of quantitative points of departure (POD) based on sensory irritation.
- When selecting appropriate endpoints and PODs, it is preferable to match the route of exposure and duration of interest.
- Two primary studies chosen (one intentional exposure, one observational) with four additional supporting studies (three intentional exposure, one observational).
  - The six studies under consideration were all performed via inhalation, the exposure route of interest.

Sensory Irritation Data Set – Study Selection

- Primary Studies:
  - Kulle, TJ et al., 1987: J Air Poll Ctrl Assn 37: 919-924. Kulle et al. 1993: Inhal Tox 5(3): 323-332.
  - Hanrahan, LP et al. 1984: Am J Public Health 74: 1026-1027. (observational)
- Supporting Studies
  - Andersen, I and Mølhave, L, 1983 (In: Gibson, J.E., ed. Formaldehyde toxicity, pp. 154-165).
  - Mueller, JU et al. 2013: Int Archives Occup Environ Health 86: 107–117.
  - Lang, I. et al. 2008: Regulatory Toxicology and Pharmacology 50: 23–36.
  - Liu, KS et al. 1991: Environmental Health Perspectives 94:91-94. (observational)

Selected Studies – Kulle et al. (1987, 1993)

- Controlled human exposure study in healthy non-smoking male/female adults (n=10/9)
  - 3-hr exposures on 5 occasions, with exercise during some exposure periods. Exposure concentrations range from 0.5 to 3 ppm.
  - Odor and eye irritation incidence increased with concentration and time
  - At 0.5 ppm for three hrs, no subjects reported eye irritation.
  - At 1.0 ppm HCHO, 4 of 19 subjects reported mild eye irritation and 1 reported moderate eye irritation.
  - At 2.0 ppm, 6 subjects reported mild irritation and 4 reported moderate eye irritation.

Selected Studies - Kulle et al., continued

- Exercise was observed to increase the incidence of nose/throat irritation but did not alter eye irritation or odor threshold response.
- IRIS derived a BMC/2 of 0.34 ppm for sensory irritation.
- The HSRB deemed this study as scientifically sound, providing reliable data for use in a weight of evidence analysis.

Selected Studies – Hanrahan et al. (1984)

- Residential observational study of male/female teenagers and adults (n=61, 24M/37F) in mobile homes. Mean age = 48 yrs, 20 smokers
  - Two one-hr avg HCHO measurements to determine household exposure estimates. Logistic regression model adjusted for age, sex, and smoking.
  - Symptoms reported: respiratory irritation, dry/sore throat, coughing.
  - IRIS found statistically significant concentration-responses reported for burning eyes and eye irritation. Dose-response curves similar to those observed in human chamber studies.
  - Regression model showed higher prevalence of eye irritation in younger people. HCHO concentration not associated with presence of smokers or gas appliances in home.
  - IRIS derived a BMCL of 0.09 mg/m^3 (0.071 ppm) for sensory irritation

Supporting Studies – Andersen and Mølhave (1983)

- Controlled human exposure study in healthy male/female adults (n=5/11, 6 smokers)
  - 5-hr exposures, 4 consecutive days. Concentrations ranged from 0.24-1.61 ppm
  - Up to 2 hrs, no reported discomfort at 0.24 or 0.40 ppm. Remaining exposure duration, discomfort reported at 0.24 and 0.40 ppm
  - 0.81 and 1.61 ppm, discomfort reported in the first hour
  - Subjects reported conjunctival irritation, and dryness of nose and throat in increasing numbers with increasing concentration
  - HSRB recommended, with caveats, that Andersen and Mølhave (1983) could be used qualitatively to support a weight of evidence

Supporting Studies – Mueller et al. (2013)

- Controlled human exposure study in healthy, non-smoking adult males (n=41)
  - 4-hr exposures over 5 days, with exercise during some exposure periods. Exposures ranged from 0.3 to 0.7 ppm, with/without peaks of 0.6 or 0.8 ppm, hyper-, hyposensitive individuals.
  - Tear film break-up time increased in the 0.4/0.8 ppm and 0.5 ppm exposure groups (both hypo- and hypersensitive individuals).
  - Nasal flow rates increased in hypersensitive subjects at 0.7 ppm.

Supporting Studies – Mueller et al. (2013)

- SPES survey sum score significantly increased in hypersensitive subjects at 0.3/0.6 ppm and 0.4/0.8 ppm.
- Eye irritation - significantly increased scores for hypersensitive males at 0.3/0.6 ppm and borderline significance for 0.5 ppm.
- Olfactory irritation - significant increases compared to control for all hypersensitive exposure groups; for hyposensitive at 0.4/0.8 ppm and 0.5 ppm.

- IRIS rated the quality of this study as high.
- IRIS found it “difficult to define a meaningful magnitude of change…considered minimally adverse for the selection of a POD.”

Supporting Studies - Lang et al. (2008)

- Controlled human exposure in healthy, non-smoking male/female adults (n=11/10)
  - 4-hr exposures, 10 consecutive work-days. Exposure concentrations 0.15 to 0.5 ppm with/without peaks (0.6 or 1.0 ppm), with/without ethyl acetate
  - At 0.5/1.0 ppm blinking frequency, conjunctival redness, and eye, olfactory, and nasal irritation symptoms significantly increased
- IRIS rated the quality of this study as high.
- IRIS found it “difficult to define a meaningful magnitude of change…considered minimally adverse for the selection of a POD.”

Supporting Studies – Liu et al. (1991)

- Residential seasonal observational study (summer n=1394; winter n=1096). M/F =47/53%, 25% smokers, 33% >65 years of age, 33% reported chronic respiratory disease or allergies.
  - 7-day average (from passive HCHO monitor) ranged from 10 ppb-460 ppb.
  - Logistic regression adjusted for age, gender, smoking status, time spent at home, and chronic respiratory/allergy status.
  - In summer, significant associations with burning/tearing eyes, and stinging/burning skin. In winter, significant associations with burning/tearing eyes, chest pain, and sore throat. Burning/tearing eyes were higher in females in regression models.

OCSPP Acute Exposure Durations

- 3 acute exposure durations needed for OCSPP Assessments:
  - Peak - short-term, immediate exposure level (not to be exceeded during a 15-minute period).
  - 8 hours - representative of a typical workday.
  - 24 hours - used to assess exposures to the general population and for residential scenarios.

Proposed Peak Point of Departure

- Kulle et al. (1987) was selected for the peak POD based on:
  - Controlled human exposure study continuously measured the concentration of formaldehyde.
  - Subjects asked to rate their level of discomfort before, immediately after the exposure period, and again after 24 hours.
  - Results supported by Andersen and Mølhave (1983), Lang et al. (2008), and Mueller et al. (2013).
- Limitations of Kulle et al. (1987) include:
  - The sample size is small (n=19) and the study participants were young (mean = 26.3 ± 4.7 years), healthy volunteers and may not be representative of the exposed population.
  - The formaldehyde concentrations were high, so there is uncertainty regarding the responses at the lower end of the exposure distribution.

Proposed POD for Peak Exposures

Kulle et al. (1987, 1993)	**BMC/2 = 0.34 ppm**
Andersen and Mølhave (1983)	No effects up to 0.4 ppm for first 2 hours
Lang et al. (2008)	NOAEL = 0.5 ppm continuous or 0.3 ppm with peaks of 0.6 ppm
Mueller et al. (2013)	Objective Symptoms: No effects at 0.5 ppm Subjective Symptoms: Effects in hypersensitive subjects in treatment groups with higher continuous concentration or with peak exposures

Proposed POD for 8-Hour Exposures

- Kulle et al. (1987) was selected for the acute 8-hour POD based on:
  - Controlled human exposure study that continuously measured the concentration of formaldehyde.
  - Subjects were asked to rate their level of discomfort before, immediately after the exposure period, and again after 24 hours.
  - The results were supported by the data from Andersen and Mølhave (1983), Lang et al. (2008), and Mueller et al. (2013).
- Limitations of Kulle et al. (1987) include:
  - The sample size is small (n=19) and the study participants were young (mean = 26.3 ± 4.7 years), healthy volunteers and, therefore, may not be representative of the exposed population.
  - The formaldehyde concentrations were high, so there is uncertainty regarding the responses at the lower end of the exposure distribution.

Duration Adjustments

- Duration adjustment of inhalation PODs typically applied for human health risk assessment unless there is evidence that the chemical does not follow Haber's Law.
  - Extrapolate exposure duration from a study to a longer duration of interest under evaluation.
  - Higher concentrations for shorter time periods elicit same effect following lower concentrations over a longer exposure time.
- Haber's Law indicates that the incidence and/or severity of a toxic effect depends on both the exposure (i.e., concentration) and duration (i.e., time).
  - Studies with HCHO at higher concentrations (1-2 ppm or higher) demonstrated sensory irritation effects occur immediately, but do not become increasingly severe or debilitating over time which appears to counter Haber's Law.
  - However, incidence and severity of symptoms associated with the lower concentrations tested (e.g. 0.24 and 0.4 ppm in Andersen and Mølhave, 1983) appear to increase over time, consistent with Haber's Law.

Duration Adjustments

- OCSPP has taken a health protective approach and has assumed that sensory irritation from HCHO at lower concentrations adheres to Haber's Law
- For example, duration adjustment of POD in Kulle et al. of 0.34 ppm from 3-hour exposure to 8 hour anticipated occupational exposure:

$$Duration\ Adjusted\ POD\ = POD\ \times \frac{Study\ Exposure\ Duration}{Anticipated\ Exposure\ Duration}$$

$$= 0.34\ ppm\ \times \frac{3\ hr}{8\ hr}\ = 0.13\ ppm$$

Proposed POD for 8-Hour Exposures

Study	Exposure period (hrs.)	POD (ppm)	Duration adjusted POD (ppm)
Kulle et al. (1987, 1993)	3 hrs	0.34	**0.13**
Andersen and Mølhave (1983)	5 hrs	0.15	0.09
Lang et al. (2008)	4 hrs	NOAEL = 0.5 ppm continuous or 0.3 ppm with peaks of 0.6 ppm	
Mueller et al. (2013)	4 hrs	Objective Symptoms: No effects at 0.5 ppm Subjective Symptoms: Effects in hypersensitive subjects in treatment groups with higher continuous concentration or with peak exposures	

Proposed POD for 24-hour Exposures

- 5 studies considered for deriving an acute 24-hour POD: Andersen and Mølhave (1983), Hanrahan et al. (1984), Kulle et al. (1987), Lang et al. (2008), and Mueller et al. (2013).
- Hanrahan et al. (1984) was selected for the acute 24-hr POD based on:
  - Evaluated exposures that could potentially represent a 24-hour exposure duration.
  - Assumes a longer exposure duration, while controlled human exposure studies were conducted for ≤ 5 hrs.
  - More representative of a diverse population with a wider age range, including teenagers, men and women, some individuals with chronic disease.

Proposed POD for 24-Hour Exposures

- Limitations of Hanrahan et al. (1984):
  - Sampling conducted for only 1 hr and other studies (e.g., Meyer and Hermanns, 1985) have shown as much as a 5-fold difference in HCHO concentrations depending on time of day and temperature.
  - Uncertainty around the magnitude and duration of formaldehyde exposure associated with the reported effects.
    - How many hours a day individuals spend in their homes
    - Individuals exposed for more than a single day
  - Participants instructed to close windows prior to air sampling, shut off gas appliances, not to smoke during sampling.
  - Other co-exposures or confounders that may contribute to sensory irritation were not measured (e.g., VOCs, dust, mold).

Proposed POD for 24-Hour Exposures

Study	Exposure period (hrs.)	POD (ppm)	Duration adjusted POD (ppm)
Hanrahan et al. (1984)	Observational	**0.071**	--
Kulle et al. (1987, 1993)	3 hrs	0.34	0.04
Andersen and Mølhave (1983)	5 hrs	0.15	0.03
Liu et al. (1991)	Observational	0.07 (reported cumulative exposure)	
Lang et al. (2008)	4 hrs	NOAEL = 0.5 ppm continuous or 0.3 ppm with peaks of 0.6 ppm	
Mueller et al. (2013)	4 hrs	Objective Symptoms: No effects at 0.5 ppm Subjective Symptoms: Effects in hypersensitive subjects in treatment groups with higher continuous concentration or with peak exposures	

Summary of Proposed PODs

Acute POD Type	Value (ppm)	Value (mg/m^3)	Basis
Peak (15 min)	0.34	0.42[B]	Kulle et al. (1987)
8-hr[A]	0.13[A]	0.16[B]	Kulle et al. (1987)
24-hr	0.071	0.087[B]	Hanrahan et al. (1984)

A. This value is duration-adjusted from the 3 hour study to the 8 hour exposure (i.e. 0.34 ppm * 3/8 = 0.13 ppm)
B. mg/m^3 = PPM * 1.23 mg/m^3 per ppm

Charge Question

- OCSPP developed a weight of evidence for acute inhalation endpoints for formaldehyde that considered multiple studies and proposed acute inhalation PODs for 3 durations (15-min peak, 8-hr, and 24-hr PODs).
  - Please comment on the use of the 4 chamber studies reviewed by HSRB (Kulle et al, 1987; Andersen and Mølhave, 1983; Lang et al, 2008; Mueller et al, 2013) in OCSPP's weight of evidence for acute inhalation endpoints and the proposed PODs.

Thank you!

Newly added: Formaldehyde Irritation

- HCHO causes chemical-induced irritation by trigeminal nerve stimulation (different from olfactory stimulation). This leads to reflex responses such as sneezing, lacrimation (watery eyes), rhinorrhea (runny nose), coughing, vasodilatation, and changes in the rate and depth of respiration.
- Other examples of sensory irritation used as an endpoint (by EPA)
- A human sensory irritation study for chloropicrin revealed that eye irritation was the most sensitive endpoint. Specifically, phase three of the human study identified a range of concentrations in which sensitive subjects (e.g., young adults) were capable of detecting chloropicrin in the eyes without changes in the upper respiratory tract. The human study also suggests that the transient eye irritation experienced from an hour of exposure does not carry over from day to day. Protection of eye irritation therefore likely protects against changes in upper respiratory parameters.

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- The controlled human exposure studies showed that the irritant response to formaldehyde is an immediate phenomenon apparent at concentrations of 0.1 mg/m3, the lowest concentration evaluated, and higher. The irritation resolves when exposure is removed {Andersen, 1979;Andersen, 1983,;Krakowiak, 1998, Sauder, 1986,}.
- Concentration was related to both prevalence and severity of symptoms. In addition, a large variability in sensitivity to the irritant properties of formaldehyde at specific concentrations was observed {Berglund, 2012,;Mueller, 2013,}. Because of the wide variability in responses, it has been difficult for experimental studies to characterize the exposure-response relationship in the lower range of concentrations experienced by the general population.
- Sensory irritation is understood to occur as a result of direct interactions of formaldehyde with cellular macromolecules in the nasal mucosa leading directly or indirectly to stimulation of trigeminal nerve endings located in the respiratory epithelium.

HSRB additional study recommendations

US EPA should consider Pazdrak et al. (1993) and Krakowiak et al. (1998) when assessing acute inhalation risks. Both studies included human subjects with potentially increased sensitivities to HCHO exposures (humans with asthma or pre-existing skin sensitization). Both studies monitored changes in nasal lavage, which may serve as a more responsive health effect indicator from acute HCHO inhalation exposure.

- While the two studies are both part of the broader WOE considered by IRIS and they do qualitatively support our POD selection, IRIS has low confidence in these two studies due to uncertainties/limitations in exposure characterization. For the purposes of this WOE analysis, we focused on describing the key studies most directly informative to POD selection

IRIS Evaluation of Krakowiak (1998) and Pazdrak (1993)

System	Exposure	Endpoint(s)	Results	Utility and notes
Krakowiak, 1998				
Human occupationally exposed (n=10 males and females) with positive reaction to FA: "allergic"; 11 "nonallergic" control males	Formalin[1] 0.4 ppm for 2 hr with follow-up out to 16−18hr	Nasal lavage cell and protein counts[2]	Increased number of eosinophils, albumin, and total protein; N/C basophils. Increased proportion of eosinophils and decreased proportion of epithelial cells; N/C in proportion of basophils, neutrophils, or mononuclear cells (i.e., lymphocytes and monocytes). Effects max 10 min after exposure and declining, but still significant, at 16−18 hr; effects observed regardless of "allergy"	**Low Confidence [formalin; short duration; somewhat small sample size; lack of investigator blinding (nonissue for automated albumin measures)]** Note: Acute; authors noted albumin changes may indicate increased mucosal permeability: albumin percentage, also called the "permeability index," was elevated at 10 min postexposure only
Pazdrak, 1993				
Human workers with bronchial asthma or healthy subjects (n=10 each)	Formalin[1] 0.4 ppm for 2 hr with follow-up out to 24 hr	Nasal lavage cell and protein counts[2]	Increased eosinophils, leukocytes, total cell counts, and permeability index at 30 min after exposure, but not at 4 hr or 24 hr after exposure; N/C in basophils (changes were observed regardless of asthmatic designation). N/C in mast cell tryptase or eosinophil cationic protein	**Low Confidence [formalin; short duration; small sample size; lack of investigator blinding (nonissue for automated albumin measures)]** Note: Acute; albumin percentage, aka "permeability index" was used to indicate mucosal permeability; no effect on FEV_1, etc.

1. Formalin was assumed; the test article not reported.
2. Changes were associated with scoring measures of nasal symptoms (e.g., sneezing; edema)

Weight of Evidence determinations

- From OSA Risk Assessment Principles and Practice (2004): Risk assessment involves consideration of the weight of evidence provided by all available scientific data. In other words, “weight of evidence evaluation is a collective evaluation of all pertinent information so that the full impact of biological plausibility and coherence is adequately considered” (USEPA, 1999b). Judgment on the weight of evidence involves consideration of the quality and adequacy of data and consistency of responses induced by the stressor.
- The weight-of-evidence approach considers all relevant information in an integrative assessment that takes into account the kinds of evidence available, the quality and quantity of the evidence, the strengths and limitations associated with each type of evidence and explains how the various types of evidence fit together. Details as to the Agency’s approach to integrating a body of evidence depend on the type of decision or action being undertaken (USEPA, 2003)