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

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Special Guest

Dr. Isabelle Lang

Overview from Day 1

- The Office of Pesticide Programs (OPP) and the Office of Pollution Prevention and Toxics (OPPT) are evaluating the risks from exposure to formaldehyde under their respective statutes.
- The Agency is seeking HSRB recommendations on the scientific and ethical acceptability for 2 of 4 intentional human exposure studies that examined responses to short term inhalation exposures to formaldehyde.
- The Agency is also consulting with the HSRB on its weight of evidence (WoE) of human studies to support derivation of the acute Reference Concentration (RfC) for the OPP and OPPT assessments.

Formaldehyde and chemosensory irritation in humans: A controlled human exposure study.

Isabelle Lang, Thomas Bruckner, Gerhard Triebig (2008).

Regulatory Pharmacology and Toxicology 50: 23-38.

Lang et al. Background

- OPP made multiple attempts to request the raw data and documentation of the ethical conduct of the study
  - Dr. Lang-Zwosta could not provide access to the raw data; provided her recollections about the ethical conduct orally and recently located the consent form
  - Dr. Triebig retired and was not able to provide information about the study
  - Dr. Bruckner retired and could not be contacted
  - The study sponsor could not locate any of the files
- The Institute where the research was conducted was closed/reassigned within the University of Heidelberg
- German law only requires research records to be kept for 10 years
- Documentation of these efforts to obtain the raw data and Dr. Lang-Zwosta's recollection about the ethical conduct of the study were provided in EPA's ethics review memo

Lang et al. Purpose

- In 2008, the German occupational 8-hour time weighted average ("MAK") value was 0.3 ppm HCHO with peaks that correspond to 0.6 ppm for four 15-minute periods per working shift with a ceiling of 1 ppm that should never be exceeded.
- The European Union Occupational Exposure Limit (OEL) in 2008 was 0.5 ppm.
- These levels informed the dose levels and exposure regimen selected.
  - It should be noted that the OEL was updated in 2015 to be consistent with the MAK value of 0.3 ppm.

Lang et al. Experimental Design

- Measured the effects of formaldehyde vapor exposure on the occurrence of sensory irritation and subjective symptoms in human volunteers exposed to formaldehyde concentrations relevant to occupational exposure, including peak exposures.
- 21 healthy students, 10 females and 11 males.
  - 26.3 years - average age
  - 19-39 years - age range
  - Medical history and physical examinations performed 1 week prior to study start
  - Pulmonary function, spirometry, rhinomanometry, and cotinine test (to exclude smokers) also performed
- Written informed consent obtained from all subjects.
- Inclusion criteria for this study: adults up to 40 years of age in good health; adequate German language skills; written informed consent and voluntary participation.

Lang et al. Experimental Design

- Exclusion criteria for this study:
  - age below 18 or over 40 years
  - smoking (status was verified by cotinine test)
  - severe allergy and/or manifest skin diseases
  - acute infection
  - consumption of more than 50 g alcohol per day
  - drug abuse
  - use of contact lenses
  - exposure to formaldehyde at the workplace or in the community
  - acute or chronic diseases of the upper airways, lungs, heart or skin
  - (potential) pregnancy

Lang et al. Experimental Design

- The 2-week exposure sequences were randomized.
- Exposure to HCHO and effect measurements were conducted in a double-blind fashion.
- Ethyl acetate (EA) was used as a masking agent in 4 of 10 exposure conditions.
  - EA was chosen as it has a characteristic typical intensive odor and was considered a good candidate to mask the odor of formaldehyde.

Lang et al. Experimental Design

- Exposure Conditions
  - 10-day, randomized
  - 4-hour exposures
  - Peaks occurred 4 times for 15 mins each

Scenario	HCHO continuous exposure (ppm)	HCHO peaks (ppm)	EA (ppm)
A	0	-	-
B	0.15	-	-
C	0.3	-	-
D	0.3	4 x 0.6	-
E	0.5	-	-
F	0.5	4 x 1.0	-
G	0	-	12-16
H	0.3	-	12-16
I	0.5	-	12-16
K	0.5	4 x 1.0	12-16

HCHO = formaldehyde; EA – ethyl acetate

Lang et al. Parameters Assessed

- Objective measurements: conjunctival redness, blinking frequency, nasal resistance and flow, pulmonary function, and reaction times to stimuli.
- Subjective symptoms and complaints measured by Swedish Performance Evaluation system (SPES) questionnaire: eye, nasal, respiratory, and olfactory irritation.
  - Ratings of symptom strength/severity further documented on a 0-100 mm visual analog scale.
  - Influence of emotional affectivity on subjective scoring also examined using a Positive and Negative Affect Schedule (PANAS) questionnaire.

Lang et al. Experimental Design

The order of daily examination was as follows:

- A preliminary examination before the start of exposure: SPES questionnaire and rhinomanometry; pulmonary function was examined on day one
- Exposure to formaldehyde (or clean air) with or without EA for 4 hours
- Three 15-min periods on a cycle ergometer at 80 watts: at the beginning of exposure, at 120 mins, and at 195 mins of exposure
- Post-exposure tests: SPES questionnaire, rhinomanometry, and reaction time measurements; carried out immediately after exposure
- Last exposure day, post-exposure: physical examination and pulmonary function

Lang et al. Statistical Analysis

- Dr. Sorina Eftim from ICF (Memorandum, S. Eftim et al, ICF, 2023) performed statistical analysis of the data in Lang et al. (2008).
  - Due to lack of raw data, ICF assumed independence between responses at different doses. Several statistical approaches were utilized.
  - Fisher's exact test was used to test whether the response rates at different doses are equal. Mean differences before and after exposure, or between any exposure scenario and control condition were tested using Student t-test.
- Discomfort and sensory irritation data were analyzed for the probability of a response as a function of dose using EPA's Benchmark Dose Modeling Software (BMDS). A BMR of 10% was assumed.

Lang et al. Formaldehyde Exposure

- Chamber exposure concentrations to HCHO in agreement with intended target values

Table 6
Measured formaldehyde and EA concentrations in the exposure chamber

Target formaldehyde concentration (ppm)	Formaldehyde concentration (real-time monitoring) (ppm)	Formaldehyde concentration (HPLC) (ppm)	EA concentration (real-time monitoring)
0	0.05 ± 0.05	0.02 ± 0.01	—
0.15	0.16 ± 0.00	0.14 ± 0.03	—
0.3	0.30 ± 0.01	0.28 ± 0.04	—
0.3 + 4 peaks at 0.6	0.30 ± 0.00	0.26 ± 0.04	—
0.5	0.50 ± 0.01	0.48 ± 0.03	—
0.5 + 4 peaks at 1.0	0.47 ± 0.02	0.46 ± 0.04	—
0 + EA	0.06 ± 0.01	0.04 ± 0.01	12.4 ± 2.7
0.3 + EA	0.30 ± 0.00	0.29 ± 0.03	15.4 ± 3.3
0.5 + EA	0.50 ± 0.00	0.49 ± 0.05	15.8 ± 1.8
0.5 + 4 peaks at 1.0 + EA	0.49 ± 0.02	0.45 ± 0.04	12.9 ± 4.3

Data shown as daily means ± SD ($n = 5$); air samples for HPLC analysis of formaldehyde concentrations were not taken during peak exposures, EA, ethyl acetate.

Lang et al. Sensory Irritation Results

- Objective Symptoms
  - No significant effects of treatment on nasal resistance and flow, pulmonary function, and reaction times to stimuli.
  - Blinking frequency and conjunctival redness significantly increased at 0.5/1.0 ppm.
- Subjective Symptoms
  - SPES total symptom score significantly increased at 0.5/1.0 ppm.
  - Eye irritation significant at 0.3/0.6 ppm compared to 0 ppm.
  - Olfactory irritation as low as 0.3 ppm compared to 0 ppm.

Lang et al. Sensory Irritation Results

- Subjective Symptoms
  - Respiratory Symptoms – significantly increased at 0.3 ppm, 0.5/1.0 ppm.
  - Nasal irritation significant at 0.5/1.0 ppm.
  - When negative affectivity co-variate applied from PANAS questionnaire, 0.3 ppm dropped out and 0.5/1.0 ppm remained significant for eye, olfactory, and nasal symptoms.
- At 0.5/1.0 ppm blinking frequency, conjunctival redness, and nasal irritation symptoms significantly increased.

Strengths/limitations of Lang et al.

Strengths:

- Study included both males and females.
- Males and females represented equally.
- Study employed several concentrations to examine concentration response.
- Parameters measured are relevant to assessing acute adverse effects from inhalation exposure to HCHO.
- Results characterize both the incidence and severity of the concentration-response and time dependence of responses based on concentration exposures.

Strengths/limitations of Lang et al.

Limitations:

- There were measurable levels of formaldehyde in the chamber air for the control groups.
- Results of pulmonary function measurements were not presented in the paper.
- Results of cycling ergometry on concentration-response to inhalation exposures to formaldehyde were not presented or discussed in the paper.
- Study participants were young, healthy volunteers, not representative of the age distribution and health status in the general population.

Overall Conclusions – Lang et al. (2008)

- The study was well conducted and provides quantitative information for derivation of an acute reference concentration (RfC) value for formaldehyde as part of a weight-of-evidence approach.
- This study provides concentration-response data for assessing adverse effects from acute/short-term inhalation exposures to formaldehyde.

Charge Question - Lang et al. (2008) study

Is the research described in the published study "Formaldehyde and chemosensory irritation in humans: A controlled human exposure study," published in Regulatory Toxicology and Pharmacology 50: 23–36, scientifically sound, providing reliable data for use in a weight-of-evidence to determine a point of departure for acute inhalation exposures to formaldehyde?

Thank you!