EPA Reviewer: Tim McMahon, Ph.D **Signature**: _____
Risk Assessment Branch II, Antimicrobials Division **Date**: _____
EPA Secondary Reviewer: Deborah Burgin, Ph.D., DABT **Signature**: _____
Risk Assessment Branch II, Antimicrobials Division **Date**: _____

DATA EVALUATION RECORD

STUDY TYPE: Controlled Human Exposure to Formaldehyde by Inhalation; non-guideline

PC CODE: 043001 **DP BARCODE:**
TXR#:

TEST MATERIAL (PURITY): Formaldehyde vapor (generated through heating of paraformaldehyde). Purity not explicitly stated.

SYNONYMS: HCHO

CITATION: Andersen and Molhave (1983): Chapter 14: Controlled Human Studies with Formaldehyde. In: Formaldehyde Toxicity, James E. Gibson ed. Hemisphere Publishing Group, Washington D.C. Open literature study.

LABORATORIES: Institute of Hygiene, Arhus, Denmark.

EXECUTIVE SUMMARY:

This controlled human exposure study measured effects of formaldehyde vapor exposure on nasal mucociliary flow, nasal airflow resistance, forced expiratory vital capacity, and irritation threshold. Sixteen human subjects (5 male, 11 female, age range 20-33 years; 5 smokers, one heavy smoker) were examined in groups of four. Each group of four subjects underwent four different exposures on four consecutive days to air concentrations of 0, 0.3, 0.5, 1.0, and 2.0 mg/m^3 (0, 0.24, 0.40, 0.81, 1.62 ppm) formaldehyde. The order of exposure to the four concentrations of formaldehyde was random. Baseline measurements of nasal mucociliary flow, nasal airflow resistance, forced expiratory vital capacity, and odor threshold were made during a 2-hour control exposure period, in which subjects were exposed to clean filtered air from outside. Following the 2-hour control period, formaldehyde was added to the air, and after 'about one hour' a steady state concentration of formaldehyde was achieved and maintained for the duration of the experiment that day. Each exposure concentration to which subjects were exposed lasted 4-5 hours. Parameter measurements were made after 2-3 hours of exposure to formaldehyde, and again after 4-5 hours of exposure to formaldehyde.

During the formaldehyde exposures, subjects were also asked to perform tasks involving addition, multiplication, and card punching for 30 minutes duration three times during each exposure period, during the control exposure, at 2-3 hours into the formaldehyde exposure, and at 4-5 hours into the formaldehyde exposure. Each task lasted 15 minutes' duration. The addition test was performed during each evaluation period, the multiplication test was performed during the first exposure period only, and the card punching test performed in the control period and second exposure period.

Nasal mucociliary flow was measured by motion of a resin particle placed on the superior surface of the nasal turbinate. Nasal resistance was measured through an oro-nasal plastic mask attached to a pneumotachometer. Forced expiratory vital capacity was measured but details of how were not provided. Degree of nasal irritation was measured subjectively. Subjects were asked to adjust a pointer on a voting machine using a scale of 1 (complete comfort) to 100 (severe discomfort) to express degree of irritation. No other explanation of the scaling system was given.

A significant decrease in nasal mucociliary flow was observed in the anterior portion of the nasal turbinates at the lowest (0.3 mg/m^3) concentration of formaldehyde, with an apparent threshold (no further reduction in flow rate) at the 0.5 mg/m^3 concentration and above. The posterior portion of the nasal turbinates was not affected. In the middle third of the nasal turbinates, there was no significant difference on reduction of average mucociliary flow rate between 1-3 hours and 4-5 hours exposure.

Results of airway resistance measurements showed no significant effect of formaldehyde inhalation exposure on vital capacity, forced expiratory flow, or forced expiratory volume at any concentration tested.

Results of the irritation assessment showed that after 2 hours exposure, there was no reported discomfort after exposure to 0.3 or 0.5 mg/m^3 formaldehyde. In the remaining part of the exposure period (presumably 4-5 hours), discomfort was reported at0.3 and 0.5 mg/m^3 formaldehyde . At the 1.0 and 2.0 mg/m^3 exposure concentrations, discomfort was reported in the first hour of exposure. Subjectively, test subjects reported conjunctival irritation and dryness of the nose and throat following formaldehyde exposures. Incidence of reported symptoms was 3, 5, 15, and 15 subjects in the 0.3, 0.5, 1.0, and 2.0 mg/m^3 exposure groups respectively. These symptoms had dissipated by the following morning.

This study is classified as **acceptable/non-guideline.** It was not submitted for fulfillment of a guideline study. This study was examined by the agency for quantitative use in deriving a point of departure (POD) for formaldehyde inhalation exposures of short-term duration. Deficiencies

exist in this study relative to the OPP guidance for literature review for use quantitatively. However, the study can be used quantitatively as part of a weight-of-evidence determination for deriving a point of departure for inhalation exposure to formaldehyde.

COMPLIANCE: This is a published study and as such, did not contain statements of compliance or confidentiality.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Materials:

	Formaldehyde
Description:	Generated from paraformaldehyde
Lot/Batch #:	Not provided
Purity:	Not provided
CAS # of TGAI:	50-00-0

2. Vehicle and/or positive control: Fresh outdoor air, filtered through absolute filters and charcoal filters. No positive control was utilized.

B. STUDY DESIGN and METHODS:

The objective of the present study was to determine effects of formaldehyde on human subjects from inhalation of formaldehyde vapor from short-term exposures of up to 5 hours.

Sixteen human subjects (5 male, 11 female, age range 20-33 years; 5 smokers; one heavy (>20 cigarettes per day) were examined in groups of four. Each group underwent four different exposures on four consecutive days. Air concentrations of 0, 0.3, 0.5, 1.0, and 2.0 mg/m^3 formaldehyde were used in this study. Baseline measurements of nasal mucociliary flow, nasal airflow resistance, forced expiratory vital capacity, and odor threshold were made during a control period in which subjects were exposed to clean filtered air from outside for 2 hours. Following the control measurements, formaldehyde was added to the air, and after 'about one hour' a steady state concentration of formaldehyde was achieved and maintained for the duration of the experiment that day. Parameter measurements were then made after 2-3 hours of exposure to formaldehyde, and again after 4-5 hours of exposure to formaldehyde.

Study Participants

There was no information provided on the recruitment of the participants in this study.

For this study, *inclusion criteria* were not stated.

Exclusion criteria were not stated.

IRB Approval and Informed Consent

No information was provided on IRB approval or consent to the study in the paper.

Inhalation Study

The intent of this study was to determine the effect of inhaled formaldehyde vapor on nasal mucociliary flow, nasal airflow resistance, forced expiratory vital capacity, and irritation threshold. Sixteen human subjects (5 male, 11 female, age range 20-33 years; 5 smokers, one heavy smoker) were examined in groups of four.

Each group of four subjects underwent four different exposures on four consecutive days to air concentrations of 0, 0.3, 0.5, 1.0, and 2.0 mg/m^3 formaldehyde. Baseline measurements of nasal mucociliary flow, nasal airflow resistance, forced expiratory vital capacity, and odor threshold were made during a 2-hour control exposure period, in which subjects were exposed to clean filtered air from outside. Following the 2-hour control period, formaldehyde was added to the air, and after 'about one hour' a steady state concentration of formaldehyde was achieved and maintained for the duration of the experiment that day. Each exposure concentration to which subjects were exposed lasted 4-5 hours. Parameter measurements were made after 2-3 hours of exposure to formaldehyde, and again after 4-5 hours of exposure to formaldehyde.

During the formaldehyde exposures, subjects were also asked to perform tasks involving addition, multiplication, and card punching for 30 minutes duration three times during each exposure period. Each task lasted 15 minutes' duration. The addition test was performed during each exposure period, the multiplication test was performed during the first exposure period only, and the card punching test performed in the control period and second exposure period.

Nasal mucociliary flow was measured by motion of a resin particle placed on the superior surface of the nasal turbinate. Nasal resistance was measured through an oro-nasal plastic mask attached to a pneumotachometer. Forced expiratory vital capacity was measured but details of how were not provided. Degree of nasal irritation was measured subjectively. Subjects were asked to adjust a pointer on a voting machine using a scale of 1 (complete comfort) to 100 (severe discomfort) to express degree of irritation. No other explanation of the scaling system was given.

Reported results in this study did not differentiate between effects in smokers vs. non-smokers.

Formaldehyde concentration in the chamber air was measured by collection of 1h air samples and analysis by the chromotropic acid method. The variation was within ±20 percent from the target values.

During the exposures, subjects were also asked to perform tasks involving addition, multiplication, and card punching of 15 minutes' duration. The addition test was performed during each exposure period, the multiplication test during the first exposure period only, and the card punching test in the control period and second exposure period.

Statistical analysis

In a statistical analysis submitted by Dr. Jonathan Cohen (memorandum dated September 5, 2022, from Dr. Jonathan Cohen/ICF to USEPA, appended to this review), Dr. Cohen noted that with regard to the results reported for nasal mucociliary flow, airway resistance, and odor threshold, "The statistical analyses described in the [Andersen] papers consisted of non-parametric tests followed by an analysis of variance. Since the graphical results only show averages and the raw data were not provided, it is not possible to validate the statistical analyses."

For the discomfort/irritation measurements, the available data were used to conduct statistical analyses using Fisher's exact test (to test whether the response rates at different doses are equal), and the Cochran-Armitage trend test (a statistical test of the null hypothesis that the response rates are the same at every dose against the alternative one-sided hypothesis that the response rates increase with the dose).

The results of discomfort and sensory irritation experiments were also analyzed by fitting statistical models for the probability of a response as a function of the dose. A variety of statistical models are fitted to the data and the best-fitting statistical model is selected. For these analyses the EPA's Benchmark Dose Modeling (BMD) method was followed, using BMD Software (BMDS) and, as noted in the IRIS draft report on formaldehyde (EPA, 2022), the model with the lowest Akaike Information Criterion (AIC) statistic was chosen as the best model.

RESULTS

Nasal Mucus Flow

Results of inhalation exposure to formaldehyde on nasal mucus flow are shown in the following figure, reproduced as Figure 4 of the publication. As shown in the figure, for the anterior sections of the nasal cavity, inhalation exposure to formaldehyde vapor at 0.3 and 0.5 mg/m^2 resulted in a decrease in nasal mucus flow. Above the 0.5 mg/m^2 concentration, there was no further effect of formaldehyde on mucus flow. The posterior sections of the nasal cavity (slits 4-5 and 5-6 in the figure) were not significantly affected by formaldehyde inhalation exposure. As noted by Dr. Cohen in his analysis, "The statistical analyses described … consisted of non-parametric tests

followed by an analysis of variance. Since the graphical results only show averages and the raw data were not provided, it is not possible to validate the statistical analyses

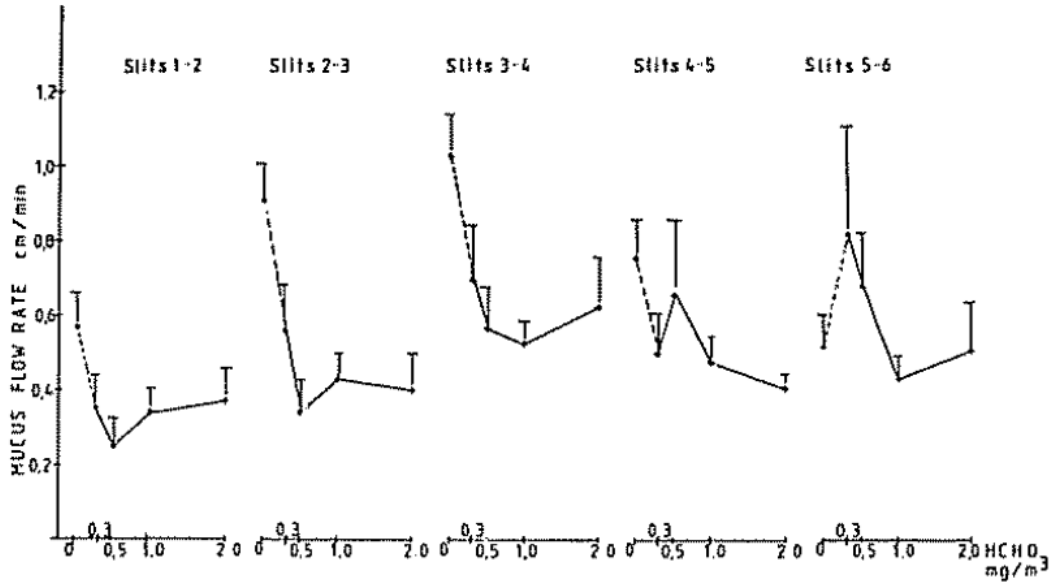

Figure 4 The average mucus flow rate in clean air (0) and after 4-5 h exposure to formaldehyde at four concentrations. Slits 1-3, 3-4, and 4-6 represent the anterior, middle, and posterior thirds of the ciliated part of the nose, respectively. One standard deviation of the mean is shown as a vertical bar.

Airway Resistance

The results of airway resistance experiments are shown in the following figure, reproduced as Figure 6 from the publication. As noted in this figure, no significant changes in airway resistance measurements were observed at any concentration of formaldehyde tested in this study.

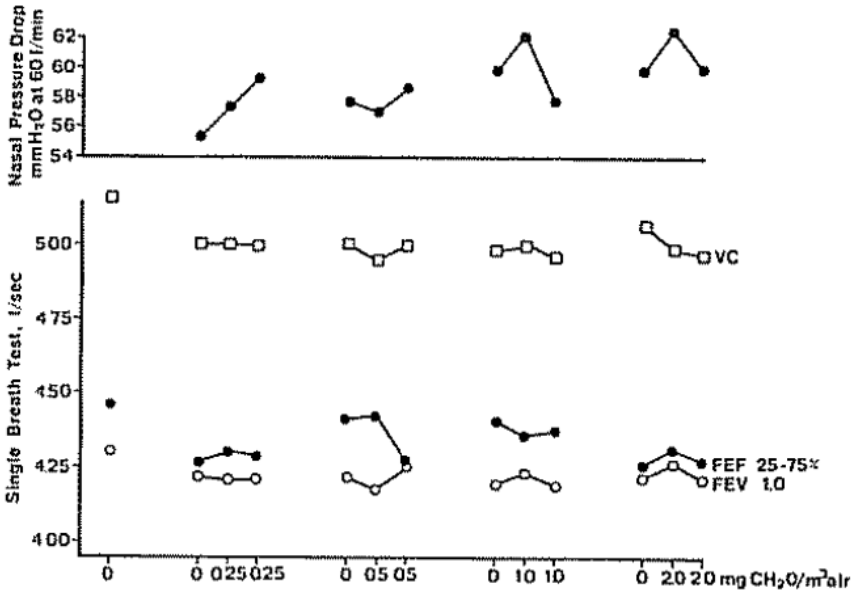

Figure 6 The variation with time of the averages of nasal pressure drop (upper part), of vital capacity (VC), forced expiratory flow ($FEF_{25-75\%}$), and forced expiratory volume during the first second of the expiration ($FEV_{1.0}$) (lower part). The interval between the measurements each day is approximately 2 h.

Discomfort/Irritation

Results of the evaluation of subjects for feelings of discomfort during formaldehyde inhalation exposures are shown in the following figure, reproduced as Figure 7 from the publication. As noted in the figure, for the first 2 hours of inhalation exposure, there was no increase in subjective feelings of discomfort at the 0.3 and 0.5 mg/m^3 concentrations of formaldehyde. At the 1.0 and 2.0 mg/m^3 concentrations, discomfort was already reported during the first hour of exposure. After 2.5 hours of exposure, discomfort was reported in 3,4,7, and 8 subjects at the 0.3, 0.5, 1.0, and 2.0 mg/m^3 concentrations respectively.

Following exposures, the subjects were asked to describe the symptoms experienced. Subjects reported the symptoms experienced as mainly conjunctival irritation and dryness of the nose and throat. The incidence of these symptoms (out of the 16 subjects in this study) reported was 3, 5, 15, and 15 subjects at the 0.3, 0.5, 1.0, and 2.0 mg/m^3 concentrations respectively. Results are shown in Figure 7, taken from the publication.

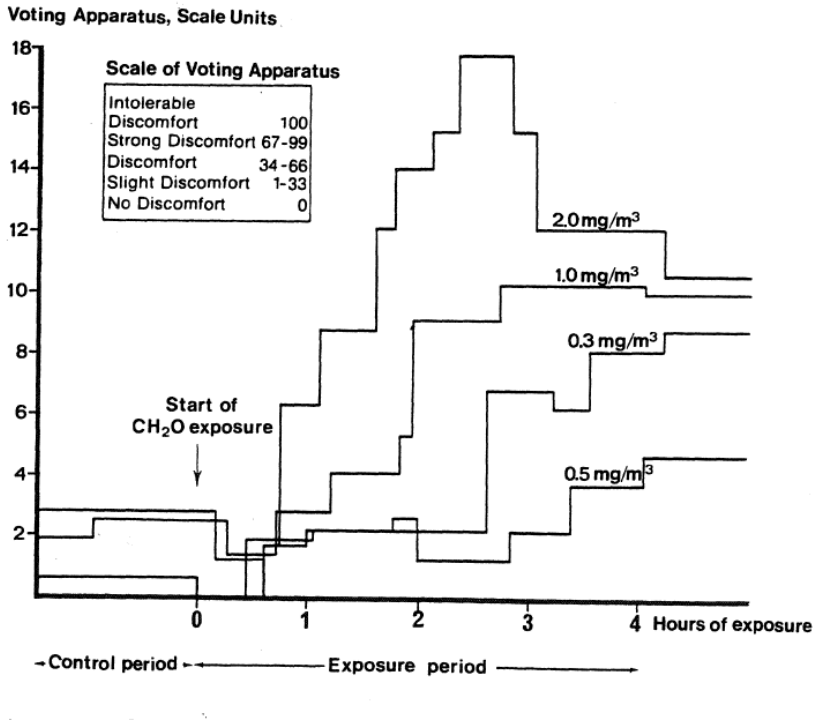

Figure 7. Variation with time of the mean discomfort vote in scale units at the four different concentrations of formaldehyde. In the control period, clean air without formaldehyde was supplied to the subjects.

E. REVIEWER'S CONCLUSIONS:

The current study was conducted to examine concentrations of inhaled formaldehyde on nasal mucociliary flow, nasal airflow resistance, forced expiratory vital capacity, and irritation threshold in 16 human subjects. All but 5 of the subjects were non-smokers, and according to the publication, none had been exposed to formaldehyde, and all had 'apparently healthy upper airways' with no history of chronic or recent acute respiratory disease. There was no further information provided to support these statements. Smokers were reported by other studies to be less sensitive to formaldehyde so this should be considered a deficiency of the study.

Nasal mucus flow was primarily affected in the anterior portion of the nasal cavity, with a decrease noted at the 0.3 mg/m^3 concentration of formaldehyde. No further decrease was noted at the concentrations tested above 0.3 mg/m^3, and the posterior sections of the nasal cavity did not show a decrease in mucus flow, indicating absorption occurs in the anterior portion of the nose. Airway resistance measurements were not affected at any of the concentrations of formaldehyde

tested. Indications of irritation (subjective responses during the formaldehyde exposures and responses to questions after exposures) were noted at the 0.3 mg/m^3 concentration and above, and were also dose- and time-dependent, with symptoms reported earlier in exposures at the 1.0 and 2.0 mg/m^3 concentrations and with increased reported levels of discomfort. Conjunctival irritation and dryness of the nose and throat were reported by 3, 5, 15 and 15 subjects after 5 hours of formaldehyde exposure at 0.3, 0.5, 1.0 and 2 mg/m^3, respectively.

It is suggested from the data in this study that exposure to 0.3 mg/m^3 formaldehyde for 5 hours by inhalation results in mild irritation reactions and decreases in nasal mucus flow. A formal point of departure was not calculated in this study.

As this study was obtained from the peer reviewed open scientific literature, the OPP guidance document "Guidance for Considering and Using Open Literature Toxicity Studies to Support Human Health Risk Assessment (USEPA, 2012)," is also applicable when considering the use of open literature studies for risk assessment purposes. This guidance document presents criteria for screening of studies, and criteria for whether the study is of sufficient quality to be used quantitatively. Screening criteria include the following:

1. The toxic effects are related to defined chemical exposure;
2. The toxic effects are on an appropriate test animal species;
3. The presence or absence of toxicological effects is observed;
4. A chemical concentration/dose or application rate is reported;
5. An explicit duration of exposure is included;
6. Toxicology information is reported for the chemical of interest or its structural analog;
7. The article is available in the English language;
8. The study results are presented as a full article (i.e., not an abstract);
9. The paper is a publicly available document;
10. The paper is the primary source of the data;
11. Treatment(s) are compared to acceptable controls;
12. The location of the study (e.g., laboratory vs. field) is reported;
13. Adequate data are provided on the chemical tested (i.e., test article characterization);
14. Adequate data are provided on the species tested;
15. The study results (findings) are adequately reported; and
16. The study findings are relevant to assessing human health risks

The current study is deficient in screening criteria #13 (test article was not adequately characterized). However, from review of this study, it is concluded that the study can provide data for quantitative use as part of a weight of evidence determination in conjunction with other human exposure studies for deriving a point of departure for short-term inhalation exposures to formaldehyde. This is concluded based on the interpretation of the criteria as established in the guidance as follows:

• The point of departure from this study is lower *(i.e.,* more sensitive) than the PODs from cited inhalation animal toxicology studies in the formaldehyde final work plan that examined shorter-term inhalation exposures (EPA-HQ-OPP-2015-0739).
• The open literature data are reported in (or have the ability to be converted to) units that can be compared to other study results- results are reported in mg/cm^2, which can be compared to other studies – this criterion is met.
• Sufficient information is provided in the open literature to substantiate whether the study conclusions/endpoints/doses are accurate, reliable, and reasonable and a judgement can be made that the study findings could potentially be replicated – this study provided enough information to make a judgement on the reliability and reproducibility of the findings.

This study is classified as **acceptable/non-guideline.** It was not submitted by the registrant for fulfillment of a guideline. The study can be used quantitatively as part of a weight-of-evidence determination for inhalation hazard assessment of formaldehyde.