EPA Reviewer: Colleen M. Rossmeisl, DVM **Signature**: _____
OPP/Antimicrobials Division/Risk Assessment Branch 2 **Date**: _____
EPA Secondary Reviewer: John Allran, MS, DABT **Signature**: _____
OPPT/Existing Chemicals Risk Assessment Division/RAB 6 **Date:** _____

DRAFT DATA EVALUATION RECORD

STUDY TYPE: Skin Sensitization non-guideline (Occluded/Non-occluded patch tests, Repeated Open Application Test) - Human

PC CODE: 043001 DP BARCODE**:** N/A

TASK GROUP No.: NA

TEST MATERIAL (PURITY): Formaldehyde, Germall 115 (Imidazolidinyl urea, a formaldehyde releaser) (% purity not provided)

SYNONYMS: None provided

CITATION**:** Flyvholm, MA, Hall, BM, Agner, T, Tiedemann, E, Greenhill, P, Vanderveken, W, Freeberg, FE and T Menné. (1997). Threshold for Occluded Formaldehyde Patch Test in Formaldehyde-Sensitive Patients. Contact Dermatitis. 36: 26-33.

EXECUTIVE SUMMARY:

The purpose of this study was to investigate the eliciting threshold concentration of formaldehyde in formaldehyde-sensitive individuals in occluded and non-occluded patch tests, and to evaluate the relationship to repeated open application test (ROAT) with a product containing a formaldehyde releaser.

A total of 36 formaldehyde-sensitive patients were recruited as subjects for the study. Of the 36 patients recruited, 20 formaldehyde-sensitive individuals agreed to participate in the study (14 women and 6 men; age range 32 - 71 years). The control group consisted of 20 healthy volunteers with negative patch tests to formaldehyde (12 women, 8 men; age range 22-54 years). Occluded and non-occluded patch tests were conducted with formaldehyde solutions in concentrations of 0, 25, 50, 250, 500, 1,000, 5,000 and 10,000 ppm (equivalent to 0, 0.0025 %,

0.0050 %, 0.025 %, 0.050 %, 0.1 %, 0.5 %, and 1 %) and ROAT for 1 week with a leave-on cosmetic product containing on average 300 ppm (equivalent to 0.03 %) formaldehyde, were carried out simultaneously on each subject.

In the occluded patch test, 19 of the 20 formaldehyde-sensitive subjects reacted to 10,000 ppm formaldehyde, 9 reacted to 5,000 ppm, 3 reacted to 1,000 ppm, 2 reacted to 500 ppm and 1 reacted to 250 ppm. No definite positive reactions for the formaldehyde-sensitive subjects were observed in the non-occluded patch test or in the ROAT, but follicular reactions were observed in 6 and 5 formaldehyde-sensitive subjects in these tests, respectively. No positive reactions were observed in the control group to any of the test procedures.

Based on the study results, formaldehyde can elicit a response in sensitive individuals at exposure as low as 250 ppm (0.025 % or 7.5 $\mu g/cm^2$) based on occluded patch testing results. A LOAEL value of 250 ppm (0.025 % or 7.5 $\mu g/cm^2$) and a NOAEL value of 50 ppm (0.005 % or 1.5 $\mu g/cm^2$) are established from this study.

This study is classified as **acceptable/non-guideline.** It was not submitted by the registrant for fulfillment of a guideline requirement. The study provides quantitative information on elicitation thresholds for formaldehyde in humans and can be considered as part of endpoint selection and POD derivation for elicitation of dermal sensitization from dermal exposure.

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, Germall 115 (Imidazolidinyl urea, a formaldehyde releaser)

Description:	Not provided
Lot/Batch #:	Not provided
Purity:	Not provided
CAS # of TGAI:	50-00-0, 39236-46-9

2. Sample Preparation, Vehicle and/or Positive Control: Detailed information was not provided on sample preparation. Reagents for solution analysis were of analytical grade or pharmaceutical quality. The vehicle used for the formaldehyde occluded and non-occluded patch tests was water (no additional details provided). Occluded patch testing was also made with formaldehyde (1% aqueous [aq]) and paraben mix from the European standard series (15% in petrolatum standard mix of 3% each of methyl-, ethyl-, propyl-, butyl- and benzyl-parahydroxybenzoate), Germall 115 (2% pet. imidazolidinyl urea) (Hermal, Germany) and rubber from finger cots that were used for the ROAT. The ROAT leave-on cosmetic was preserved with parabens (methyl paraben 0.1 %, propyl paraben 0.1 %) and Germall 115 (imidazolidinyl urea) (0.3 %) as an oil-in-water emulsion. A positive control was not used in this study. There was no solubility and stability analysis of the test substance or dilutions with the vehicle.

The publication describes the methodology for patch testing as follows:

> "The occluded patch testing included formaldehyde solutions of 0, 25, 50, 250, 500, 1,000, 5,000 and 10,000 ppm. The non-occluded patch testing included formaldehyde solutions of 0, 25, 50, 100, 250, 500, 1,000, 5,000 and 10,000 ppm. The formaldehyde solutions were coded and placed on the back in a randomized way.
>
> "In addition to the above-mentioned formaldehyde solutions, occluded patch testing was made with formaldehyde (1% aqueous [aq]) and paraben mix from the European standard series (15% petrolatum [pet]), Germall 115 (imidazolidinyl urea) (2% pet.) (Hermal, Germany) and rubber from finger cots used for ROAT." (Flyvholm et al. 1997, p. 28).

The concentration of the formaldehyde in solutions was analyzed by an iodine titration method. Free formaldehyde and total formaldehyde were measured in the product used for ROAT testing by a High Performance Liquid Chromatography (HPLC) method, using a modification of methodology described for the determination of free formaldehyde in cosmetic products. (Commission Directive, 1990).

B. STUDY DESIGN and METHODS:

The purpose of this study was to investigate the eliciting threshold in formaldehyde-sensitive individuals using occluded and non-occluded patch testing with formaldehyde in water and repeat open application test (known as ROAT) of a formaldehyde releasing leave on cosmetic product.

Study Participants

Details on study participants from the publication is reproduced below (pg. 27):

> "All consecutive patch test patients seen between September 1993 and May 1995 at the Department of Dermatology, Gentofte Hospital, who had a positive patch test to formaldehyde (1% aqueous) and negative patch tests to paraben mix, Germall 115 and rubber from finger cots used in the ROAT, were invited to participate in the study. Additional exclusion criteria included dermatitis or other skin diseases at or near the skin sites to be used for testing, and diseases, exposure or use of medication which could be expected to interfere with the testing." (Flyvholm et al. 1997, p. 27).

"A total of 36 patients suitable for the study were recruited. 20 formaldehyde-sensitive patients (14 women, 6 men; age 32-71) agreed to participate in the study. 16 patients (12 women, 4 men; age 32-68) refused to participate for various reasons (44% of the total relevant patients)." (Flyvholm et al. 1997, pg. 27). The study authors reported that "in addition, 4 {of the 16 rejected} patients were excluded because their sensitivity to formaldehyde could not be confirmed, and 3 {of the 16 rejected} were excluded because of positive reactions to Germall 115. A control group of 20 healthy volunteers (12 women, 8 men; age 22-54), with negative patch tests to formaldehyde, parabens, Germall 115 and rubber from finger cots, were tested with the same procedures and test materials." (Flyvholm et al. 1997, pg. 27). The reviewers assume that because the data shows 20 treated individuals, the excluded individuals were among the aforementioned group that refused.

Additional information on the formaldehyde-sensitive individuals included in the study, formaldehyde-sensitive individuals that refused the study, and the control group are provided in **Table 1** below.

Table 1. Sex-ratio, mean age, age range and patch test reactions to 1% formaldehyde for participating patients, patients who refused to participate and the control group (copied from Flyvholm et al. 1997; p.27, Table 1)

	n	F/M	Mean age (years)	Age range (years)	Reaction to patch test with 1% formaldehyde
Patients included	20	14/6	48	32–71	19 positive[a]: 9 with + 8 with ++ 2 with +++
Patients refused	16	12/4	44	32–68	15 positive[b]: 10 with + 5 with ++
Control group	20	12/8	39	22–54	All negative

[a] 1 patient with negative reaction to 1% formaldehyde had positive reaction to 0.5% formaldehyde.
[b] 1 patient with negative reaction to 1% formaldehyde had positive reaction to 2% formaldehyde.

Institutional Review Board Approval and Informed Consent

All subjects gave written consent to participate in the study after receiving oral and written information. The study was approved by the Ethical Committee of the Copenhagen Municipality.

Experimental Design

Occluded patch tests were conducted with formaldehyde solutions in concentrations of 0,25, 50, 250, 500, 1,000, 5,000 and 10,000 ppm (equivalent to 0, 0.0025 %, 0.0050 %, 0.025 %, 0.050 %, 0.1 %, 0.5 %, and 1 %). Non-occluded patch tests were conducted with formaldehyde solutions in concentrations of 0, 25, 50, 100, 250, 500, 1,000, 5,000 and 10,000 ppm (equivalent to 0, 0.0025 %, 0.0050 %, 0.010 %, 0.025 %, 0.050 %, 0.1 %, 0.5 %, and 1 %). ROAT was conducted for 1 week with a leave-on cosmetic product containing on average 300 ppm (equivalent to 0.03 %) formaldehyde.

The occluded and non-occluded patch tests, and ROAT were carried out simultaneously on each subject. The tests were coded and randomized and located on the back of subjects. Formaldehyde-sensitive individuals and controls were instructed not to wash the test areas for the duration of the test.

Occluded patch test

Patch testing methodology was described in the publication as follows (pg. 29):

> "Occluded patch testing was conducted by applying 15 µl of the formaldehyde solutions, formaldehyde, paraben mix, Germall 115 (imidazolidinyl urea) and rubber from finger cots used for ROAT) to the upper back by Finn Chambers (diameter 0.8 cm) on Scanpor tape (Norgesplaster, Oslo). The tests were applied for 2 days, and readings were

performed at the end of the application on Day 2, and subsequently on Day 3, and on Days 6-9. Readings were made according to the International Contact Dermatitis Research Group (ICDRG) recommendations" (Flyvholm et al. 1997, p. 29).

Non-occluded patch test

Non-occluded patch testing was conducted at the concentrations specified above for the occluded patch testing, but instead of using Finn chambers, 15 µl of formaldehyde solutions were applied to a 1 cm^2 area of the forearm and allowed to dry at room temperature. Readings were performed at the same intervals as described for the occluded patch testing.

Repeated open application test (ROAT)

For the ROAT, "the patients were instructed to apply approximately 0.1 ml of the test material by means of the finger cots to a 5 x 5 cm area of the flexor mid-aspect of the left upper arm twice daily for a maximum period of 1 week. Reading of the test site was done after 1 week unless a positive reaction was observed beforehand. If a positive reaction was noted by the patient before the end of 1 week, the patient was instructed to come to the laboratory for evaluation." (Flyvholm et al. 1997; pg. 30)

Evaluations

Patch test interpretations were based on references provided in Flyvholm et al.1997 and are provided in **Table 2** below.

Table 2. Patch test reading designations and descriptions (summarized from Fregert, S. 1981)

Patch test reading	Description
+?	doubtful reaction; faint erythema only
+	weak positive reaction; erythema, infiltration, possibly papules
++	strong positive reaction; erythema, infiltration, papules, vesicles
+++	extreme positive reaction; intense erythema and infiltration and coalescing vesicles
-	Negative reaction
IR	Irritant reaction of different types

For ROAT grading, the study authors stated that "any skin changes in the test area were described according to the following terms: (i) slight dryness and scaling in the test area without redness; (ii) slight uneven redness without infiltration (edema) in the test area; (iii) papular, follicular reaction in the test area; (iv) even redness, infiltration (edema) and scaling in the test area. In addition, papules and vesicles may also be observed. In the reading of the ROAT, only term (iv) was defined as a positive outcome of the test." (Flyvholm et al. 1997; pg. 30).

Statistical Analysis

The authors of the study did not perform a statistical analysis of the data. EPA, in consultation with the ICF statistics contractor, determined additional statistical analyses or dose response modeling was not feasible (ICF, 2023, memorandum).

II. RESULTS

Regarding control groups, the author reported that "no positive or irritant reactions were observed in the control groups for any test procedures" (Flyvholm et al. 1997, p. 30) without additional details.

Occluded Patch Test Results

All subjects included in the study had previous positive patch test results to formaldehyde (1% aqueous;10,000 ppm). A summary of the study results for the occluded test is provided in **Table 3** below. It was noted in the publication that the individual that tested positive at 250 ppm was retested one year later at 50, 100 and 250 ppm and was negative at all 3 concentrations.

Table 3. Occluded patch test results (number positive per concentration tested).

Concentration tested (in varying units)[1]			**Positive results (% of tested)**
ppm	**%**	**µg/cm^2**	
10,000	1	300	19/20 (95 %)
5,000	0.5	150	9/20 (45 %)
1,000	0.1	30	3/20 (15 %)
500	0.05	15	2/20 (10 %)
250	0.025	7.5	1/20 (5 %)
50	0.005	1.5	0/20
25	0.0025	0.75	0/20
0 (Control)	0	0	0/20

[1] Conversion to % based on 10,000 ppm = 1%; conversion to µg/cm^2 based on 15 µl solution used and 0.8 cm diameter of Finn test chamber (e.g., the Finn Chamber concentration was converted to an equivalent dose µg/cm^2 as follows: 1% = 10,000 ppm = 10,000 mg/L; and (10,000 mg/L)(1000 µg/1 mg)(15 µL/Π(0.4 cm)^2)(1 L/10^6 µL) = 300 µg/cm^2*)*

The two figures below are excerpts from the publication. **Figure 1** depicts the number of positive dermal sensitization reactions at each concentration, and the strength of the reaction in each patient. This figure is a graphical depiction of the data in **Table 3** above and indicates a concentration-dependent increase in the number of subjects exhibiting positive tests for dermal reaction. **Figure 2** compares the strength of the reaction in the 10,000 ppm (1%) test to the lowest concentration giving positive reaction, and the data indicate that the individuals with the strongest reaction to the 10,000 ppm diagnostic patch test had the lowest threshold concentration for eliciting dermal effects indicative of sensitization.

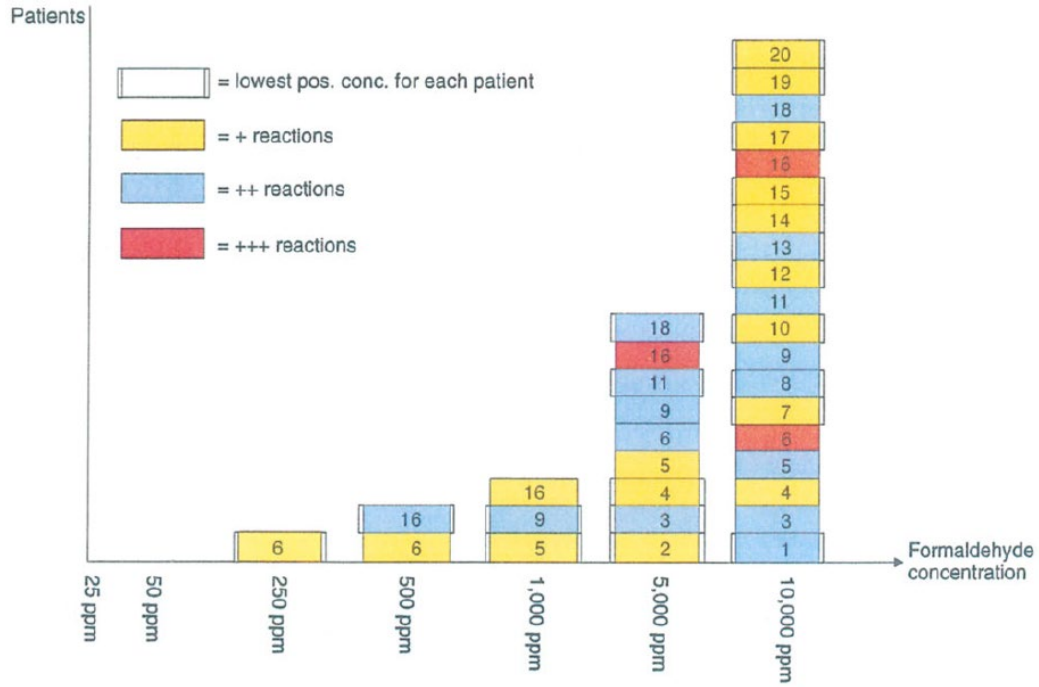

Figure 1. Positive patch test reactions to formaldehyde in occluded patch testing or in diagnostic patch testing (10,000 ppm) among 20 formaldehyde-sensitive subjects. The strength of reaction is depicted by color-coding, and the number of positive reactions at each test concentration is denoted by the number of rectangles (e.g., bar graph), with the number in each rectangle representing the patient identification number (Flyvholm et al. 1997, Figure 2, p. 28).

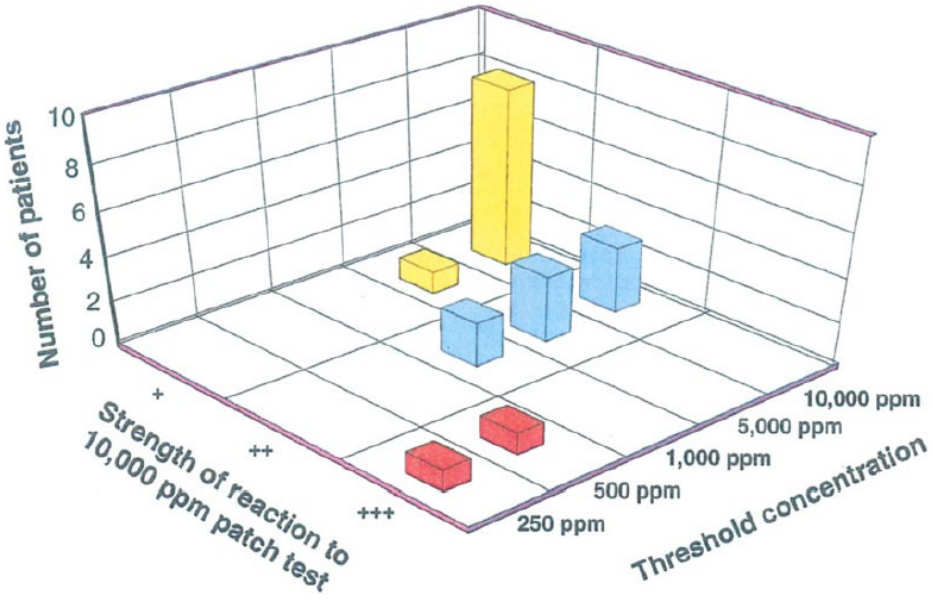

Figure 2. Lowest formaldehyde concentrations giving positive reactions in occluded patch testing, compared to the strength of the reactions in the diagnostic patch testing (10,000 ppm) among 19 formaldehyde-sensitive eczema subjects (Flyvholm et al. 1997, Figure 3, p. 29).

Further characterization of the lowest reactors in the occluded patch tests is provided in **Table 4** below.

Table 4. Patch test reactions for 4 formaldehyde-sensitive subjects reacting to the low formaldehyde concentrations (1,000 ppm and lower) in the occluded patch test (Flyvholm et al 1997, Table 2, p. 30).

	Dilution series						Standard series 1% 10,000 ppm
Patient number	25 ppm	250 ppm	500 ppm	1,000 ppm	5,000 ppm	10,000 ppm	
#5	2 foll.	–	–	+	+	++	++
#6[a)]	–	+	+	foll.[b)]	++	++	+++
#9	–	3 foll.	foll.	++	++	++	++
#16	–	foll./+ ?[c)]	++	+	+++	+++	+?

[a)] Retest 1 year later with 50 ppm, 100 ppm and 250 ppm was negative.
[b)] Follicular reactions: more than 3 follicular papules. All follicular reactions were considered negative.
[c)] Even redness and follicular papules in the test area.

Non-occluded patch test results

No positive reactions based on the criteria above were observed in the nonoccluded patch test. In 6 out of 20 formaldehyde-sensitive subjects, weak reactions showing erythema without infiltration or follicular reactions were observed (but did not meet the criteria for a positive reaction).

ROAT results

No positive reactions were observed in the ROAT as defined in the criteria. A few follicular papules were observed in 5 of 20 formaldehyde-sensitive subjects. The concentration of free formaldehyde in the ROAT cream was 300 ppm, but the actual dose varied across subjects from 0.71 µg/cm^2 to 2.91 µg/cm^2, due to variation of the amount of cream applied by each subject.

Although no positive reactions were observed, additional analysis was provided of those that showed mild follicular reactions compared to concentrations in patch test that elicited a response (see **Table 5** below).

Table 5. Reactions in the ROAT test and lowest positive formaldehyde concentrations in the occluded patch test for subjects with follicular reactions in the ROAT (reproduced from Table 3, Flyvholm et al. 1997, pg. 30).

	Occluded patch test[a]		Repeat open application test (ROAT)		
Patient number	Lowest positive concentration (ppm)	mg/cm^2		Concentration (ppm)[b]	Dose (µg/cm^2)
#7	10,000 (+)	0.3	1 foll. (day 5, 6)	291	0.71
#9	1,000 (++)	0.03	foll. (day 7)	280	2.92
#10	10,000 (+)	0.3	2 foll. (day 2)	258	0.84
#13	10,000 (++)	0.3	2 foll. (day 3)	289	1.12
#18	5,000 (++)	0.15	5 foll. (day 7)	367	1.81

[a] This table was reproduced from data in Table 3, Flyvholm et al. 1997. In the publication, the column for dose for the occluded patch test in Table 3 was mislablled in the table as µg/cm^2 instead of mg/cm^2. This has been corrected herein. Units for the ROAT of µg/cm^2 were correct as reported in the publication.
[b] The cream used by the individual patients was analyzed for free formaldehyde.

III. REVIEWER'S CONCLUSIONS:

The purpose of this study was to determine a minimum elicitation threshold of formaldehyde in formaldehyde-sensitive individuals, utilizing occluded and non-occluded patch tests, as well as a ROAT with a cosmetic product containing a formaldehyde releaser.

In the occluded patch test, there was a concentration-dependent increase in the number of formaldehyde-sensitive subjects exhibiting positive tests for dermal reaction: 19 of the 20 subjects reacted to 10,000 ppm formaldehyde, 9 reacted to 5,000 ppm, 3 reacted to 1,000 ppm, 2 reacted to 500 ppm and 1 reacted to 250 ppm. Furthermore, individuals with the strongest reaction to the 10,000 ppm diagnostic patch test had the lowest threshold concentration for eliciting dermal effects indicative of sensitization. In the 250 to 1000 ppm groups, strength of reaction ranged from follicular reactions to strong positive reaction (++) scores. Only 1 person tested positive in the 250 ppm group (weak positive (+) reaction), but 1 other individual had a follicular reaction, and another had a questionable positive (+/?) and follicular reaction. The individual with the positive reaction at 250 ppm was retested one year later and was negative at 50, 100 and 250 ppm. However, no additional information was provided on the retesting

methods or conditions, and retesting was not conducted at higher concentrations to confirm positive reactions. For these reasons, the initial positive reaction at 250 ppm is still considered as a valid reaction to this test concentration in a formaldehyde-sensitive individual. Based on the concentrations tested in the occluded patch tests, the Minimum Elicitation Threshold or Lowest Observed Adverse Effect Level (LOAEL) was 250 ppm (0.025% or 7.5 $\mu g/cm^2$), and the No Observed Adverse Effect Level (NOAEL) was 50 ppm (0.005% or 1.5 $\mu g/cm^2$).

No definite positive reactions were observed in the non-occluded patch test or in the ROAT. Follicular reactions were seen in both of these test groups, but did not meet the criteria for a positive response for sensitization. It was noted in the study that subjects applied the cream themselves and variability in the amount applied resulted in a wide range of exposure between subjects. Possible reasons for the lack of reaction to the ROAT include testing at too low of a concentration, short exposure time, or potential evaporation of formaldehyde after application to the skin.

No positive or irritant reactions were observed in the control groups for any test procedures. The authors state "occluded patch testing was made with formaldehyde (1% aq.) and paraben mix from the European standard series (15% pet.), Germall 115 (imidazolidinyl urea) (2% pet.) (Hermal, Germany) and rubber from finger cots used for ROAT" (Flyvholm et al. 1997, p. 28) but specific results of these tests were not reported. It is stated in the beginning of the report that the population of potential study participants were all negative for sensitivity to paraben mix, Germall 115 and rubber from finger cots used in the ROAT.

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 does not fully meet all of the screening criteria as outlined below:

-Criterion 13 was not fully met as detailed information was not provided on the test article, including the purity of chemical or any stabilizers in the initial solution, such as methanol. While not all characteristics are provided for the test article, there was sufficient information to draw some conclusions about the article as a whole. The final dilution concentrations are provided and it is assumed, regardless of the starting purity of the chemical, dilutions were made up to reach this final concentration. It is also stated that the patch test dilution was analyzed by an iodine titration method and the ROAT concentrations were confirmed by HPLC. The study also states when discussing the purpose of the study that "Free formaldehyde was measured in all formaldehyde-containing test materials." (Flyvhom et al. 1997, pg. 27).

-Criteria 14 and 15 are not fully met as raw data for individual test results by study participant were not provided, although results based on each individual number was provided.

Although some uncertainties exist in this study, it is concluded that the study is appropriate for quantitative use and can be considered as part of endpoint selection and POD derivation for elicitation of dermal sensitization from dermal exposure. This is concluded based on the criteria as established in the guidance (USEPA, 2012) as follows:

• The dose from the open literature study is lower (i.e., more sensitive) than the lowest dose from a comparable registrant-submitted study – this criterion is met; there was no registrant-submitted study, but the proposed point of departure is lower than data from other published studies.
• 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 $\mu g/cm^2$, 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 – it is the judgement of the reviewer that this criterion has been met.

Study limitations or weaknesses are outlined below:

As detailed in the uncertainties above, limited information was provided on the test substance, including the purity or source of formaldehyde, or whether there were stabilizing compounds present. While the study authors indicate the test material was analytical grade formaldehyde, formaldehyde in aqueous solution is commonly formulated with stabilizers given the relative instability of the chemical in water. Methanol is one of the common stabilizers used with formaldehyde. While methanol is an irritant, it is not a known dermal sensitizer, which is considered in weighing the impact this uncertainty may have on the study results. Analyses for solubility and stability on the test substance or dilutions with the vehicle were not reported in the study. The results from the additional occluded patch tests on the paraben mix, the Germall 115, and rubber from the finger cots were not discussed. Although readings were performed after 2

days, 3 days and 6-9 days, the results from each day were not provided and it is unknown on which day the information that was provided occurred.

V. REFERENCES

Commission Directive of 4 April 1990 amending the Second Directive 82/434/EEC on the approximation of the laws of the Member States relating to methods of analysis necessary for checking the composition of cosmetic products (90/207/EEC). *Official Journal of the European Communities* 1990: *L108:* 92-99.

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