Clinical Standardization of the TRUE Test™ Formaldehyde Patch

Fischer, T; Andersen, K; Bengtsson, U; Frosch, P; Gunnarsson, Y; Kreilgård, B; Menné, T; Shaw, S; Svensson, L; Wilkinson, J. (1995). In Exogenous Dermatology: Advances in Skin-Related Allergology, Bioengineering, Pharmacology and Toxicology. Current Problems in Dermatology

Fischer et al. 1995

- OPP made multiple attempts to request the raw data and documentation of the ethical conduct of the study and did not receive responses
- Purpose of this study
  - To present clinical data used in the development of the TRUE Test™ formaldehyde patch test system
- Study consisted of 5 different test groups
  - Five different groups were utilized to determine levels at which irritation versus sensitivity occur, as well as assess reactions in patients sensitive and not sensitive to formaldehyde
  - Groups 2 and 4 used a series of test concentrations with the TRUE Test system and compared it to Finn chamber aqueous formaldehyde patch tests
- EPA primarily focused on Group 2 testing
  - Group 4 also tested a dilution series; however, very limited information was provided in the results section and was therefore of limited utility

Fischer et al. 1995

- 25 study participants in Group 2
- All had previous positive patch tests to formaldehyde
- Individuals used for both TRUE Test patch system and formaldehyde patch test exposure

Fischer et al. 1995

- TRUE Test patch test system
  - Patches were formulated from the proallergen N-hydroxymethylsuccinimide (HMS) in the vehicle polyvidon (PVP)
    - Authors state succinimide shows no skin irritation with topical and intradermal testing in guinea pigs, no allergic potential in guinea pig maximization tests and no adverse effects in humans with clinical use in the treatment of nephrolithiasis and epilepsy
  - Formaldehyde concentrations equivalent to negative, 10, 20, 30, 40, 80, 100, 120, 150, 190, 260, 330, 570 and 1,120 µg/cm^2
- Concentration of the formaldehyde in solutions reported as analyzed by colorimetric method

Fischer et al. 1995

- Control patch test system used Finn chambers and formaldehyde aqueous solutions
- Performed with dilutions of formaldehyde 1% in water
  - 15 µL of the formaldehyde preparations applied in Finn chambers
- Tested at concentrations of negative, 0.015, 0.032, 0.063, 0.13, 0.25, 0.5 and 1.0% (equivalent to 4.5, 9.6, 19, 39, 75, 150 and 300 µg/cm^2)
- No information provided on how sample concentrations were verified; referenced as prepared by Chemotechnique Diagnostics AB, Malmo, Sweden

Fischer et al. 1995

- Patch test series were applied on the upper back
  - Left/right application varied at random
- Test strips remained on the back for 48 h, evaluated after 72 or 96 h
- Tests were evaluated according to ranking scale recommended by International Contact Dermatitis Research Group (ICDRG)

Fischer et al. 1995

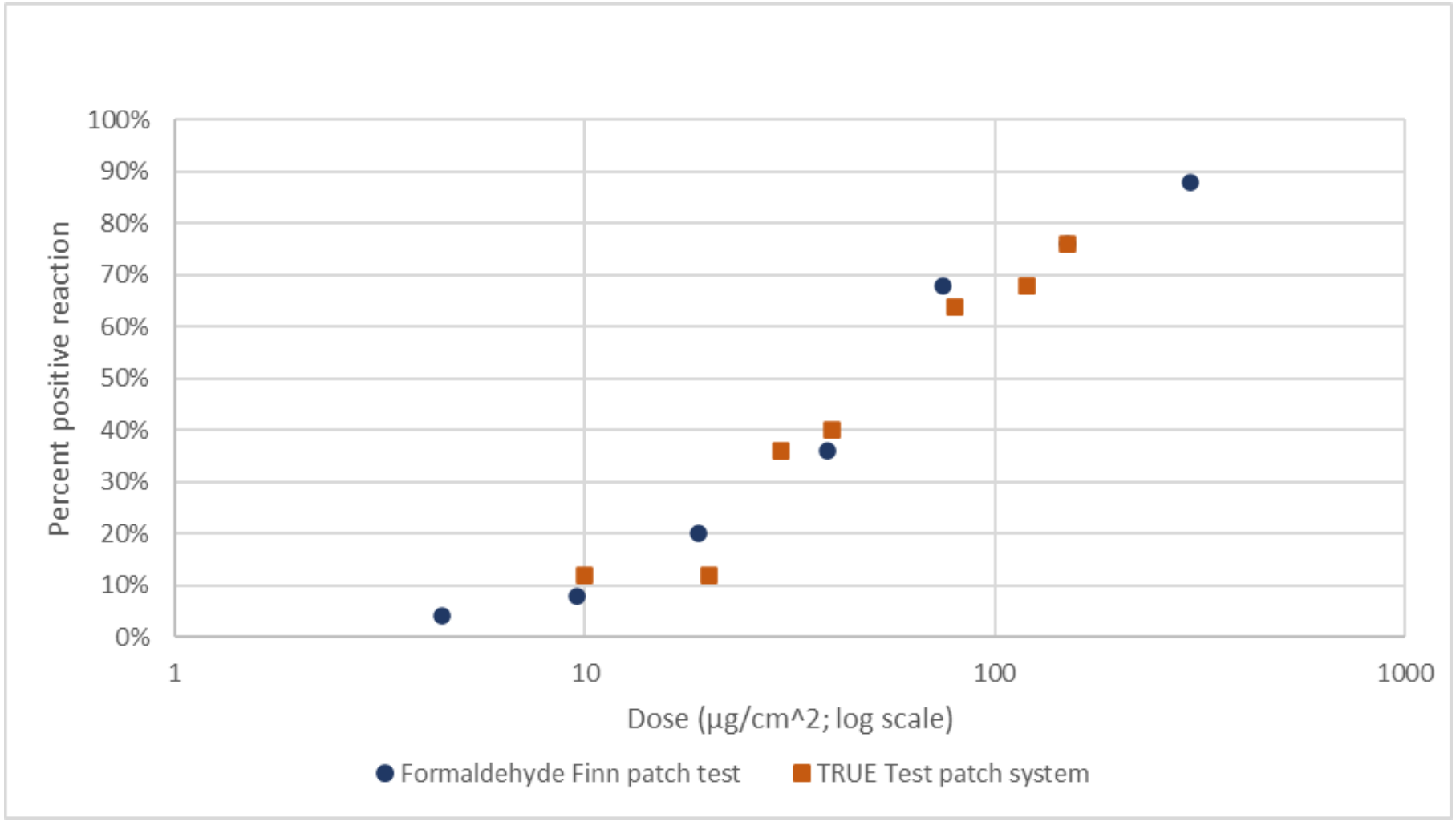
- Criteria for positive reaction (International Contact Dermatitis Research Group)

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

Fischer et al. 1995 Results

Finn chamber formaldehyde concentration (%)/ dose (µg/cm²)	Positive results in Finn Chamber (number positive/ number in test group)	TRUE Test formaldehyde dose (µg/cm²)	Positive results in TRUE Test (number positive/ number in test group)
1 / 300	22/25	150	19/25
0.5 / 150	19/25	120	17/25
0.25 / 75	17/25	80	16/25
0.13 / 39	9/25	40	10/25
0.063 / 19	5/25	30	9/25
0.032 / 9.6	2/25	20	3/25
0.015 / 4.5	1/25	10	3/25

Fischer et al. 1995: Finn Patch and True Test results



Fischer et al. 1995

- EPA's attempts to obtain the raw data from the study authors were unsuccessful.
- EPA in conjunction with our statistics contractor ICF, reviewed and attempted to reproduce the statistical analyses described in the study
- No additional statistical analyses were feasible for the study based on the lack of reported raw data

Strengths/limitations of Fischer et al. 1995

Strengths:

- Adequate number of participants in this study
- Individuals with previously confirmed sensitivity to formaldehyde participated
- Information on degree of response provided
- Experimental design to examine dose-response relationship for elicitation threshold for formaldehyde; a LOAEL can be identified.
- Skin loading in Fischer et al. aligns with potential skin loading from expected uses (e.g., FIFRA registered uses at 370 ppm formaldehyde, loading estimates approximately 3.8 µg/cm^2)

Strengths/limitations of Fischer et al. 1995

Limitations:

- Limited information was provided on the test substance, including the purity or source of formaldehyde or if stabilizers were present (such as methanol)
  - Methanol is an irritant but not a known dermal sensitizer
  - Formaldehyde commonly formulated with stabilizers present, so may represent actual exposures
- No information on confirmation of formaldehyde test concentrations used in Finn chamber system, other than reference to preparing lab
- Separate and historical information cited for succinimide, but data not provided

Overall Conclusions – Fischer et al. 1995

- Based on the concentrations tested in the occluded patch tests, the Lowest Observed Adverse Effect Level (LOAEL) based on aqueous formaldehyde exposure through the occluded Finn chamber system was 0.015 % or 4.5 µg/cm^2. A No Observed Adverse Effect Level (NOAEL) was not obtained.

- The study was well-conducted and provides quantitative information for deriving a minimum elicitation threshold for formaldehyde such that it can be considered as part of endpoint selection and POD derivation

Charge Question

Is the research described in the published study *"Fischer, T; Andersen, K; Bengtsson, U; Frosch, P; Gunnarsson, Y; Kreilgård, B; Menné, T; Shaw, S; Svensson, L; Wilkinson, J. (1995). Clinical Standardization of the TRUE Test™ Formaldehyde Patch. In Exogenous Dermatology: Advances in Skin-Related Allergology, Bioengineering, Pharmacology and Toxicology. Current Problems in Dermatology*" scientifically sound, providing reliable data such that it can be considered as part of endpoint selection and POD derivation for elicitation of dermal sensitization from dermal exposure?