DRAFT Protocol: Study on the Effectiveness of the QRA

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“Intervention Study”

- Not designed to be the only study done; considered to be used with additional studies
- Study design must include a pilot study to test the methodology, reliability and feasibility of the protocol, study population recruitment and retention, study design and assess human subjects protection issues

Objective

- To measure the effectiveness of QRA2 in preventing the induction of contact allergy, in comparison to the original risk assessment method used by RIFM and IFRA
- We will use a patch test before and following controlled exposure to a novel fragrance ingredient that has not been marketed and with no intention of marketing the material.

Study Design

- Randomized controlled trial
  - 3 Test Groups
  - Target Material
  - Initial Patch Test
  - Product Use - for at least 6 months
  - Final Patch Test
- Final study design based on pilot study outcome

Test Groups

- **Group 1**
  - use products containing this target fragrance ingredient at QRA2 levels.
- **Group 2**
  - use same products with the target material at levels designated by the methodology used prior to the introduction of QRA methodology.
- **Group 3**
  - (control group) will use the exact same formulation of products without the target fragrance ingredient.

What is the study testing?

1. Testing whether the QRA2 results in fewer subjects (lower proportion of subjects) developing a contact allergy than the Control Group

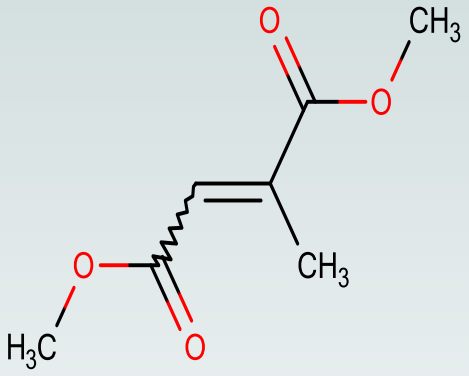
2. Testing (secondary hypothesis) whether the QRA2 results in fewer subjects developing a contact allergy than the original risk assessment method used by RIFM and IFRA

Target Material

- Fragrance ingredient that is a dermal sensitizer
- Never been marketed and with no intentions of marketing the material
- Material cannot be found in nature and is not used as a flavor ingredient
- Should not likely cross-react with known allergens present in the environment
- As detailed in the QRA methodology, identify a No-Expected-Sensitization-Level (NESIL) using a weight of evidence approach.
- Acceptable use levels determined in two ways:
  - QRA2 methodology - Using the NESIL determine the acceptable use levels in various consumer products
  - Risk assessment method used by the fragrance industry prior to the initiation of the QRA1 methodology

Proposed Target Material

- CAS 617-54-9,
  Dimethyl citraconate
- Dermal sensitizer
- Not a flavor material
- IFRA prohibited since 1976
- Not reported to occur in nature
- No close structurally similar materials
- Michael addition alert
- Predicted to react with proteins
- 1984 – last patch test data reported



Dimethyl Citraconate

Test	Protocol	Results	Reference
Draize Test	10 induction injections followed by a challenge injection 2 weeks later. Vehicle was saline	0.5% 0/19 0.1% 0/50	Marzulli, 1982
Buehler Test	Vehicle was petrolatum	12% 0/30	Marzulli, 1982
GPMT Magnusson-Kligman	Vehicle was petrolatum for skin and saline for intradermal injection	12% 4/49	Marzulli, 1982
FCAT	Vehicle was petrolatum. Vehicle was 5% ethyl alcohol in distilled water.	12% 2/30 0.1% 0/10	Marzulli, 1982 Fritzshe, 1966
Modified FCAT	Vehicle was petrolatum. Test material dermal induction was conducted after cyclophosamide injection.	12% 0/30	Marzulli, 1982
OET	20 Topical non-occlusive induction applications. Vehicle was petrolatum.	12% 0/20	Marzulli, 1982 Klecak, 1985
OET	DMSO pretreatment before the induction applications	12% 0/20	Marzulli, 1982

Dimethyl Citraconate

Test	Protocol	Results	Reference
Human Max	Vehicle was petrolatum	12% 8280 µg/cm^2 1?/19	Epstein, 1974
Human Max	Vehicle was petrolatum	12% 8280 µg/cm^2 3/25	Kligman,1975
HRIPT	Modified Draize procedure. The vehicle was petrolatum or alcohol. The test site was covered with a square occlusive Band Aid; no perforations	12% 0/104	Marzulli, 1980 Marzulli, 1982

Dimethyl Citraconate

Test	Protocol	Results	Reference
Patch Test	Four male bakers, aged 18-26 years old, with contact dermatitis, The vehicle was petrolatum	Concentration not provided 0/4	Malten, 1979
Patch Test	182 patients with contact sensitization due to cosmetics were patch tested with the standard ICDRG series and a fragrance series containing 22 fragrance raw materials.	Positive effects	Malten, 1983
Patch Test	Vehicle was petrolatum	24 % 0/ 27 patients 12 % 0/34 patients	Malten, 1984

Initial Patch Test

- **Every subject will participate in a patch test with the target material. Any subject who reacts positively to this initial patch test will not participate in the full study.**

Study Population

- Male and female subjects from the general population that are not fragrance sensitive?
- Size of population needed in each group to test the hypotheses?
  - What assumptions about the population, detectable difference between QRA2 and control group, power, and type 1 error rate will be made?
  - Explore whether the number of subjects needed in the study can decrease if a sensitive population is evaluated
    - Will the results still be interpretable?
- Random selection of subjects with documented procedure

Final Patch Test

- **The study will conclude with a final patch test.**

Selection of Products

A review of the data in the Creme RIFM Aggregate Exposure Model showed that for the products in the model, the products with the highest number of users reporting application of at least one product to the particular application site on EACH of the seven days of the diary.

Area of the Body	Number of users reporting application of at least one product
Hands	34,325
Lips	29,777
Mouth	28,016
Palms	35,061
Underarms	23,524

Selection of Products

From the Creme RIFM Aggregate Exposure Model, the products listed in the table details the products with the highest number of users

Product Type	Number of Users who Consumed the Product
BarSoap	17,992
Deodorant Products	15,382
FaceMoisturizer	5,583
LiquidHandSoap	29,359
Shampoo	5,018
Showergel	5,907
Toothpaste	27,244

Selection of Products

- **Recommend products to include focus on underarm and palms/hands**
  - **Deodorant type product**
  - **Liquid hand soap**
  - **Moisturizer type product**

Product Use

- Use products for at least 6 months
- Need to assess control of exposure by advising subjects of expected use and measuring use
  - Subjects will need to come to a lab on a regular basis
  - Need regular dermatological examinations
  - Consider other information needed to document to be able to describe compliance to the protocol
    - Detailed history administered by trained personnel
    - Details on other fragranced consumer products used

To Summarize:

- A simpler study design that hopefully allows a quicker evaluation of the effectiveness of QRA2 but:
- Need protocol approval from an Ethical Review Board – emphasize the benefits of the study very clearly
- Study design must include a pilot study to test the methodology, reliability and feasibility of the design
  - Is the study feasible? Size of population needed?
  - Can a sensitive population be used; will this pose a greater risk?; will the data be more difficult to interpret?
- Additional sensitization information is needed on the material
  - Need to find a company to manufacture the material and compound the material into consumer-ready products

More Information

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