

# RIFM Case Study



→ Creme Global

# About Creme RIFM Model

The Research Institute for Fragrance Materials (RIFM) and Creme Global partnered to develop an aggregate exposure model for fragrance materials. The Creme RIFM Aggregate Exposure Model has made a substantial impact on both the improvement of consumer safety and the reduction of animal testing.

RIFM is a not-for-profit organization that gathers, analyses, and publishes scientific data related to the safe use of fragrance ingredients. RIFM is funded by industry but all research, protocol and results, is reviewed by an independent Expert Panel for Fragrance Safety ([www.fragrancesafetypanel.org](http://www.fragrancesafetypanel.org)). Panel members are renowned dermatologists, pathologists, toxicologists, environmental, and respiratory scientists with no commercial ties to the fragrance industry.

The fragrance industry is a multi-billion dollar business. Fragrance ingredients are used in cosmetics, personal care products, air care products, household cleaning

products, and more. There are more than 3,000 unique materials and 80,000 unique blends currently used in commerce. They are essential to nearly all consumer products to make them appealing and smell nice. In order for fragrances to continue their valuable role in consumer products, we need to ensure that consumers are only exposed to safe levels of these materials. Traditionally, safe levels were assigned using animal testing and previous methods used to calculate consumer exposure were not as sophisticated or refined as those in use now. Animal testing is highly undesirable from an ethical perspective and using calculations that are less accurate to determine human health and exposure is not ideal.



# Population Exposure Modelling

We developed a consumer exposure model built on large volumes of market survey and scientific data from a wide variety of sources. The model estimates aggregate exposure to fragrances in consumer products, i.e. the total exposure coming from all different sources. When consumer exposure is below a certain level for which there are no adverse health effects (This is called the Threshold of Toxicological Concern (TTC).), no further animal testing is required. This is difficult to show using less sophisticated calculations. By using large datasets and statistical models, we dramatically refine the estimates of consumer exposure, often successfully demonstrating that they are below the level of concern.

Using advances in toxicology, data science and exposure assessment to assess fragrance safety, we:

- Dramatically improve estimates of consumer exposure to fragrances
- Reduce/eliminate the need for animal testing

Since adopting the model, we estimate that more than 120,000 animals were saved and their associated costs. This is a clear demonstration of the benefits of combining traditional science, data science and exposure assessment. The model uses a probabilistic simulation, sampling from distributions of measured variables for individuals across a population, to provide a realistic estimate of aggregate exposure to fragrance ingredients used in a range of common consumer products.

The innovative Creme RIFM Aggregate Exposure Model is a substantial advance from previous methods and the most comprehensive model of its kind. The model provides more realistic exposure data for RIFM's Safety Assessments for Fragrance Ingredients.



# The need for Creme RIFM Model

As part of RIFM's research commitment to enhance the science for continuous improvement in the safety assessment process, this methodology was developed to account for aggregate exposure of consumers to ingredients in personal care products.

Traditional deterministic calculations provided inaccurate over-estimations since:

- Consumers are unlikely to use all products under consideration on a daily basis.
- Consumers do not use the same amounts of each product.
- The ingredient will not be present at the same concentration in all products.

Probabilistic modeling eliminates these issues by using consumer habits and manufacturers' product data to accurately estimate aggregate exposure. The RIFM model:

- Reduces the need for time-consuming and expensive clinical toxicity testing, delivering significant resource and budget savings
- Provides an alternative to animal testing
- Satisfies the European Commission's request for information on aggregate exposure when assessing dermal sensitization
- Satisfies the USA Toxic Substances Control Act (TSCA) Reform legislation that specifically asks for aggregate exposure of a chemical ingredient
- Provides a unified approach to Chemical Safety Assessments under REACH
- Provides a solid scientific basis for IFRA limits for systemic effects

# How does it work?

The model calculates both ‘dermal exposure’–impact on the skin–and overall ‘systemic exposure’–impact on the whole body.

## Equation 1

Equation 1 shows the formula for calculation of a subject’s dermal exposure, at a particular application site, to a fragrance from a particular product on a particular day.

Daily Dermal Exposure (DDE)

Aggregate Exposure

=

Frequency × Amount × Retention × Concentration

Surface Area

Where:

- Frequency** refers to the number of usage occasions of the product;
- Amount** is the amount of product applied in each application;
- Retention** is the proportion of the product staying on the body after use;
- Concentration** is the proportion of the fragrance in the product by mass, and
- Surface area** is the area of the site of application.

## Equation 2

Equation 2 shows the formula for calculation of a subject’s systemic exposure, at a particular application site, to a fragrance from a particular product on a particular day.

Daily Systemic Exposure (DSE)

Aggregate Exposure

=

Frequency × Amount × Retention × Concentration × Penetration

Body Weight

Where:

- Frequency** refers to the number of usage occasions of the product;
- Amount** is the amount of product applied in each application;
- Retention** is the proportion of the product staying on the body after use;
- Concentration** is the proportion of the fragrance in the product by mass
- Penetration** is the amount of material absorbed through the skin, and
- Body Weight** is the weight of the individual.

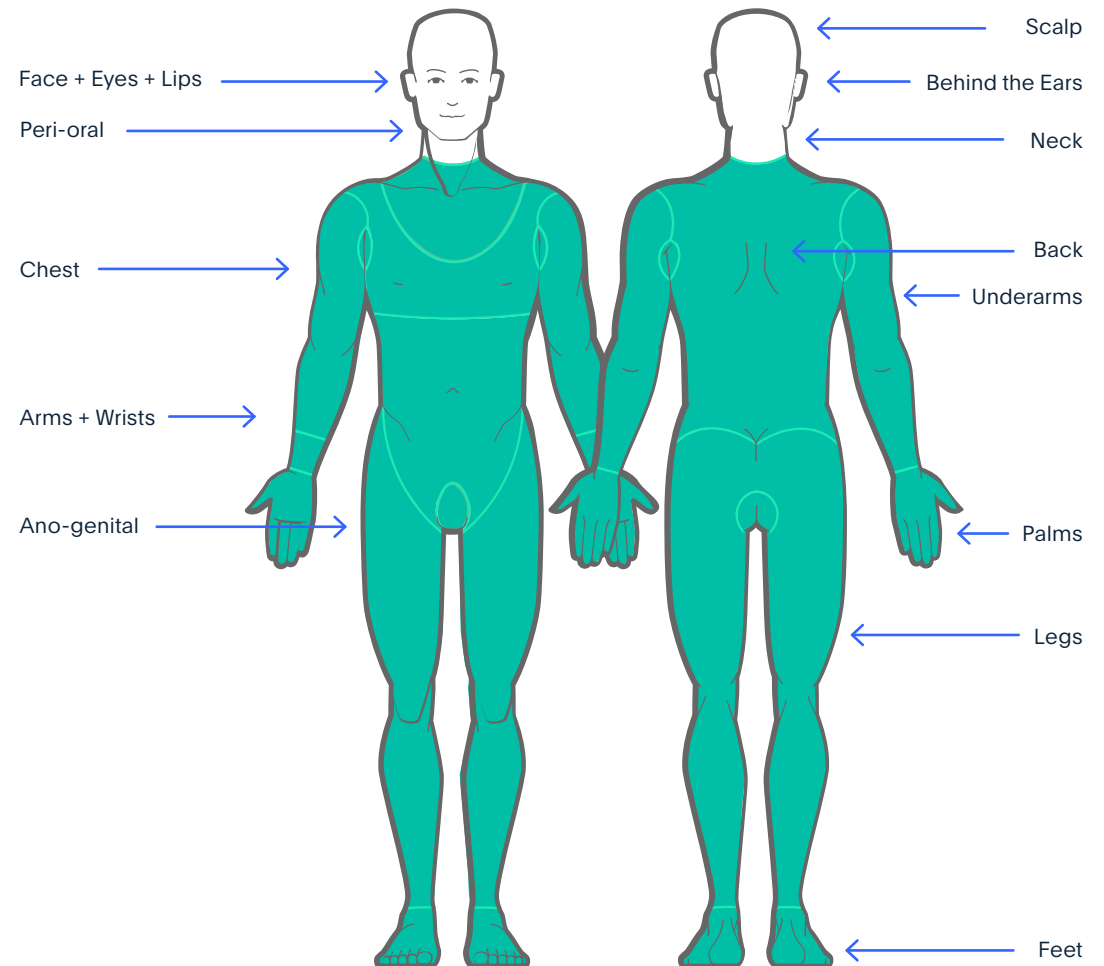
The essence of the CREME RIFM Aggregate Exposure Model is that, in place of using a single constant value in equation (1) or equation (2), it draws on a database of real-world measurements to calculate tens of thousands of individual consumer exposures to a fragrance from multiple sources.

Our understanding of how products are used (how often and where on the body) is now based on real-life data—daily use records of fragranced products by more than 36,000 people in the United States and Europe. A series of studies by the cosmetics industry provide information on the quantities of products used. Data from manufacturers of fragrances and consumer products provide information on the concentration of fragrance materials in final products. Real-life data is used for average height and weight to calculate skin surface areas.

The methodology identifies 18 different body sites, from scalp to feet, grading each body site according to relative sensitivity and length of time fragrance remains on the skin.

The model estimates three routes of exposure—ingestion, inhalation, and dermal. In the latter case, it produces application site specific estimates. The three routes are combined to estimate systemic exposure. Exposure estimates can be reported in absolute terms, or relative to body weight, or skin surface area according to the particular exposure in question.

Where a subject uses a number of products, each of which may contain the fragrance material of interest, the total material exposure can be calculated by summing the contributions from the individual products (for that subject). The method of aggregation is simply to sum the individual contributions from the different products at the individual subject level. Population exposure can also be calculated.



# Products included in the model

The Creme RIFM Aggregate Exposure Model estimates aggregate exposure to fragrance ingredients in personal care products, cosmetics and air care products.

The 25 products covered by the model are grouped into nine categories as shown in Table 1. The model produces exposure estimates for an individual product, in a category or for a number of products in one, several or all categories. Exposure is estimated for normal use in adult consumers, male and female. Currently, professional use and exposure in young children or adolescents is not covered. The model draws on data obtained from the US and Western Europe making it most reliable in those geographical regions.

The model is being expanded to:

- Include household cleaning products
- Add several more cosmetic and personal care products
- Add habits and practices data from other European countries
- Update the habits and practices data to include results from the 2013-2014 survey conducted by Kantar Worldpanel
- Include habits and practices data for the 13-17 year old demographic for Europe and the USA
- Investigate whether presence probabilities for fragrance ingredients can be assessed

## Creme RIFM Model Products And Categories

### Body Lotion

Mass Market  
Prestige  
Other

### Oral Care

Toothpaste  
Mouthwash

### Hydroalcoholics

Eau de Toilette  
Eau de Parfum  
After Shave/Cologne

### Moisturisers

Face Moisturiser  
Hand Cream

### Air Care

Aerosols  
Scented Candles  
Plug-Ins

### Deodorant

Deodorant/Anti-Perspirant Spray  
Deodorant/Anti-Perspirant Non-Spray  
Body Spray

### Cosmetic Styling

Lipstick  
Liquid/Makeup Foundation  
Hair Styling Products  
Hairspray

### Shower Products

Showergel / Body Wash  
Shampoo  
Rinse-off Conditioner

### Soaps

Liquid Hand Soap  
Bar Soap



# Published Methodology

RIFM published a series of papers on the methodology from 2015-2017 in, Regulatory Toxicology and Pharmacology, a peer-reviewed scientific journal.

The papers are available on the RIFM website at: [www.rifm.org](http://www.rifm.org) in the Human Health Science section, on the Creme RIFM Aggregate Exposure Model for Fragrance Ingredients page: [www.rifm.org/rifm-science-human-health-content.php?id=40&science=human#.WuHnFi7wa70](http://www.rifm.org/rifm-science-human-health-content.php?id=40&science=human#.WuHnFi7wa70) and in the Publications section. These papers can also be found on the Fragrance Material Safety Assessment Resource Center, published by Elsevier: [www.fragrancematerialsafetyresource.elsevier.com](http://www.fragrancematerialsafetyresource.elsevier.com)





# The Software

RIFM is built using Expert Models platform.  
The software includes the following features:

## The Wizards

The wizards allow the user to choose inputs to run through a model. The design of the wizards came about through achieving a deep understanding of the workflow of our users.

## Data Editor

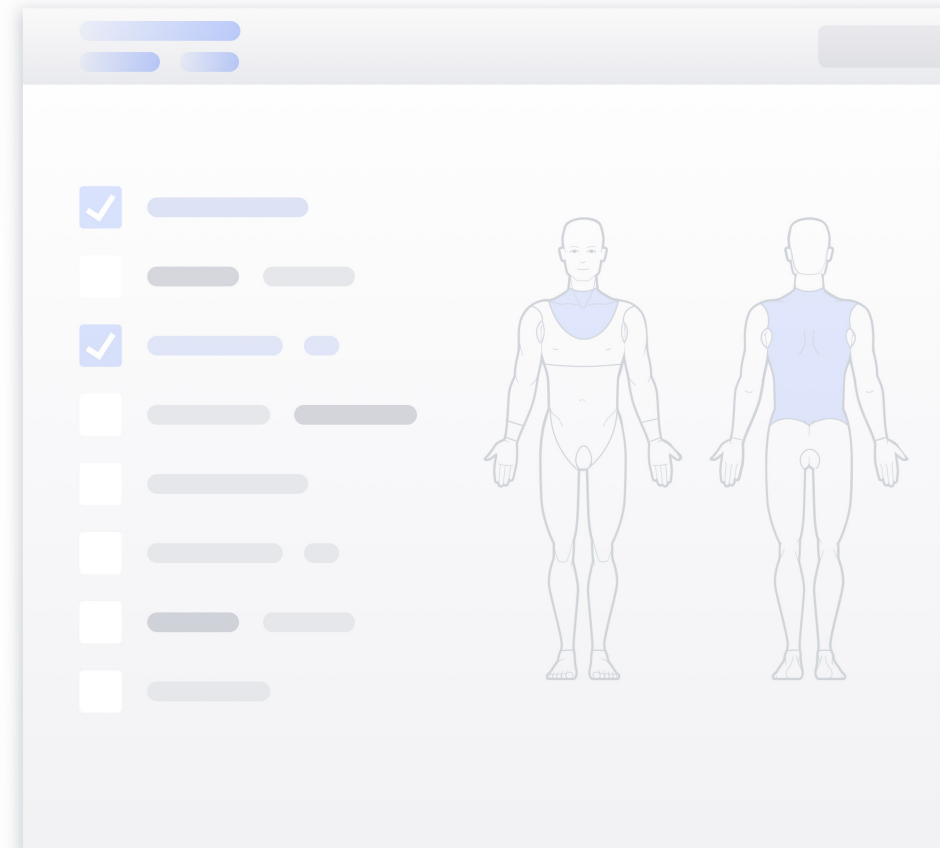
The data editor is like a simplified Excel spreadsheet but with extra features particular to data science.

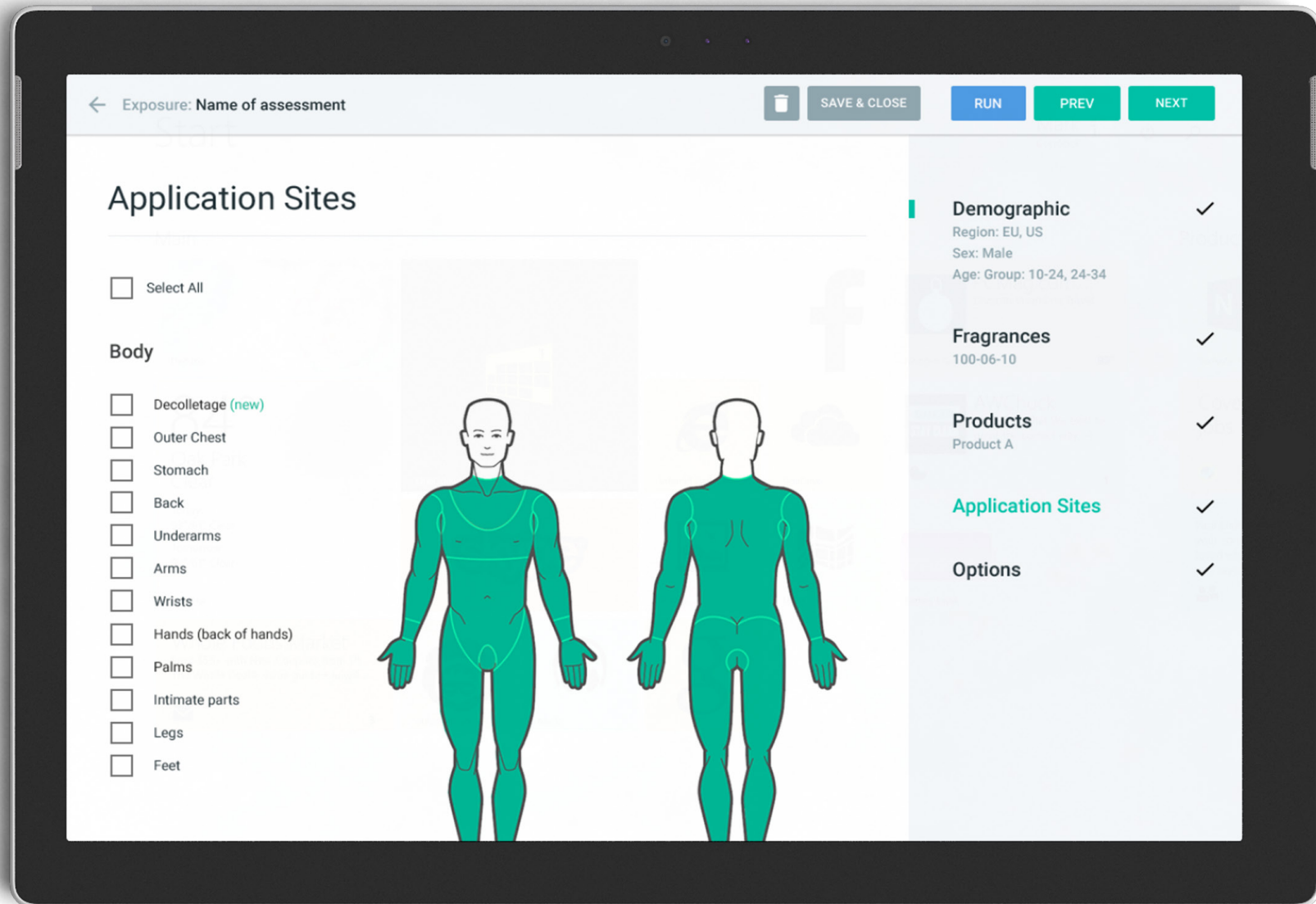
## File management system

The user can manage their tables of data and results tables from here.

## Report Viewer

Reports contain the results from both models. Reports are presented in a report viewer which also has tabs for inputs, outputs and useful supporting information.





Assessment Wizard Step: Choosing applications sites

← Exposure: Name of assessment

SAVE & CLOSE

RUN

PREV

NEXT

## Fragrances

Are you including Fragrances?

Option 1  
Default RIFM Fragrances & concentrations

Option 2  
Custom Fragrances & concentrations ✓

Option 3  
Product Exposure  
(No fragrances)

Fragrances Table  
nameOfFile

CHOOSE NEW

REMOVE

### Choose Fragrances

Maximum 10 Fragrances Allowed

Search

☐ 100-06-10  
☐ 100-06-10  
☐ 100-06-10  
☐ 100-06-10  
☐ 100-06-10  
☒ 100-06-12

Fragrances selected (including product)

☒ 100-06-12

Demographic ✓

Region: EU, US

Sex: Male

Age: Group: 10-24, 24-34

Fragrances ✓

Products

Application Sites

Options

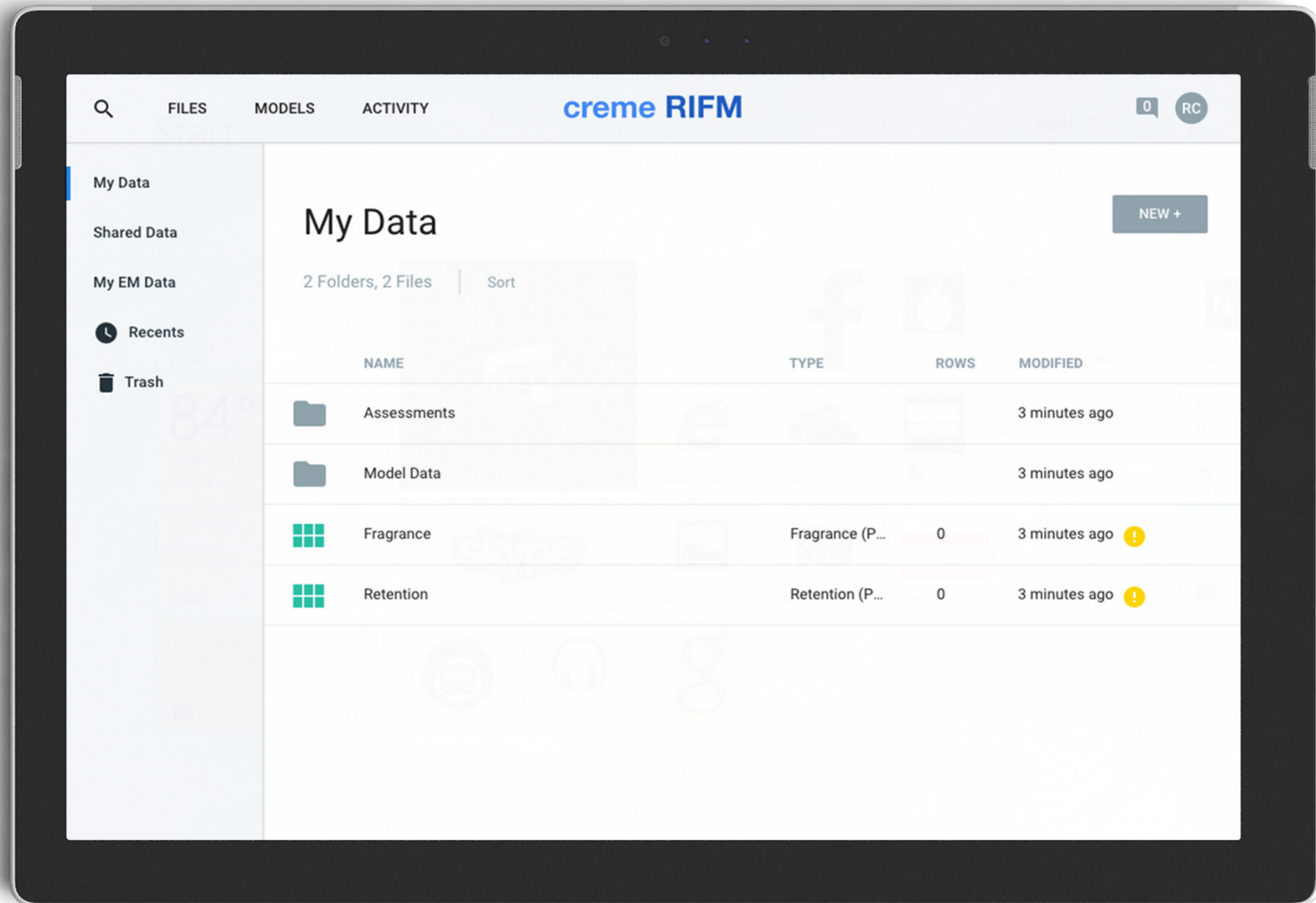
Assessment Wizard Step: Choosing Fragrances

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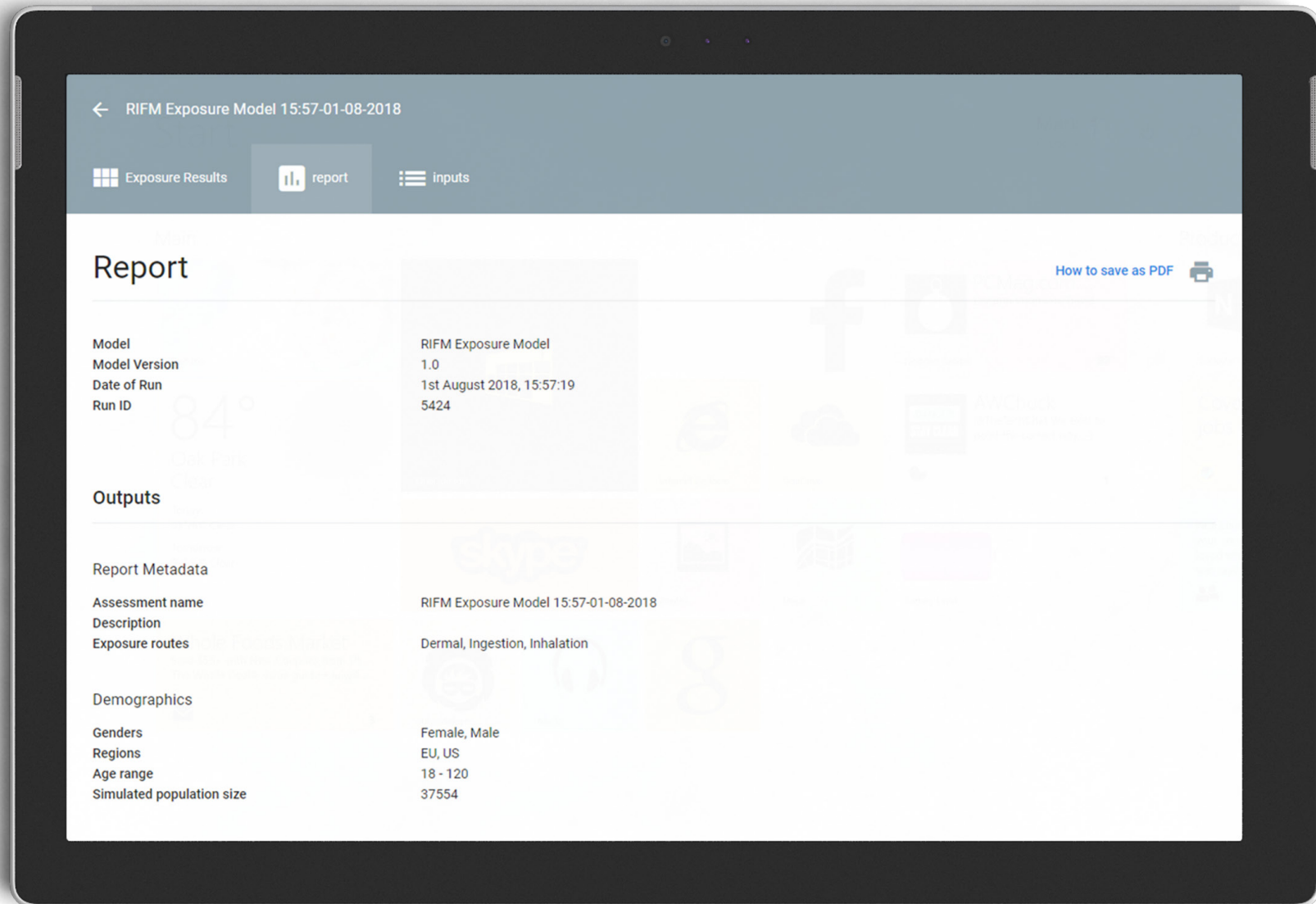


Fragrance (0 ROWS)				
	Product	Substance	Ingredient Mixture Concentration	Mixture Product Concentration
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				
22				

Data Editor



File management system



Report Viewer





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